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RESEARCH

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Metabolic status is a key factor influencing proteomic changes in ewe granulosa cells induced by chronic BPS exposure

Marie-Emilie Lebachelier de la Riviere^{1†}, Ophélie Têteau^{1†}, Coline Mahé¹, Olivier Lasserre², Alice Desmarchais¹, Svetlana Uzbekova¹, Pascal Papillier¹, Daniel Tomas^{1,3}, Valérie Labas^{1,3}, Virginie Maillard¹, Marie Saint-Dizier¹, Aurélien Binet^{4,5} and Sebastien Elis^{1*}

Abstract

Background Bisphenol S (BPS) is the main substitute for bisphenol A (BPA), a well-known plasticiser and endocrine disruptor. BPS disrupts ovarian function in several species. Moreover, a few studies have reported that the effects of BPS might be modulated by the metabolic status, and none have characterised the granulosa cell (GC) proteome after chronic BPS exposure.

Objectives This study aimed to decipher the mechanisms of action of chronic BPS exposure on the proteome of ewe GCs while considering the interaction between a deliberate contrasted metabolism and reproductive function.

Methods Forty ewes were split into two groups with contrasted diets: restricted (R, $n = 20$) and well-fed (WF, $n = 20$). The R and WF ewes were subdivided according to the dose of BPS administered through the diet (0–50 $\mu\text{g}/\text{kg}/\text{day}$), forming four groups: R0, R50, WF0 and WF50. After 3-month BPS daily exposure, GCs were recovered during the pre-ovulatory stage and proteins were analysed by nano-liquid chromatography coupled with tandem mass spectrometry.

Results Chronic exposure to BPS affected the GC proteome differently according to the ewe metabolic status. Fifty-nine out of 958 quantified proteins were differentially abundant between groups and are mainly involved in carbohydrate and lipid pathways. Unsupervised hierarchical clustering of differentially abundant proteins (DAPs) identified four clusters of 34, 6, 5 and 14 proteins according to the BPS exposure and diet interaction. Pairwise comparisons between groups also revealed a strong effect of BPS exposure and diet interaction. Functional analysis of DAPs highlighted that BPS upregulated β -glucuronidase (GUSB; $p = 0.002$), a protein especially able to deconjugate bisphenol glucuronides (BP-g). Moreover, among unexposed ewes, GUSB was detected only in well-fed ewes.

Discussion Conjugation of glucuronides inhibits the oestrogenic activity of bisphenols. Upregulation of GUSB in ewes dosed with BPS would prolong the oestrogenic effects of BPS by deconjugating BPS-g into free BPS. In addition,

[†]Marie-Emilie Lebachelier de la Riviere and Ophélie Têteau contributed equally to this work.

*Correspondence:
Sebastien Elis
sebastien.elis@inrae.fr

Full list of author information is available at the end of the article



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literature has reported an up-regulation of GUSB in people suffering from obesity. Therefore, people suffering from obesity could be subjected to prolonged and aggravated exposure to BPS. These data highlighted the deleterious effects of BPS and its interaction with metabolic status.

Keywords Bisphenol S, Diet, Metabolic status, Adiposity, Granulosa cells, Protein, Proteomic, Ewes, Ovary

Introduction

Bisphenol A (BPA), one of the most widely produced plasticisers throughout the world [1], is recognised as an endocrine disruptor [2]. Several studies have highlighted the harmful effects of BPA on human health, particularly on female reproduction through alterations in steroidogenesis (oestradiol, progesterone, etc.), ovarian diseases (polycystic ovary syndrome), unfavourable pregnancy outcomes and reduced fertility [3–5]. The main route of exposure is oral ingestion, due to the transfer of bisphenol molecules from food packaging to its contents, given that BPA is widely used in the food industry. The most important detoxification reaction for bisphenols is the conjugation reaction with glucuronic acid, which promotes urine excretion of these molecules [6]. Given its status as an endocrine disruptor, BPA has been banned in the food industry in Canada, Belgium and France [2, 7] and replaced by its structural analogues, in particular bisphenol S (BPS) [8]. BPS has been detected in human fluids, such as urine [9], follicular fluid [10–12] and serum [12, 13]. BPS is known as an oestrogen mimetic that can modulate steroidogenesis by binding to oestrogen receptors [14, 15]; moreover, it has been reported to exhibit an androgenic effect, although these results are controversial [16, 17]. Granulosa cells (GCs) are somatic cells surrounding the oocyte in the ovarian follicle; they are involved in follicle growth and steroidogenesis, enabling oocyte maturation. There is also a dialogue between these cells and the oocyte, which is essential for ovulation [18]. Several *in vitro* studies in different mammalian species have demonstrated BPS-induced disruption of oestradiol and/or progesterone secretion in GCs, although these effects varied according to the dose and duration of BPS exposure [10, 11, 19–22]. The deleterious effects of BPS on health, in particular reproductive function and/or metabolic disorders, are sometimes even worse than those of BPA [23].

In female mammals, reproduction requires adaptations to energy metabolism [24]. Indeed, an insufficient body fat mass leads to a loss of cyclicity and, conversely, overweight or obesity can lead to complications such as an increased risk of miscarriage, impaired cumulus-oocyte complex development and impaired early embryonic development [25]. A higher body mass index (BMI) can also be associated with alterations in the follicular fluid composition, with increased follicular insulin, glucose and lactate concentrations [26], and obesity exerts effects on sex hormone secretion and metabolism, resulting

in changes in the bioavailability of both oestrogens and androgens [27].

BPA has been associated with obesity in humans [28, 29] and promotes adipogenesis [30] and lipid accumulation by impacting lipid and glucose metabolism via the peroxisome proliferator-activated receptor gamma (PPAR γ) receptor signalling pathway [4]. Therefore, bisphenols are able to modulate energy metabolism, which adversely affects female reproduction and cellular functions. For example, bisphenols are able to impair steroidogenesis of cumulus cells, granulosa cells and/or theca cells in several species including bovine [19, 31], rodent [32], ovine [22] and human [11]. BPS also altered ewe oocyte developmental capacity by inducing a decrease in oocyte maturation rate, in embryo cleavage rate and in blastocyst rate in ovine [33]. Finally, the negative effect of BPS may be exacerbated by the metabolic status. Indeed, oestradiol increased in the follicular fluid of only well-fed animals while there was no effect in animals on a restricted diet [34]. Therefore, excess in diet can contribute to impaired reproduction. Similarly, an interaction between chronic exposure to BPS and the metabolic status has been reported to affect the efficiency of *in vitro* embryo production negatively, whereas BPS or diet alone had no effect in ewes receiving contrasted diets (restricted or well fed) [35].

The aim of this study was to investigate the mechanisms of action of chronic BPS exposure, according to the metabolic status of the animal, on ewe GCs by proteomic analysis to consider the interaction between metabolism and ovarian follicular function. Forty ewes were fed contrasted diets and exposed or unexposed to oral BPS for at least 3 months. The GCs were collected at the pre-ovulatory stage of the cycle; protein was extracted, pooled and analysed by nano-liquid chromatography coupled to tandem mass spectrometry (nanoLC-MS/MS).

Results

Validation of the diet model and detection of BPS and its metabolite in the follicular fluid of exposed ewes

Ewe body weight (BW) and body condition score (BCS) differed significantly between the WF and R groups (Table 1) [34]. The mean BW and BCS of restricted ewes were lower than well-fed ewes, with a mean difference of 11 kg in BW (52.6 ± 1.2 kg vs. 63.5 ± 1.2 kg in restricted and well-fed ewes, respectively, $p < 0.001$) and almost 1 BCS point (2.05 ± 0.07 vs. 2.88 ± 0.05 in restricted and well-fed ewes, respectively, $p < 0.001$). Despite

Table 1 Zootechnical parameters of ewes chronically exposed or not to BPS

	Mean ± SEM				p-value		
	R0	R50	WF0	WF50	Diet effect	BPS effect	Diet × BPS effect
Body weight (kg)	53.2 ± 2.1 ^a	51.9 ± 1.4 ^a	64.0 ± 1.7 ^b	62.9 ± 1.7 ^b	<0.001	0.511	1.000
Body condition score	2.02 ± 0.12 ^a	2.08 ± 0.08 ^a	2.78 ± 0.08 ^b	2.98 ± 0.06 ^b	<0.001	0.136	0.387
Plasma glucose (mg/L)	638 ± 29.6	674 ± 35.6	731 ± 57.9	822 ± 81.5	0.039	0.260	0.661
Plasma NEFA (µmol/L)	173 ± 48.3	164 ± 23.8	326 ± 57.9	276 ± 93.1	0.035	0.611	0.761
Plasma BPS (nM)	0.29 ± 0.29 ^a	2.95 ± 0.8 ^b	0.12 ± 0.12 ^a	2.14 ± 0.36 ^b	0.294	<0.001	0.506
Plasma BPS-g (nM)	0.03 ± 0.02 ^a	201 ± 15.7 ^b	0.38 ± 0.38 ^a	188 ± 11.5 ^b	0.510	<0.001	0.491

A body condition score is graded from 1 to 5, 2 corresponding to a slim ewe and 4 corresponding to a fat ewe. Tukey post-hoc tests are indicated by letters and values with different letters are significantly different ($p < 0.05$). Two-way ANOVA p-values are presented for the effects of diet, dietary exposure to BPS and the interaction of these effects. Bold text indicates significant differences ($p < 0.05$)

overfeeding (165% of their maintenance energy requirements), well-fed ewes were not overweighted (BCS=2.88 instead of 4 for typical overweighted animals); however, the plasma glucose and non-esterified fatty acids (NEFA) concentrations were increased compared with the restricted ewes (glucose: 778 ± 50 vs. 657 ± 23 mg/L, $p = 0.039$; NEFA: 301 ± 54 vs. 168 ± 26 µmol/L, $p = 0.035$). Ewes in the R50 and WF50 groups were exposed to BPS for an average of 5.4 ± 0.1 months (range: 3.6–7.9 months) before sample collection. BPS and its glucuronide conjugate BPS glucuronide (BPS-g), a marker of internal BPS exposure, were detected in the plasma of all exposed ewes at the time of slaughter (i.e. 24 h on average after the last exposure; Table 1), with no difference regarding diet effect. BPS-g was detected in 3 among 20 unexposed ewes at a significantly lower level compared to BPS exposed ewes ($p < 0.001$).

Proteins identified in ewe granulosa cells (GCs)

A total of 958 proteins were identified by at least two unique peptides in GCs (Supplementary Table S1). Among these proteins, 641 proteins were common to all conditions (Fig. 1). There were 2 specific proteins identified that were common to the R0 and WF0 groups, 20 specific proteins common to the R50 and WF50 groups, 17 specific proteins common to the R0 and R50 groups and 9 specific proteins common to the WF0 and WF50 groups. The most abundant proteins among the 641 common proteins are mainly circulating/blood proteins (serum albumin, fibrinogen alpha chain, fibrinogen beta chain, fibrinogen gamma chain, immunoglobulin and haemoglobin) and structural proteins (histones and heat shock protein family A member 5; Supplementary Table S1). The 958 proteins identified in GCs are involved in metabolism, the processing of genetic or environmental information and the cellular organisation system (see Fig. 2).

Venn diagram showing the overlap between the different conditions (diet × BPS exposure) and histogram showing the number of proteins identified in each condition. R0 – restricted diet, no BPS, R50 – restricted diet and 50 µg/kg/day BPS exposure, WF0 – well fed diet,

no BPS, WF50 – well fed diet and 50 µg/kg/day BPS exposure.

Proteomaps were generated using the KEGG (Kyoto Encyclopedia of Genes and Genomes) Pathway gene classification. Functional categories and proteins are represented by polygons. The polygon areas illustrate the normalised abundance of proteins in each condition. Functions and related proteins are organised into common regions and coded using similar colours. R0 – restricted diet, no BPS, R50 – restricted diet and 50 µg/kg/day BPS exposure, WF0 – well feed diet, no BPS, WF50 – well feed diet and 50 µg/kg/day BPS exposure.

Global analysis of DAPs in GCs from restricted or well-fed ewes exposed or not exposed to BPS

To assess more specifically the impact of BPS exposure and of contrasting diets on protein abundance, PCA of the 59 DAPs (ANOVA and chi-square $p \leq 0.05$; Supplementary Table S2) of the 16 GCs samples was performed (Fig. 3). The PCA explained 57% of the variance of the data (Dim1 at 37.9%, light and dark blue and Dim2 at 19.2%, turquoise and green). WF0 did not correlate well in this PCA with the horizontal or vertical axis as it was close to the center of the PCA. On the contrary, R0 (dark blue) was negatively correlated to the horizontal axis while R50 (light blue) is mainly positively correlated to the vertical axis. WF50 was positively correlated to the horizontal axis and negatively correlated to the vertical axis. There was therefore a clear discrimination between these 3 groups (R0, R50 and WF50) as they do not correlate with the same axis. Therefore, the difference between unexposed ewes or ewes exposed to BPS might be greater in the restricted groups. The heatmap representation shows the differences in significant DAPs after ANOVA and chi-square test (Fig. 4). Unsupervised hierarchical clustering identified four DAP clusters (C1–C4): C1 (green) comprises 34 proteins (including FHIT, GUSB, VAPB and TTR) that were more abundant in BPS-exposed ewes (WF50 and R50) and WF0 than in R0. C2 (orange) comprises 6 proteins (including AKR7A2, FDFT1, HSDL1 and TNPO2) that were more abundant in BPS-exposed (WF50 and R50) than unexposed ewes.

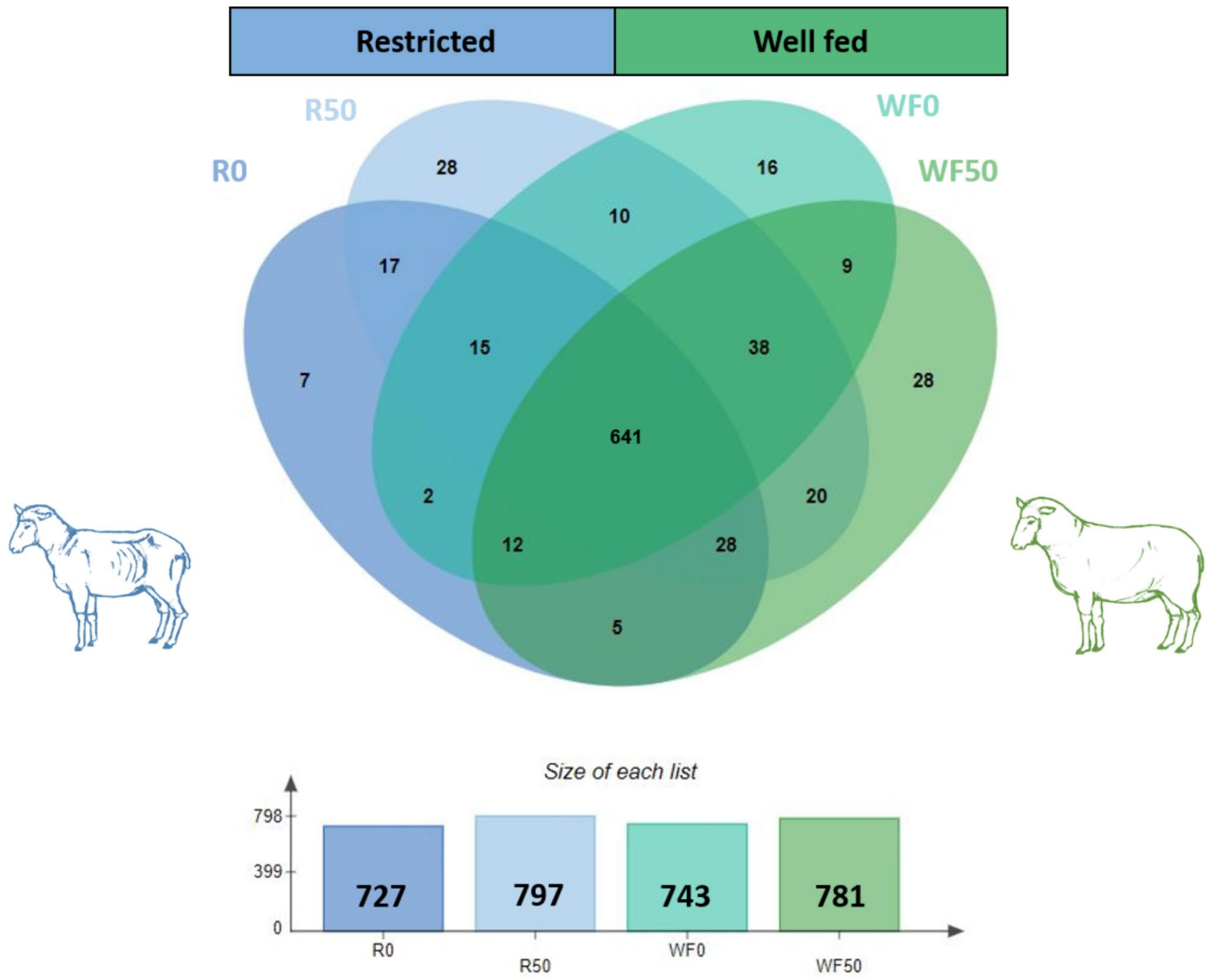


Fig. 1 Comparative analysis of proteins identified in ewes Granulosa Cells (GCs)

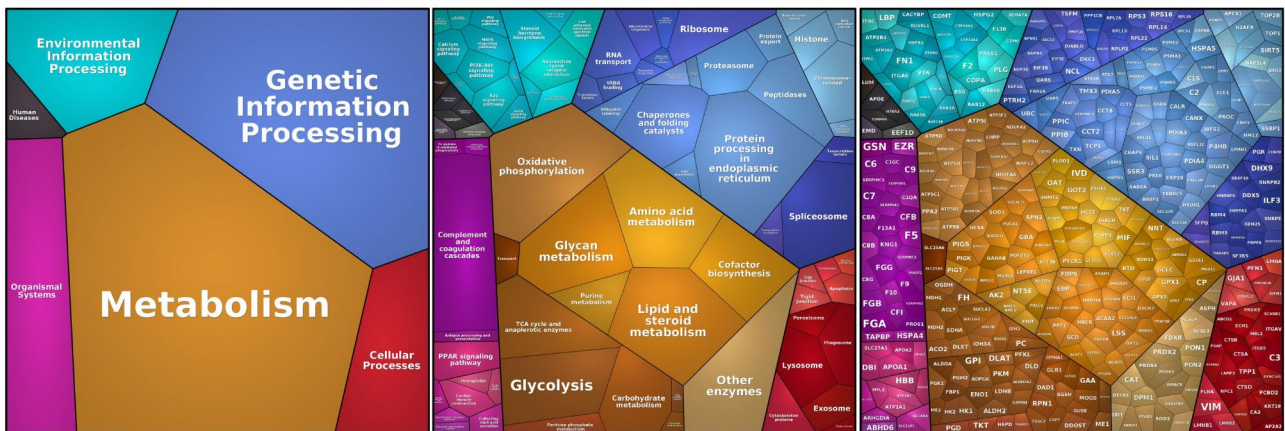


Fig. 2 Proteomaps analysis of the 958 quantified proteins in ovine GCs

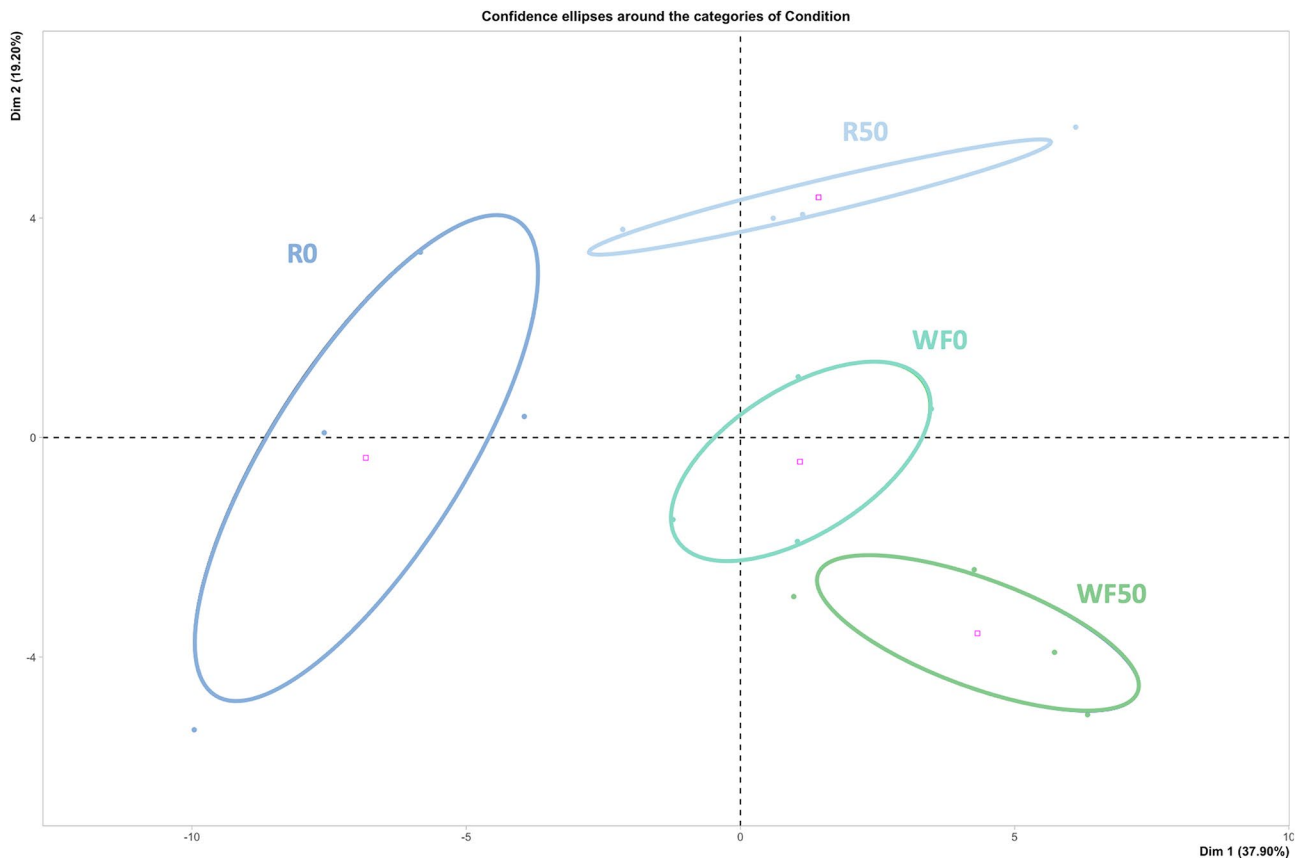


Fig. 3 Principal component analysis of the 59 differentially abundant proteins according to the diet and BPS exposure

C3 (blue) comprises 5 proteins (including DCD, APOA1, CLEC3B and AMBP) that were more abundant in WF50 than in the three other conditions. Finally, C4 (pink) includes 14 proteins (including TST, NCSTN, SLC27A1 and PRKCSH) that were less abundant in the WF50 group compared with the three other groups (Table 2 and Supplementary Table S2).

Principal component analysis of the 59 DAPs (ANOVA $p \leq 0.05$) showing a separation of the 16 GCs samples between diet (light and dark blue: restricted (R); turquoise and green: well-fed (WF)) and BPS exposure (0–50 $\mu\text{g}/\text{kg}/\text{day}$). Each point represents a biological sample with a different diet, exposed or not to BPS (see legends for corresponding colour). The square in each confidence ellipse indicates the mean of the data for a given region. The percentage on each axis (dimension) represents the total variance of data (horizontal axis, dimension 1 and vertical axis, dimension 2). Ellipses represent the 95% interval of confidence for each group.

Each line corresponds to a DAP (ANOVA or Chi-square $p \leq 0.05$). For a given protein, blue lines represent lower abundance, white lines represent median abundance, while red lines represent higher abundance values relative to the other conditions. Four groups of proteins were identified by unsupervised hierarchical clustering

(multicoloured vertical bars on the left). Orange bars indicate groups with higher abundance in ewes exposed to BPS. Green bars indicate a group with lower abundance in R0, blue bars indicate groups with higher abundance in ewes WF50 while pink bars indicate a group with lower abundance in WF50. The proximity between proteins is illustrated by the hierarchical tree at the left side. R0 – restricted diet, no BPS, R50 – restricted diet and 50 $\mu\text{g}/\text{kg}/\text{day}$ BPS exposure, WF0 – well feed diet, no BPS, WF50 – well feed diet and 50 $\mu\text{g}/\text{kg}/\text{day}$ BPS exposure.

Pairwise comparisons of proteins in GCs from ewes exposed or not exposed to BPS and presenting contrasted metabolic status

Pairwise comparisons were performed on the lists of the 958 quantified proteins (t-test $p \leq 0.05$ and $\text{FC} \geq 2$ or ≤ 0.5 ; chi-square test $p \leq 0.05$; Supplementary Table S2). Figure 5 shows the distribution and overlap of DAPs between the comparisons. The different comparisons showed relatively similar number of DAPs (34 for R0 vs. R50, 26 for WF0 vs. WF50, 37 for R0 vs. WF0, and 48 for R50 vs. WF50). Most of the DAPs were specific to each comparison and there was no DAP shared among all the comparisons.

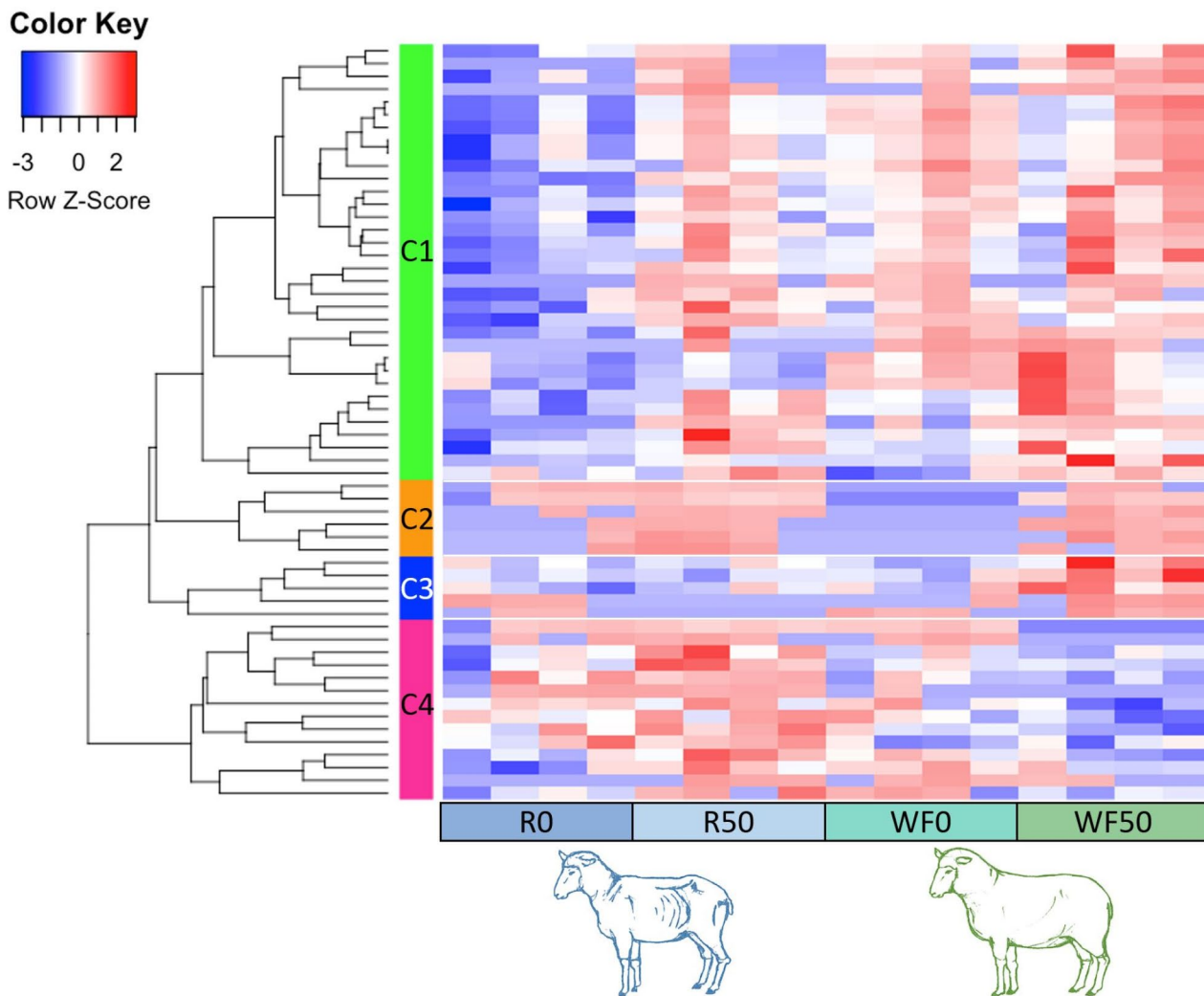


Fig. 4 Heatmap and hierarchical clustering of the 59 differentially abundant proteins according to the diet and BPS exposure

The gene symbols for the DAPs were used for GO enrichment analysis of biological processes with Metascape (Supplementary Figure S1). The R50 vs. WF50 comparison highlighted a higher number of enriched biological processes compared with the other comparisons (Supplementary Figure S1D). The functional enrichments of DAPs for R0 vs. R50 is related to metabolism and detoxification (carbohydrate metabolic process and cellular detoxification) and proper functioning of the cells (intracellular protein transport, intracellular chemical homeostasis, organic anion transport, negative regulation of amide metabolic process and of cell development; Supplementary Figure S1A). The functional enrichments of DAPs for WF0 vs. WF50 is related to cells and organism balance and development (protein localisation to nucleus, negative regulation of cellular component organisation and of the immune effector process, positive regulation of cell migration, chordate embryonic development, and protein maturation) or in metabolism

(alcohol and carbohydrate metabolic process; Supplementary Figure S1B). The functional enrichment of DAPs for R0 vs. WF0 is related to oxidative stress (response to reactive oxygen species) and proper cell functioning (endoplasmic reticulum membrane organisation, electron transport chain, cellular homeostasis, regulation of vesicle-mediated transport; Supplementary Figure S1C). Finally, the functional enrichment of DAPs for R50 vs. WF50 is related to metabolism (generation of precursor metabolite and energy, carbohydrate derivative biosynthetic and metabolic process and lipid modification), the immune response (regulation of leucocyte migration and defence response to bacterium) and proper cell functioning (positive regulation of substrate adhesion-dependent cell spreading, small molecule biosynthetic process, mitochondrial transmembrane transport, maintenance of location, regulation of establishment of protein localisation, homeostasis of the number of cells, response to hypoxia and negative regulation of cell adhesion).

Table 2 Examples of main differential proteins in each cluster of the heatmap

Heatmap cluster	Protein name	Gene symbol	Accession number	Molecular weight	Test	p-Value (ANOVA or Chi-square)	Mean quantitative value in RO	Mean quantitative value in R50	Mean quantitative value in WF0	Mean quantitative value (detection rate %) in WF50
C1	bis(5'-adenosyl)-triphosphatase isoform X1	<i>FHIT</i>	XP_011954617.2	17 kDa	Chi-square	0.0117	N.D. (0%)	6.5 (50%)	5.76 (75%)	7.3 (100%)
	beta-glucuronidase	<i>GUSB</i>	XP_027817734.1	74 kDa	Chi-square	0.0019	N.D. (0%)	6.88 (100%)	6.18 (50%)	6.6 (100%)
	vesicle-associated membrane protein-associated protein B/C	<i>VAPB</i>	XP_017913111.1	27 kDa	ANOVA	0.00037	6.56	7.49	7.57	7.7
C2	transthyretin precursor	<i>TTR</i>	NP_001009800.1	16 kDa	ANOVA	0.0028	8.33	8.55	8.58	9.17
	afatoxin B1 aldehyde reductase member 2	<i>AKR7A2</i>	XP_027821430.1	41 kDa	Chi-square	0.0070	6.76 (75%)	7.03 (100%)	N.D. (0%)	7.21 (100%)
	inactive hydroxysteroid dehydrogenase-like protein 1	<i>HSDL1</i>	NP_001092341.1	37 kDa	Chi-square	0.00270	6.17 (25%)	6.21 (100%)	N.D. (0%)	6.76 (75%)
	squalene synthase isoform X2	<i>FDFT1</i>	XP_004004500.1	48 kDa	Chi-square	0.012	6.56 (75%)	6.63 (100%)	N.D. (0%)	6.59 (50%)
C3	transportin-2 isoform X4	<i>TNPO2</i>	XP_027825368.1	103 kDa	Chi-square	0.003	6.32 (25%)	6.44 (75%)	N.D. (0%)	6.82 (100%)
	dermcidin isoform 1 preproprotein	<i>DCD</i>	NP_444513.1	11 kDa	Chi-square	0.046	5.47 (50%)	N.D. (0%)	5.94 (75%)	6.41 (75%)
	apolipoprotein A-I	<i>APOA1</i>	XP_011950887.2	30 kDa	ANOVA	0.0019	9.17	9.14	9.33	9.87
	tetranectin precursor	<i>CLEC3B</i>	NP_001039677.1	22 kDa	ANOVA	0.022	7.07	7.13	6.97	7.47
	protein AMBP isoform X2	<i>AMBP</i>	XP_005684398.1	39 kDa	ANOVA	0.033	6.97	7.07	7.14	7.53
	thiosulfate sulfurtransferase	<i>TST</i>	XP_014950344.2	33 kDa	Chi-square	0.0027	6.99 (75%)	6.91 (100%)	5.87 (25%)	N.D. (0%)
	nicastatin isoform X2	<i>NCSTN</i>	XP_012039753.2	67 kDa	Chi-square	0.028	6.58 (50%)	6.8 (75%)	6.68 (75%)	N.D. (0%)
	long-chain fatty acid transport protein 1	<i>SLC27A1</i>	XP_027825247.1	71 kDa	ANOVA	0.0066	6.6	7.16	6.59	6.52
	glucosidase 2 subunit beta	<i>PRKCSH</i>	XP_027825495.1	60 kDa	ANOVA	0.023	7.22	7.94	7.91	7.53

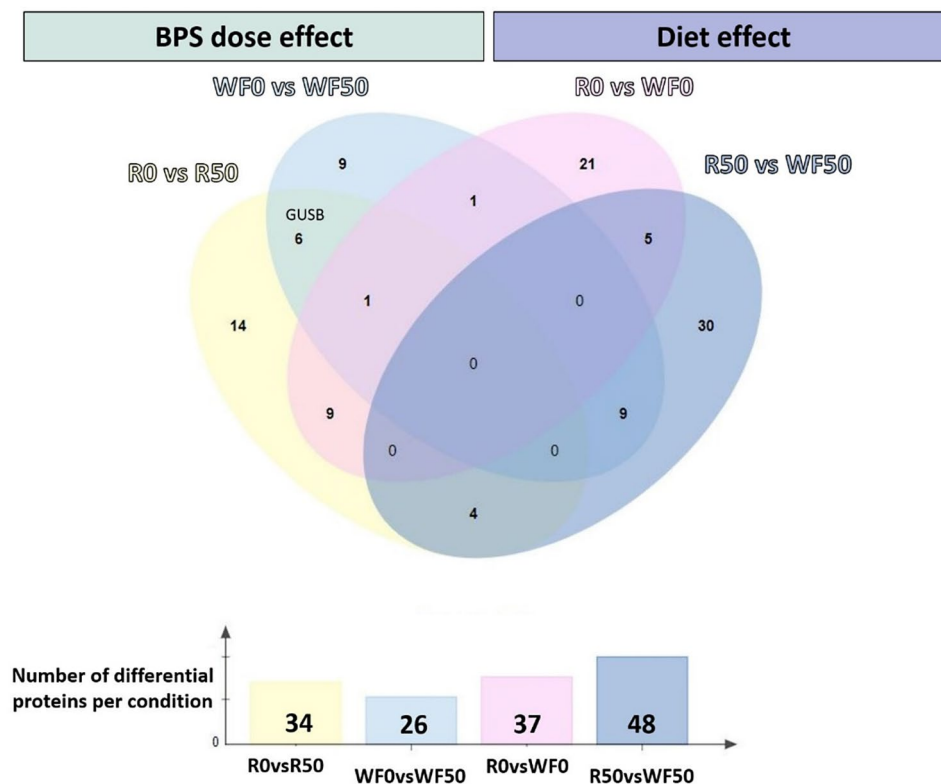


Fig. 5 Comparative analysis of differentially abundant proteins identified in ewes Granulosa Cells

To decipher the impact of BPS, proteomaps of the DAPs for the R0 vs. R50 and WF0 vs. WF50 comparisons were generated by using the KEGG pathways database (Fig. 6A and B). One of the common functions between both comparisons is carbohydrate metabolism, including the β -glucuronidase (GUSB), which is present in both proteomaps. This protein was detected in all BPS-exposed ewes (the R50 and WF50 conditions), whereas it was not quantified in the R0 samples and was detected in 50% of the WF0 samples (Supplementary Table S3). Another common protein, nucleoprotein translocated promoter region (TPR)—which is involved in the processing of genetic information, more specifically in RNA transport—is also found in both proteomaps (Fig. 6A and B). This protein was more detected in R50 and WF50 (75% detection rate) compared with R0 (25% detection rate) and WF0 (0% detection rate; Supplementary Table S3). The diet effect, visualised as R0 vs. WF0 and R50 vs. WF50, showed proteins that are mainly involved in lipid and glycan metabolism, oxidative phosphorylation and purine and amino acid metabolism, including proteins like thiosulfate sulfurtransferase (TST), farnesyl-diphosphate farnesyltransferase 1 (FDFT1) and bis(5'-adenosyl)-triphosphatase (FHIT). Both TST and FDFT1 were detected more frequently in restricted than well-fed ewes (Fig. 6C and D). TST was detected in 75% and 100% of R0 and R50 samples, respectively, whereas it was detected

in 25% and 0% of WF0 and WF50 samples, respectively. Similarly, FDFT1 was detected in 75% and 100% of R0 and R50 samples, respectively, whereas it was detected in 0% and 50% of WF0 and WF50, respectively. On the contrary, FHIT was detected in 0% and 50% of R0 and R50 samples, respectively, whereas it was detected in 75% and 100% of WF0 and WF50, respectively, and was therefore found more often in well-fed ewes than in restricted ewes. Interestingly, proteins involved in oxidative stress were found in the R0 vs. R50 proteomaps, namely glutathione peroxidase 7 (GPX7), and in the R0 vs. WF0 proteomaps, namely NADH dehydrogenase 1 alpha sub-complex subunit 7 (NDUFA7). GPX7 was more abundant in R50 compared with R0 (FC=15.6) and NDUFA7 was more abundant in WF0 compared with R0 (FC=5.6; Supplementary Table S2). Lipopolysaccharide (LPS)-binding protein (LBP), a protein involved in the NF-kappa B signalling pathway; nicastrin (NCSTN), a protein involved in the Notch signalling pathway; and apolipoprotein A1 (APOA1), a protein involved in the PPAR signalling pathway, were also found in the WF0 vs. WF50 and R50 vs. WF50 proteomaps. LBP was less abundant in WF0 compared with WF50 (FC=0.34), and less abundant in R50 compared with WF50 (FC=0.06). NCSTN was detected more frequently in WF0 (75%) compared with WF50 (undetected), and more frequently detected in R50 (75%) compared with WF50 (undetected). APOA1 was more

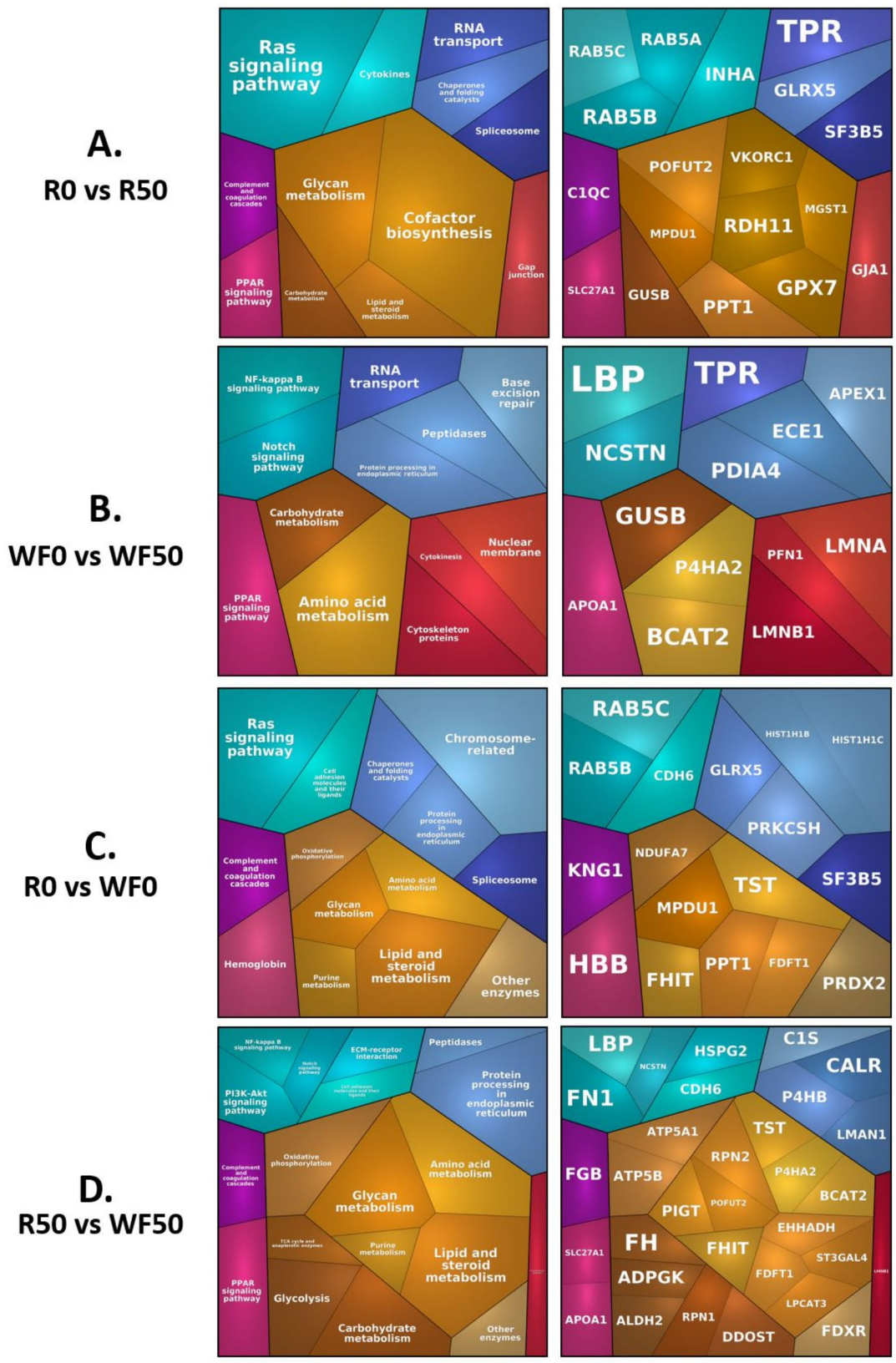


Fig. 6 Proteomaps of differentially abundant proteins in R0 vs. R50 (A) and WFO vs. WF50 (B), R0 vs. WFO (C) and R50 vs. WF50 (D)

abundant in WF50 compared with WF0 (FC=2.35) and R50 (FC=2.48). Lastly, ras-related protein Rab-5B (RAB5B) and ras-related protein Rab-5 C (RAB5C), involved in protein transport, were found in the R0 vs. R50 and R0 vs. WF0 proteomaps. They were more abundant in R50 (FC=2.45 and 3.10, respectively) and WF0 (FC=3.23 and 3.84, respectively) compared with R0.

Venn diagram shows the overlap of the DAPs from the pairwise comparisons (p -value t -test ≤ 0.05 and fold change ratio $\text{Log}_2(\text{FC}) \geq 1$ or ≤ -1 ; feed \times BPS exposure) and histogram representing the number of proteins identified in each condition.

Protein maps were generated using the KEGG (Kyoto Encyclopedia of Genes and Genomes) Pathway gene classification. Proteomaps were created from the average of the quantification values of the overabundant or most detected DAPs in each pairwise comparison with a $\text{Log}_2(\text{FC}) \geq 1$ or ≤ -1 minimum. In the left column, functional categories are represented by polygons, and in the right column, proteins are represented by the same polygons. The polygons illustrate the normalised abundance of proteins in each condition. Functions and related proteins are organised into common regions and coded using similar colours.

Discussion

This study aimed to characterise the effects of chronic BPS exposure on the proteome of ewe GCs, considering the interaction between metabolism status and reproductive function. Even though some deleterious impacts of BPS on GCs have already been reported *in vitro* [10, 11, 19–22], this is the first study to characterise the GC proteome after chronic BPS exposure. Furthermore, this study compared the BPS effects on the GC proteome in ewes with a contrasted metabolic status. These results have highlighted the interaction between metabolism and BPS exposure by identifying specific proteins in each comparison. In addition, proteins related to the BPS effect were also identified, in particular GUSB, which was significantly overexpressed in the GCs of BPS-exposed compared with non-exposed ewes. Because GUSB is able to remove the glucuronide conjugate from bisphenol molecules and thus to restore the oestrogenic activity of bisphenols, it could worsen the effects of this exposure.

BPS – metabolism interaction

Chronic BPS exposure of adult ewes affected the GC proteome; and its effects varied depending on the metabolic status of the ewes. Most of the DAPs and predicted pathways and functions were specific to one comparison. According to the Venn diagram, only 5 common proteins were identified between the R0 vs. WF0 and R50 vs. WF50 comparisons (diet effect). On the contrary, 21 proteins were identified specifically for the R0 vs. WF0

condition and 30 for the R50 vs. WF50 condition. Therefore, most of the proteins corresponding to the diet effect (21 and 30 proteins) differ depending on the BPS exposure. Similarly, for the BPS effect, 6 proteins common to the R0 vs. R50 and WF0 vs. WF50 comparisons (BPS effect) were identified. On the contrary, 14 proteins were identified specifically for the R0 vs. R50 comparison and 9 for the WF0 vs. WF50 comparison, again suggesting that the 14 and 9 proteins differ depending on diet. This highlighted the interaction between the BPS effect and metabolic status. In addition, the interaction between BPS exposure and the metabolic status was also highlighted by the unexpected common DAPs shared between pairwise comparisons mixing BPS and diet effects. Indeed, there were 9 common DAPs between the R0 vs. R50 (BPS effect) and R0 vs. WF0 (diet effect) comparisons, and 9 common DAPs between the WF0 vs. WF50 (BPS effect) and R50 vs. WF50 (diet effect) comparisons. These results strengthen our hypothesis that the effects of BPS differed according to body condition, which is in line with the analyses previously performed on these same ewes as part of the same study [34, 35]. This interaction might be specific to ovarian cell functioning as it was not reported when studying oviduct proteome in the same ewes, the diet effect being the main effect observed [36]. Modulation of the BPS effect by the metabolic status has already been highlighted regarding the oestradiol content in the preovulatory follicular fluids from the same follicles that provided the GCs for the present proteomic analysis [34]. Indeed, after BPS exposure, the oestradiol level increased in well-fed ewes, while it did not change in restricted ewes [34]. Moreover, *in vitro* embryo production with oocytes punctured during the previous oestrous cycles of the same ewes showed that, even though there was no BPS effect on the embryo parameters, there was a BPS \times diet interaction, suggesting that the BPS effect differs according to the metabolic status [35]. Other studies on the effects of synthetic chemicals such as BPA, phthalates and microplastics have also shown the importance of considering the metabolic status when studying exposure to environmental pollutants. In rodents, exposure to BPA through intragastric gavage or oral administration combined with a high-fat diet (particularly butter) led to transgenerational dysfunction of the entire reproductive system, including an altered oestrous cycle and disrupted spermatogenesis in rats compared with a low-fat diet or a high-fat olive oil diet [37, 38]. Moreover, a study on di(2-ethylhexyl) phthalate (DEHP) oral exposure, at a dose considered safe in the environment, combined with a high-fat diet in pregnant mice suggested a negative effect on the development of placental vascularisation and foetal growth compared to a regular diet [39]. Similarly, in rats the combination of a high-fat diet and DEHP exposure had joint effects on lipid metabolism [40]. Another

study showed that oral exposure of pregnant mice to a perfluorooctanesulfonic acid (PFOA) and per- and polyfluoroalkyl substances (PFAS) mixture (PFOA/perfluorooctane sulfonate (PFOS)/perfluorohexanesulfonate (PFHxS)), combined with high-fat diet, could influence the effect of PFAS on the liver of their offspring, and could render them more sensitive to the perinatal effects of PFAS [41].

APOA1 is the main component of high-density lipoprotein and plays an important role in reverse transport of cholesterol [42], which is the precursor molecule for steroidogenesis. LBP is involved in the immune response to LPS by promoting an inflammatory response through the initiation of an inflammatory cytokine cascade which mediates the elimination of LPS [43]. Both proteins are involved in anti-inflammatory or immune functions [44, 45]. Even though the balance between both molecules is not clearly stated in the literature, LBP is increased in exacerbated lipid metabolism environment [46] while APOA1 is reduced [47], which is consistent with the present study with APOA1 being increased when LBP is decreased and vice versa. In contrast to APOA1, LBP was overabundant in R50 and WF0 compared with WF50 (FC=16.22 and 2.93, respectively), which is not consistent with the literature. Indeed, a high-fat and high-carbohydrate meal has been reported to increase the human plasma LBP concentration [48], but this phenomenon did not occur in the present study since LBP protein was overabundant in R ewes compared with WF ewes when exposed to BPS. This could be explained by the fact that LBP reduces circulating LPS levels especially through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway [43, 48]. Indeed, activation of NF- κ B by LPS treatment (leading to an increase in LBP) significantly reduced APOA1 in HepG2 cells in vitro, while NF- κ B inhibition in mice increased plasma APOA1 in vivo [49, 50]. This balance between APOA1 and LBP is involved in both diet and BPS exposure effect, as both APOA1 and LBP were found in WF0 vs. WF50 and R50 vs. WF50 comparison. Furthermore, it has been reported that BPS activates NF- κ B [51] and BPA inhibits APOA1 [52] in mouse hepatocytes, which is opposite compared with the present study. NF- κ B inhibition increases plasma APOA1 through activation of Peroxisome Proliferator-activated Receptor α [50]. In fact, our results suggested that BPS exposure and WF diet upregulate APOA1 and downregulate LBP protein. These results could be due to the activation of the NF- κ B pathway by the interaction of metabolism and BPS exposure, leading to a decrease in LBP and an increase in APOA1. The mechanism through which BPS affects NF- κ B pathway requires further investigation. This study has highlighted that the metabolic status should be considered when studying the effects of environmental factors so that their

potential effects in subgroups of the population are not underestimated.

Metabolism effect

PCA showed a clear discrimination of DAPs according to the metabolic status. There were only 5 common proteins between the R0 vs. WF0 and R50 vs. WF50 comparisons: TST, FHIT and FDFT1, which are involved in metabolism, and CDH6 and DCD, which are involved in cell function. FHIT had a significantly higher detection rate in the GCs of well-fed ewes compared with restricted ewes. This finding is in line with papers establishing a link between the *FHIT* gene in humans and BMI and waist circumference, and that it is correlated with adiposity in adulthood [53, 54]. FDFT1, also known as squalene synthase (SQS), is the first specific enzyme in cholesterol biosynthesis. FDFT1 was detected more frequently in GCs of restricted ewes. FDFT1 hepatic messenger RNA (mRNA) levels are regulated by the cholesterol status [55]. In fact, FDFT1 enzyme activity and protein and mRNA levels can decrease dramatically in response to cholesterol overabundance and increase sharply in response to cholesterol deprivation in both animals and cultured hepatic cells [55]. FHIT and FDFT1 were detected in most BPS-exposed ewes (regardless of the diet) but much less frequently or not at all in the unexposed ewes. These findings highlight the potential involvement of BPS in adiposity and/or lipid metabolism. Indeed, in vitro and in vivo studies showed that BPS could promote obesogenic effect and metabolic disorders [56], and promote adipogenesis in human preadipocytes [57]. Although our experiment was not designed to observe obesogenic effects, additional studies should include such parameters.

In addition, the basic protein profile of GCs is very metabolically oriented as shown by the proteomaps. After several months of restricted feeding, basic requirements have likely been reduced to a minimum due to the energy deficit. This is in line with the lower NEFA level in R0 ewes, indicating that these ewes, contrary to the beginning of the diet restriction, did not have the body reserve to compensate for the lower energy intake relative to the energy requirement. The metabolic functions involved in the R50 vs. WF50 comparison include lipid, carbohydrate and energy metabolism, and most of the proteins involved in these functions were overabundant or detected more frequently in R50 compared with WF50, including ATP5A1 and ATP5B involved in adenosine triphosphate (ATP) production, as a means to compensate for the low energy intake [58, 59]. Similarly, in a previous study of bovine GCs, the authors found that most DAPs (259 total DAPs among 3,409 identified proteins) from the dominant vs. subordinated follicle comparison are also involved in metabolic pathways, according to KEGG

pathway analysis [60]. Therefore, metabolism, including lipid metabolism, is expected to be crucial for the correct maturation of oocytes. Modulations of lipid metabolism could also impair the ability of GCs to perform their functions as previously reported in bovine GCs [61]. A comparative study of the fatty acid composition of oocyte lipids in cattle and sheep showed that these two ruminant species are close in terms of lipid metabolism [62]. Lipid metabolism is therefore likely crucial in ovine GCs and oocytes too.

Oxidative stress proteins such as GPX7 and NDUFA7, both involved in regulating the redox status, were overabundant in the R50 and WF0 ewes compared with R0 ewes, respectively. This suggests that the R0 condition led to an inhibition of the antioxidant response. Undernourishment in pregnant ewes alters the expression of the glutathione peroxidase genes in the blood and liver of the mother and in the foetus at the end of gestation [63]. Additional data are required to compare pregnant and non-pregnant ewes and to investigate the link between oxidative stress and food restriction.

BPS effect

BPS had a moderate effect in terms of the number of DAPs in the GCs proteome. These changes are relevant when considering the results of the embryo production and steroidome study of the same ewes [34, 35]. In fact, BPS alone only results in a moderate number of DAPs, and the interaction between BPS exposure and diet produced more DAPs. Nevertheless, the *in vivo* model is still more sensitive compared with *in vitro* experiments. Indeed, after chronic daily *in vivo* oral exposure to 50 µg/kg/day BPS, corresponding to a follicular fluid concentration of 200 nM BPS (measured as BPS-g) on average, there were changes in oestradiol secretion in the follicular fluid [34]. However, there were no differences in steroidogenesis after acute exposure up to 1 µM BPS *in vitro* in the same species [22]. It is interesting to note that the most outstanding functions in the proteomaps corresponding to the BPS effects are related to energy, glycan, carbohydrate, amino acid, lipid and steroid metabolism; the processing of genetic information, including RNA transport; and cellular processes. Studies on human cohorts have shown that exposure to BPS could be associated with elevated BMI and waist circumference, based on median urinary concentrations [56], and therefore related to changes in energy metabolism. In addition, significant disturbances in lipid and glucose metabolism, as well as an increase in fat accumulation due to BPS, were reported in the preadipocytic 3T3-L1 cell lines *in vitro* [30]. Indeed, BPS is a potent chemical responsible for the hyperglycaemic response and also alters many metabolites by hampering various biological pathways. A metabolomic pathway analysis revealed an alteration in

glycolysis or gluconeogenesis pathway upon BPS exposure in rats [64]. The possible mechanisms of action are attributed to oestrogenic or androgenic activities, favouring alterations in the genetic expression of markers linked to adipogenesis and inducing oxidative stress and an inflammatory state [56]. Of note, BPS binds to oestrogen but not to androgen receptors [17].

There were six common DAPs when comparing BPS-exposed ewes to their respective unexposed controls (R50 vs. R0 or WF50 vs. WF0) including GUSB, involved in metabolism, and HSDL1, TNPO2 and TPR, involved in the proper functioning of the cell. GUSB degrades glycosaminoglycans and participates in the degradation of polysaccharides that contain glucuronide residues [65]. GUSB helps to deconjugate various potential toxins, hormones, and various drugs in the body and is also involved in hydrolysis of glucuronides of endo- and xenobiotics in humans. GUSB has already been reported to hydrolyse conjugated BPA into free BPA as it passes through the placental barrier [66]. While BPS-g is unable to bind to oestrogen receptors [6, 67], it is still able to exert effects on cells [68], and sometimes the effect is even worse compared with free BPA [69]. Therefore, the higher abundance of GUSB in the GCs from BPS-exposed ewes suggested that metabolised BPS-g could be deconjugated into free BPS in the follicular compartment, leading to prolonged intracellular exposure to free BPS and to prolonged oestrogenic effects. Such a conversion cycle of bisphenol has not previously been described at ovarian level. Exposure to BPS likely worsens this potential effect at the ovarian level. In the present study, GUSB was not upregulated in WF50 ewes compared with R50 ewes. Nevertheless, GUSB activity in serum and plasma has been associated with higher BMI in humans [70–72]. It is important to note that in some of those studies, the BMI is closer to overweight than to obesity (i.e. it does not exceed 26.5 kg/m²) [70, 72]. In another study of menopausal and premenopausal women, GUSB activity was also positively correlated with fat mass but not with lean mass and therefore with individual adiposity [73] which is consistent with our results. Indeed, even if GUSB is not upregulated in WF0 compared to R0, it was detected in half of the samples in WF0 samples while it was never detected in the R0 sample. GUSB was therefore found in well-fed ewes, whether exposed to BPS or not, unlike in restricted ewes. It could thus be assumed that R0 corresponded to the condition exhibiting the lowest expression. As mentioned before, despite their diet, the WF50 ewes could not be considered obese (their mean BCS was 2.88). It is possible that a further increase in GUSB could be observed in obese individuals exposed to BPS, which would exacerbate exposure to free BPS in this population and, consequently, overfeeding would exacerbate the negative effects of BPS exposure. Additional studies

should assess this hypothesis because its confirmation would suggest a higher sensitivity of women with obesity to bisphenol exposure.

Limitations of the study

One of the limitations of this study is that GCs were collected with follicular fluid, which is a plasma ultrafiltrate. Therefore, blood proteins were very abundant and could potentially have masked the signal of less abundant proteins, resulting in fewer quantified proteins. In addition, serum albumin was not depleted before analysis to avoid eliminating potential albumin-binding proteins. Another limitation of this study is that the two diets used in this study were either abnormally restrictive or abnormally excessive, so neither group of ewes received 100% of their dietary requirements. Furthermore, as mentioned above, well-fed ewes with a mean BCS of 2.88 cannot be considered as obese [74], despite their elevated plasma NEFA and glucose levels. Consequently, the hypotheses put forward should be interpreted with caution and additional tests should be carried out on animals with a BCS of 4. It is difficult to discuss whether an obese phenotype would worsen the BPS effects. Nevertheless, given these limits, our data suggest that the effects of BPS exposure could vary depending on the metabolic status of the ewes and the involved energy metabolism.

Conclusion

Chronic exposure of adult ewes to BPS affected the GC protein content, and this effect was modulated by the metabolic status of the animals. A total of 958 proteins were quantified and 59 were differentially abundant in the four experimental groups. In addition, various functional pathways were affected, mainly energy metabolism pathways. GUSB was identified in the GC proteome of BPS-exposed animals. Moreover, among unexposed ewes, GUSB was detected only in well-fed ewes. GUSB could increase BPS exposure by deconjugating BPS-g into free BPS. This protein might worsen or prolong the exposure of these cells to free BPS, therefore prolonging oestrogenic effects that might be even further worsened in people with adiposity. It is difficult to discuss whether the well-fed phenotype worsens the BPS effects, as there are only few studies examining the interaction between BPS exposure and adiposity in vivo and there is no diet group corresponding to normal feeding. Here, leads are suggested but require deeper investigation. Nevertheless, the data showed, in WF ewes exposed to BPS, an alteration in in vitro embryo production, in GC steroidogenesis with increased levels of oestradiol in the follicular fluid [34, 35] and in GC proteomics, in particular GUSB abundance. All these data suggested a potentially higher sensitivity to the effects of BPS in adipose individuals. These results and those of previous studies highlight

the deleterious effect of BPS and its interaction with the metabolic status, indicating that its use in food packaging should be regulated.

Materials and methods

Ethics

All experimental procedures were conducted in accordance with the European Directive 2010/63/EU on the protection of animals used for scientific purposes and approved by the French Ministry of Nation Education, Higher Education, Research and Innovation after ethical assessment by the local ethics committee *Comité d'Ethique en Expérimentation Animale Val de Loire* (CEEA VdL) and INRAE consented to use the animals in this experimental protocol (protocols registered under APAFIS numbers 13965-2018042008519239v2 and 14014-2018030717477406v2).

Experimental design

A total of 40 primiparous Ile-de-France ewes (average age 2.5 years) were housed in a sheepfold from 2018 to 2019. The experimental design was described previously [34]. Briefly, the ewes were divided into two groups with contrasting diets: restricted (R, $n=20$) and well-fed (WF, $n=20$). The diet was designed according to the INRAE recommendations for the growth and maintenance needs of adult, non-pregnant ewes [75]. It consisted in varying the quantity of a wheat-based food supplement (Agneau-échange, AXEREALE Elevage, Saint Germain de Salles, France). The food supplement was distributed in the morning and the animals had free access to straw and water and minerals to lick. Ewes from the experiment groups were fed in order to reach the goal of a median BCS of 2 in restricted groups and of 4 in well-fed groups and the quantity was adjusted according to the mean of body weight of the group. Ewes in the restricted group were initially fed 50% of their maintenance energy requirements and, once the target BCS was reached, they were fed 80% in order to maintain the desired nutritional status. Ewes in the WF groups were fed 165% of their maintenance energy requirements until the end of the experiment. The BW (kg) and BCS (on a scale of 1 to 5, 1 corresponding to very skinny ewes and 5 to obese ewes [74]) of animals were monitored once a month. Within each group, two subgroups were defined according to BPS exposure (0–50 $\mu\text{g}/\text{kg}/\text{day}$) for at least 3 months, 5.4 ± 0.1 months (range: 3.6–7.9 months). The BPS, purchased from Sigma Aldrich (Madrid, Spain), was added to the feed in the form of a powder mixed with the cereals. Thus, there were four groups: R0 and R50 for the restricted ewes, and WF0 and WF50 for the well-fed ewes. Between September and December, the oestrus cycle of the 40 ewes was synchronised with a vaginal sponge of progesterone (Chrono-Gest® 20 mg,

MSD, Beaucauze, France) for 11 days, followed by intramuscular administration of pregnant mare serum gonadotropin (PMSG, Synchrono-Part® PMSG 400 IU, CEVA Santé Animale, Libourne, France). Two days after PMSG administration, at the presumed time of the pre-ovulatory period, the ewes were slaughtered, and follicular cells of the dominant follicles were collected by aspirating the follicular fluid containing GCs. GCs were centrifuged and washed twice with phosphate-buffered saline (PBS) and then stored dry at -80 °C until analyses. Blood samples (5 mL) were collected at the time of slaughterhouse bleeding in heparinised tubes (17 IU/mL sodium heparin, Vacutainer®; Becton Dickinson and Company, Le Pont de Claix, France), centrifuged (3,700 g for 30 min at 4 °C) and plasma samples were stored at -20 °C for further assay of glucose, NEFA, BPS and its metabolite BPS-glucuronide (BPS-g).

Plasma glucose, non-esterified fatty-acids BPS and BPS-glucuronide assays

Plasma glucose and NEFA were quantified individually ($n=80$) on a 2 and 5 μ L undiluted plasma sample, respectively, by colorimetric enzymatic methods using a Konelab 20 analyzer (Thermo Scientific, Gometz le Châtel, France) and kits provided by Bio-Mérieux (Marcy-l'Etoile, France) and Thermo Scientific (Villebon sur Yvette, France). BPS and BPS-g concentration were quantified as previously describe [35] using liquid chromatography mass spectrometry with an Acquity U-HPLC device coupled to a Xevo-TQ triple quadrupole mass spectrometer (Waters, Saint-Quentin-en-Yvelines, France) operated with positive electrospray ionization and MRM mode. All samples were quantified on the same day. The limit of quantification (LOQ) was set at 0.5 ng/mL (2 nM) for BPS and 0.05 ng/mL (0.10 nM) for BPS-g.

Protein extraction and quantification

The GC pellet was resuspended on ice with 100 μ L of lysis buffer (10 mM Tris-HCl+2% sodium dodecyl sulphate [SDS]+1X protease inhibitor). Then, it was sonicated (2 \times 20 s, five times for each sample) and centrifuged (30 min, 10000 g, 4 °C). The supernatant was transferred to a new tube kept on ice and stored at -20 °C. The protein concentration was quantified using the colorimetric BC assay Protein Quantification kit (Interchim, Montlucan, France), following the manufacturer's recommendations. The optical density at 550 nm was measured with a Thermo LabSystems plate reader at 550 nm absorbance and with Ascent software for Multiskan equipment.

Preparation of GC samples for comparative proteomic analyses

After protein extraction and quantification, 50 μ g of protein per sample was separated with 4-10% SDS-polyacrylamide gel electrophoresis (80 V, 10 min and 180 V, 50 min). After separation, the gel was stained with Coomassie blue. It was cut into four strips for each track and washed in water and acetonitrile (1:1 [v/v], 5 min) followed by 100% acetonitrile (10 min). Reduction and cysteine alkylation were performed by successive incubation with 10 mM dithiothreitol in 50 mM ammonium bicarbonate (30 min, 56 °C), then 55 mM iodoacetamide in 50 mM ammonium bicarbonate (20 min, room temperature, in the dark). The pieces were incubated with 50 mM ammonium bicarbonate with acetonitrile (1:1 [v/v], 10 min) followed by acetonitrile (15 min). Proteolytic digestion was carried out overnight using 25 mM ammonium bicarbonate containing 12.5 ng/ μ L trypsin (sequencing grade, Roche Diagnostics, Paris, France). The resultant peptides were extracted by incubation in 5% formic acid (with sonication). The supernatant was removed and incubated with acetonitrile and 1% formic acid (1:1 [v/v], 10 min). After a final incubation with acetonitrile (5 min), the supernatant was removed and saved. These two peptide extractions were pooled and dried using a SPD1010 SpeedVac system (Thermosavant, Thermofisher Scientific, Bremen, Germany).

NanoLC-MS/MS

Peptide mixtures were analysed with on-line nanoLC-MS/MS as described previously [76]. All experiments were performed on a dual linear ion trap Fourier-transform mass spectrometer (FT-MS) LTQ Orbitrap Velos Pro (Thermo Fisher Scientific, Bremen, Germany) coupled to an Ultimate® 3000 RSLC Ultra High-Pressure Liquid Chromatographer (Thermo Fisher Scientific, Bremen, Germany) controlled by Chromeleon Software (version 6.80 SR13). The samples were desalted and concentrated for 10 min at 5 μ L/min on an LCPackings trap column (Acclaim PepMap 100 C18, 75 μ m inner diameter \times 2 cm long, 3 μ m particles, 100 Å pores). The peptide separation was conducted using a LCPackings nano-column (Acclaim PepMap C18, 75 μ m inner diameter \times 50 cm long, 2 μ m particles, 100 Å pores) at 300 nL/min by applying a gradient of 2-45% B over 90 min. The mobile phases consisted of 0.1% formic acid, 97.9% water and 2% acetonitrile (v/v/v; A), and 0.1% formic acid, 19.9% water, 80% acetonitrile (v/v/v; B). The data were acquired using Xcalibur version 3.0.63 software (Thermo Fisher Scientific, San Jose, CA), in positive data-dependent mode in the 300–1800 m/z mass range. The resolution in the Orbitrap was set at $R=60,000$. The 20 most intense peptide ions with charge states ≥ 2 were isolated sequentially (isolation width 2 m/z, 1 microscan)

and fragmented in the high-pressure linear ion trap using the collision induced dissociation (CID) mode (collision energy 35%, activation time 10 ms, Q_z 0.25). Dynamic exclusion was activated for 30 s with a repeat count of 1. The lock mass was enabled for accurate mass measurements. The polydimethylcyclsiloxane ((Si(CH₃)₂O)₆, m/z 445.120025) ion was used for internal recalibration of the mass spectra MS/MS.

Protein identification and data validation

Ion searches were performed using the Mascot search engine version 2.7.0.1 (Matrix Science, London, UK) via the Proteome Discoverer 2.5 software (ThermoFisher Scientific, Bremen, Germany) against the NCBI prot_Mammals database (2021/07). The search parameters included trypsin as the protease with two allowed missed cleavages and carbamidomethyl cysteine, methionine oxidation and acetylation of the N-terminal protein as variable modifications. The tolerance of the ions was set to 5 ppm for parent and 0.8 Da for-fragment ion matches. The Mascot results obtained from the target and decoy databases searches were analysed with the Scaffold Q+S v5.1.1 and Scaffold Quant v5.0.3 softwares (Proteome Software, Portland, OR, USA) using the protein cluster analysis option (assemblage of proteins into clusters based on shared peptide evidence). Peptide and protein identifications were accepted if they could be established with a probability of >95%, in accordance with the Peptide Prophet and the Protein Prophet algorithms, respectively. Proteins were identified with a minimum of two unique peptides. Extracted ion chromatogram (XIC) is based on the normalised values of the intensities of the chromatographic peaks corresponding to the peptides of a protein. XIC data were log transformed (log₁₀ precursor intensity). The names of clusters, redundant proteins, and potential contaminants (keratin from *Homo sapiens* and trypsin) were excluded from the lists. In addition, only *Homo sapiens* and the followed herbivorous species were retained: *Ovis aries*, *Ammotragus lervia*, *Bison bison bison*, *Bos indicus*, *Bos indicus* × *Bos taurus*, *Bos javanicus*, *Bos mutus*, *Bos taurus*, *Bubalus bubalis*, *Camelus bactrianus*, *Camelus dromedarius*, *Camelus ferus*, *Capra hircus*, *Cervus elaphus*, *Cervus elaphus hippelaphus*, *Cervus hangul yarkandensis*, *Equus asinus*, *Equus caballus*, *Equus przewalskii*, *Muntiacus muntjac*, *Muntiacus reevesi*, *Muntiacus vaginalis*, *Odocoileus virginianus texanus*, *Odocoileus virginianus virginianus*, *Ovis canadensis nelson*, and *Vicugna pacos*.

Drawing up a list of differentially abundant proteins (DAPs)

Regarding the proteins detected in all conditions, DAPs were identified after analysis of variance (ANOVA) on protein abundance ($p \leq 0.05$) and t-test ($p \leq 0.05$), when the fold-change (FC) between the two conditions was

≥ 2 or ≤ 0.5 . Regarding the proteins present in one condition but not in the other, DAPs were identified after the chi-square test on the protein detection rate ($p \leq 0.05$). Briefly, proteins were considered to be present in a biological sample when they were detected at least once in one of the three technical replicates. Proteins that were not detected in any biological replicate for a condition were tested using the chi-square test for the bisphenol effect (proteins quantified for exposed and unexposed animals regardless of diet) and the effect of diet (proteins quantified for restricted and well-fed animals regardless of BPS exposure), but also for pairwise analyses (R0 vs. R50, WF0 vs. WF50, R0 vs. WF0, and R50 vs. WF50). This yielded 17 proteins with a $p \leq 0.05$ (chi-square test) for at least one of the comparisons (dose, diet or pairwise) and an average abundance (log₁₀ precursor intensity) ranging from 5.94 to 7.58. For pairwise analyses, proteins with significant differences in the detection rate according to bisphenol exposure were added to the lists of DAPs for the R0 vs. R50 and WF0 vs. WF50 comparisons; likewise, proteins exhibiting significant differences in the detection rate according to diet effect were added to the lists of DAPs for the R0 vs. WF0 and R50 vs. WF50 comparisons. Proteins that responded only to the pairwise analysis (R0 vs. R50, WF0 vs. WF50, R0 vs. WF0, or R50 vs. WF50) were added to the corresponding DAPs lists.

Principal component analysis (PCA) was performed and a heatmap was generated by using the Rstudio software (version 2023.03.0+386). PCA on DAPs (both ANOVA and the chi-square test) were carried out using the FactoMineR and ggplot2 packages. The percentage on each axis (dimension) represents the total variance of data according to dimension 1 (horizontal axis) and dimension 2 (vertical axis). Heatmap and hierarchical clustering on DAPs (both ANOVA and chi-square test $p < 0.05$) were performed using the gplots package. For DAPs from the ANOVA, missing values (in one replicate among detected values in other replicates of the condition) were treated with the missMDA package [77]. For DAPs from the chi-square test, missing values (in all replicates of a condition) were deliberately replaced by '1' because the XIC data were log-transformed (log₁₀ precursor intensity), indicating the absence of detection.

Functional analysis and prediction of biological processes of DAPs

The overlaps of DAPs between the different conditions was visualised using the online tool jvenn (<https://jvenn.toulouse.inrae.fr/app/example.html>) [78]. Gene enrichment analysis was performed separately for each pairwise comparison. Because the *O. aries* genome contains less information than the *H. sapiens* genome, the latter was used as preferential database for functional analyses.

Gene lists of DAPs were used as input into the Database for Annotation, Visualisation and Integrated Discovery (DAVID version 2021) for Gene Ontology (GO) analysis. GO terms associated with over-represented biological processes ($p < 0.05$) were considered significant. The Metascape Enrichment analysis tool was used to study the potential roles of DAPs (<https://metascape.org/>) [79]. The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways associated with 958 quantified proteins and DAPs from the pairwise comparisons were investigated using the Proteomaps software (<http://bionic-vis.biologie.uni-greifswald.de/>) [80]. For each comparison, proteomaps were created from the highest log₁₀ precursor intensity values of the overabundant DAPs in each pairwise comparison with a minimum $FC \geq 2$ or ≤ 0.5 . For the proteins quantified, proteomaps were generated by using the highest value from the four groups (R0, R50, WF0 and WF50).

Abbreviations

APOA1	Apolipoprotein A1
BCS	Body condition score
BMI	Body mass index
BPA	Bisphenol A
BPS	Bisphenol S
BPS-g	BPS glucuronide
BMI	Body mass index
BSA	Bovine serum albumin
BW	Body weight
DAPs	Differentially abundant proteins
DEHP	Di(2-ethylhexyl) phthalate
FC	Fold-change
FDFT1	Farnesyl-diphosphate farnesyltransferase 1
FHIT	Bis(5'-adenosyl)-triphosphatase
GCs	Granulosa cells
GPX7	Glutathione peroxidase 7
GO	Gene Ontology
GUSB	β -glucuronidase
LBP	Lipopolysaccharide-binding protein
LPS	Lipopolysaccharide
NCSTN	NF-kappa B signalling pathway; nicastrin
NDUFA7	NADH dehydrogenase 1 alpha subcomplex subunit 7
NEFA	Non-esterified fatty acids
NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
PBS	Phosphate-buffered saline
PCA	Principal component analysis
PFAS	Per- and polyfluoroalkyl substances
PFOA	Perfluorooctanesulfonic acid
PFOS	Perfluorooctane sulfonate
PMSG	Pregnant mare serum gonadotropin
PPAR γ	Peroxisome proliferator-activated receptor gamma
R	Restricted
RAB5B	Ras-related protein Rab-5B
RAB5C	Ras-related protein Rab-5 C
SQS	Squalene synthase
TPR	Translocated promoter region
TST	Thiosulfate sulfurtransferase
WF	Well-fed
XIC	Extracted ion chromatogram

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12864-024-11034-2>.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions

S.E. conceptualised the project, acquired and administrated the funding, S.E. and M.S.D. designed the methodology, and A.B. and S.E. supervised the work. O.T., O.L., A.D., S.U., P.P., D.T., V.L., V.M. and M.S.D. carried out the investigation, M-E.L.D.L.R., C.M., D.T. and V.L. were involved in data curation, and the formal analysis was made by M-E.L.D.L.R., D.T. and V.L. After the software exploitation by M-E.L.D.L.R., M-E.L.D.L.R., C.M., D.T., V.L. and M.S.D. proceeded to validation. M-E.L.D.L.R. and S.E. wrote the original draft; all the authors read, edited and approved the manuscript.

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Data availability

Proteomic mass spectrometry data were submitted to the ProteomeXchange Consortium via the PRIDE partner repository [70] with the identifier PXD047107.

Declarations

Ethical approval and consent to participate

All experimental procedures were conducted in accordance with the European Directive 2010/63/EU on the protection of animals used for scientific purposes and approved by the French Ministry of Nation Education, Higher Education, Research and Innovation after ethical assessment by the local ethics committee *Comité d'Ethique en Expérimentation Animale Val de Loire* (CEEA VdL) and INRAE consented to use the animals in this experimental protocol (protocols registered under APAFIS numbers 13965-2018042008519239v2 and 14014-2018030717477406v2).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹INRAE, CNRS, Université de Tours, PRC, Nouzilly 37380, France

²INRAE, PAO, Nouzilly 37380, France

³PIXANIM, INRAE, Université de Tours, CHU de Tours, Nouzilly 37380, France

⁴Service de Chirurgie Pédiatrique, CHU Poitiers, Poitiers, France

⁵CNRS UMR7267, Ecologie et biologie des interactions, Université de Poitiers, Poitiers 86000, France

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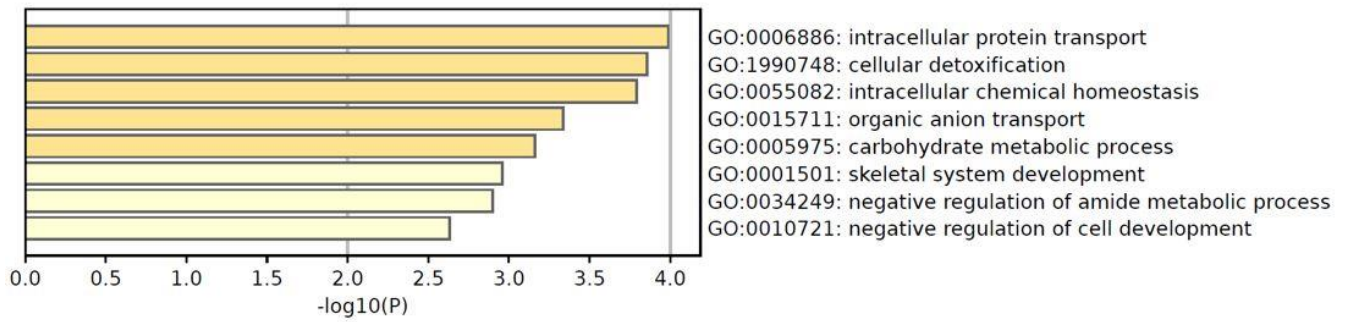
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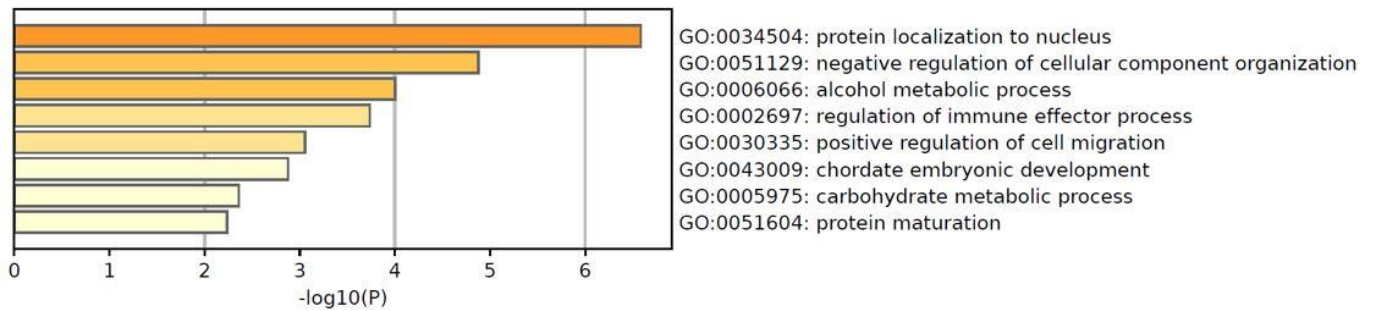
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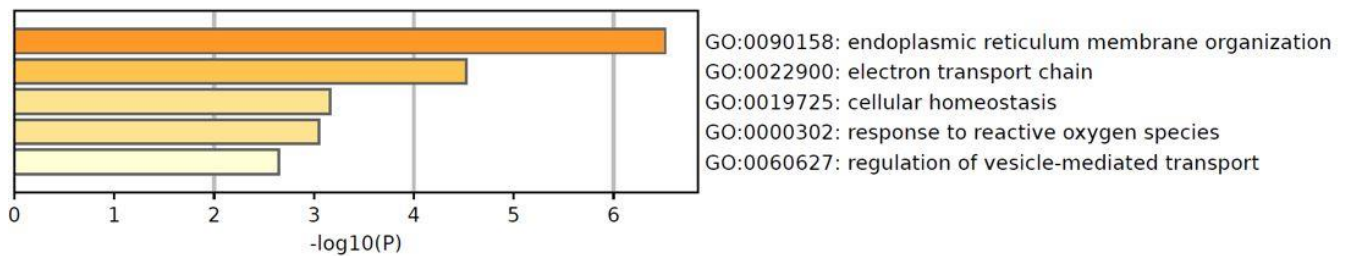
A Functional enrichment analysis of differential proteins between R0 and R50



B Functional enrichment analysis of differential proteins between WF0 and WF50



C Functional enrichment analysis of differential proteins between R0 and WF0



D Functional enrichment analysis of differential proteins between R50 and WF50

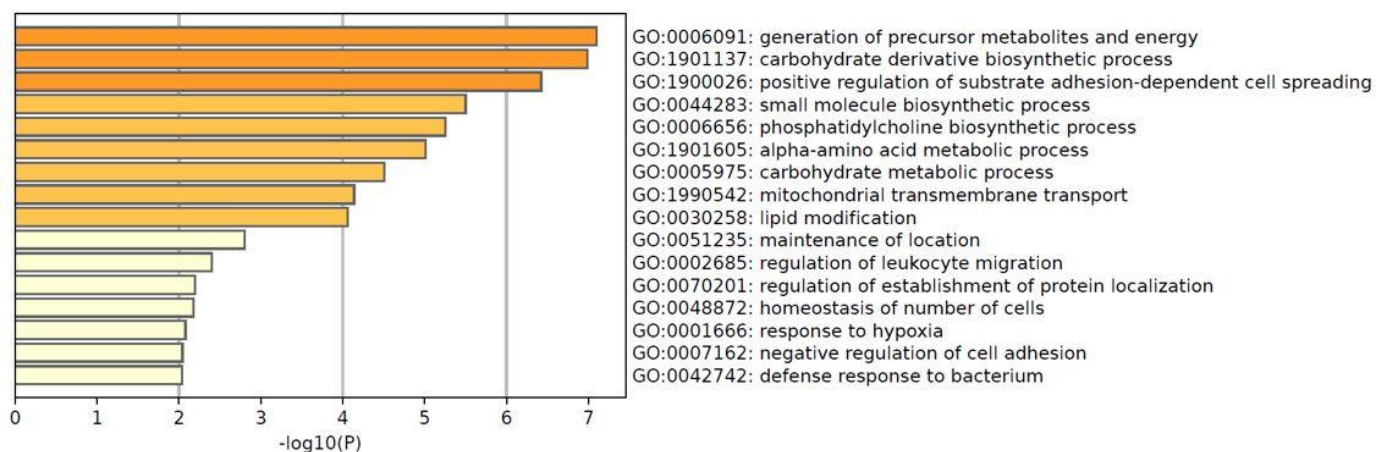


Figure S1: Functional enrichment analysis of differential proteins in ovine GCs between R0 and R50 (A), WF0 and WF50 (B), R0 and WF0 (C) and R50 and WF50 (D), performed using Metascape. (A) Bar graph of enriched biological processes in which GCs differential proteins in diet-restricted ewes, exposed or not to BPS, are involved. (B) Bar graph of enriched biological processes in which GCs differential proteins in well-fed ewes, exposed or not to BPS, are involved. (C) Bar graph of enriched biological processes in which GCs differential proteins in ewes not exposed to BPS with or without a restricted diet are involved. (D) Bar graph of enriched biological processes in which GCs differential proteins in ewes exposed to BPS with or without a restricted diet are involved.

Table S1

List of identified proteins in Granulosa Cell of Restricted (R) and Well-fed (WF) ewes exposed (50) or not (0) to bisphenol S

Protein Name	Species	Accession Number	Gene Name	Molecular Weight	Test	p-Value (ANOVA or Chi-square)	in R0 (detection rate %)	in R50 (detection rate %)	in WF0 (detection rate %)	in WF50 (detection rate %)
alfatoxin B1 aldehyde reductase member 2	Ovis aries	XP_027821430.1	AKR7A2	41 kDa	Chi-square	0.007	6.76 (25%)	7.03 (100%)	N.D. (0%)	7.21 (100%)
cadherin-6 isoform X2	Bos taurus	XP_024837107.1	CDH6	80 kDa	Chi-square	0.012	N.D. (0%)	7.55 (25%)	7.43 (25%)	7.75 (75%)
dermcidin isoform 1 preproprotein	Homo sapiens	NP_444513.1	DCD	11 kDa	Chi-square	0.046	5.47 (50%)	N.D. (0%)	5.94 (25%)	6.41 (75%)
squalene synthase isoform X2	Ovis aries	XP_004004500.1	FOFT1	48 kDa	Chi-square	0.012	6.56 (25%)	6.63 (100%)	N.D. (0%)	6.59 (50%)
bis(5'-adenosyl)-triphosphatase isoform X1	Ovis aries	XP_01195461.2	FHIT	17 kDa	Chi-square	0.012	N.D. (0%)	6.5 (50%)	5.76 (25%)	7.3 (100%)
beta-glucuronidase	Ovis aries	XP_007817734.1	GLUS8	74 kDa	Chi-square	0.002	N.D. (0%)	6.88 (100%)	6.18 (50%)	6.6 (100%)
inactive hydroxysteroid dehydrogenase-like protein 1	Bos taurus	NP_001092341.1	HSDL1	37 kDa	Chi-square	0.003	6.17 (75%)	6.21 (100%)	N.D. (0%)	6.76 (75%)
complement factor H-related protein 2	Ovis aries	XP_004013976.1	LOC101123223	31 kDa	Chi-square	0.028	6.45 (50%)	N.D. (0%)	6.05 (25%)	7.15 (75%)
sulfinyl oxidase 2 isoform X1	Capra hircus	XP_017911573.1	LOC102189594	87 kDa	Chi-square	0.003	N.D. (0%)	7.21 (75%)	6.25 (25%)	6.34 (100%)
SLC35A4 upstream open reading frame protein	Bubalus bubalis	XP_02548374.1	LOC112586898	11 kDa	Chi-square	0.012	5.41 (25%)	6.44 (75%)	N.D. (0%)	6.76 (75%)
niacinin isoform X2	Ovis aries	XP_01264075.2	NSTN	67 kDa	Chi-square	0.028	6.58 (50%)	6.8 (75%)	6.68 (75%)	N.D. (0%)
prolyl 4-hydroxylase subunit alpha-2 isoform X1	Ovis aries	XP_004008688.1	PHA2A	61 kDa	Chi-square	0.005	7.09 (75%)	6.8 (100%)	7.13 (100%)	N.D. (0%)
reticulon-4 isoform X1	Capra hircus	XP_017910740.1	RTNA	130 kDa	Chi-square	0.028	N.D. (0%)	7.14 (75%)	7.05 (75%)	6.16 (50%)
splicing factor 3B subunit 5	Bos taurus	NP_001020511.1	SF3B5	10 kDa	Chi-square	0.028	N.D. (0%)	6.56 (75%)	6.62 (75%)	6.57 (75%)
transpartin-2 isoform X4	Ovis aries	XP_027823681.1	TNPO2	103 kDa	Chi-square	0.003	6.32 (25%)	6.44 (75%)	N.D. (0%)	6.82 (100%)
nucleoprotein TPR	Capra hircus	XP_005691036.2	TPR	275 kDa	Chi-square	0.012	6.28 (25%)	6.87 (75%)	N.D. (0%)	6.02 (75%)
thiosulfate sulfurtransferase	Ovis aries	XP_014950344.2	TST	33 kDa	Chi-square	0.003	6.99 (75%)	6.91 (100%)	5.87 (25%)	N.D. (0%)
vesicle-associated membrane protein-associated protein B/C	Capra hircus	XP_017913111.1	VAPB	27 kDa	ANOVA	0.00037	6.54	7.36	7.38	7.52
lipopolysaccharide-binding protein	Ovis aries	XP_004014615.1	LBP	53 kDa	ANOVA	0.0012	7.28	7.9	7.14	6.69
apolipoprotein A-I	Ovis aries	XP_011950887.2	APOA1	30 kDa	ANOVA	0.0019	9.1	9.11	9.13	9.53
transferrin precursor	Ovis aries	NP_001009800.1	TTR	16 kDa	ANOVA	0.0028	8.27	8.44	8.39	8.8
pre-B-cell leukemia transcription factor-interacting protein 1 isoform X1	Ovis aries	XP_027831619.1	PBXIP1	90 kDa	ANOVA	0.0056	6.24	6.74	7.13	7.13
ITIH2, partial	Cervus elaphus hellephagus	OWK03472.1	-	103 kDa	ANOVA	0.0057	7.15	7.31	7.9	7.88
long-chain fatty acid transport protein 1	Ovis aries	XP_027825247.1	SLC27A1	71 kDa	ANOVA	0.0066	6.6	7.16	6.59	6.52
ras-related protein Rab-5C	Bos taurus	NP_001029915.1	RAB5C	23 kDa	ANOVA	0.0076	6.42	6.89	6.99	6.99
complement C1q subcomponent subunit C	Ovis aries	XP_027820684.1	CIQC	94 kDa	ANOVA	0.0085	Missing Value	7.26	7.21	6.92
vitronectin isoform X1	Ovis aries	XP_01831040.1	VTN	54 kDa	ANOVA	0.031	7.92	8.17	8.06	8.24
vitronectin	Capra hircus	XP_005693309.1	VTN	54 kDa	ANOVA	0.011	7.91	8.15	8.05	8.17
TPA: Inter-alpha globulin inhibitor H2 polypeptide	Bos taurus	NP_0042635.1	ITH2	106 kDa	ANOVA	0.011	7.48	7.58	8.08	8.05
ras-related protein Rab-5A isoform X1	Ovis aries	XP_014947086.1	RAB5A	24 kDa	ANOVA	0.012	6.37	6.71	6.87	6.81
ras-related protein Rab-5B	Bos taurus	NP_001193120.1	RAB5B	24 kDa	ANOVA	0.017	6.37	6.71	6.86	6.88
glutamine amidotransferase-like class 1 domain-containing protein 3A, mitochondrial	Ovis aries	NP_001156032.1	GATD3	29 kDa	ANOVA	0.017	6.27	6.82	6.75	6.91
palmitoyl-protein thioesterase 1	Ovis aries	XP_004001885.2	PPT1	34 kDa	ANOVA	0.018	6.46	6.95	6.9	6.8
receptor expression-enhancing protein 5	Ovis aries	XP_014952182.2	REEP5	21 kDa	ANOVA	0.019	6.2	6.97	6.99	7.19
inter-alpha-trypsin inhibitor heavy chain H2	Ovis aries	XP_004014227.2	ITH2	106 kDa	ANOVA	0.020	7.58	7.61	8.18	8.1
tetranectin precursor	Bos taurus	NP_001039677.1	CLEC3B	22 kDa	ANOVA	0.022	7.07	7.13	6.97	7.47
immunoglobulin heavy chain variable region, partial	Ovis aries	CAD45049.1	-	12 kDa	ANOVA	0.022	7.35	7.64	7.36	6.92
glucosidase 2 subunit beta	Ovis aries	XP_027825495.1	PRKSH	60 kDa	ANOVA	0.023	7.22	7.94	7.01	7.53
zona pellucida sperm-binding protein 4	Ovis aries	XP_027818021.1	ZP4	59 kDa	ANOVA	0.025	6.72	7.08	7.07	Missing Value
protein ERGIC-53 isoform X1	Ovis aries	XP_014959285.2	LMAN1	58 kDa	ANOVA	0.025	6.51	7.36	7.04	6.54
GDP-fucose protein O-fucosyltransferase 2 isoform X1	Ovis aries	XP_027816944.1	POFUT2	50 kDa	ANOVA	0.030	7.06	7.49	6.97	6.94
non-specific lipid-transfer protein isoform X2	Bos indicus x Bos taurus	XP_027939203.1	SCP2	52 kDa	ANOVA	0.030	5.85	6.53	6.69	6.94
histidine-rich glycoprotein	Ovis aries	XP_00400867.1	HRCG	62 kDa	ANOVA	0.031	7.45	7.7	7.12	7.63
protein AIMP isoform X2	Capra hircus	XP_005684398.1	AIMP	39 kDa	ANOVA	0.033	6.97	7.07	7.14	7.53
immunoglobulin superfamily DCC subclass member 4	Ovis aries	XP_027827301.1	IGDC4	134 kDa	ANOVA	0.034	Missing Value	6.58	6.25	6.51
dynein light chain 1, cytoplasmic-like	Bos indicus	XP_015812000.1	LOC10955509	10 kDa	ANOVA	0.037	6.41	6.84	6.83	6.85
NADH dehydrogenase 1 alpha subcomplex subunit 7	Ovis aries	XP_004008614.1	NDUFA7	13 kDa	ANOVA	0.037	5.49	6.16	6.19	6.59
NADPH-cytochrome P450 reductase isoform X1	Ovis aries	XP_027817441.1	LOC101115252	87 kDa	ANOVA	0.038	6.82	7.51	7.5	7.36
electron transfer flavoprotein subunit beta isoform X2	Odocoileus virginianus texanus	XP_020755939.1	ETF8	28 kDa	ANOVA	0.038	7.21	7.7	7.73	7.78
electron transfer flavoprotein subunit beta isoform X1	Ovis aries	XP_004015435.3	ETF8	28 kDa	ANOVA	0.038	7.21	7.7	7.73	7.78
complement component C7	Ovis aries	XP_004017066.2	C7	93 kDa	ANOVA	0.039	7.65	7.78	7.31	7.55
Ig mu chain C region membrane-bound form, partial	Ovis aries	XP_027813089.1	LOC101113211	54 kDa	ANOVA	0.040	7.82	7.79	7.79	7.41
ras-related protein Rab-8A	Bos taurus	NP_001098951.1	RAB8A	24 kDa	ANOVA	0.041	7.09	7.33	7.52	7.68
glutaredoxin-related protein 5, mitochondrial	Ovis aries	XP_004018030.1	GLRX5	17 kDa	ANOVA	0.046	6.54	7.05	6.95	7.25
vitronectin precursor	Bos taurus	NP_001030222.1	VTN	54 kDa	ANOVA	0.046	7.71	7.92	7.72	7.8
alpha-2-macroglobulin receptor-associated protein isoform X2	Ovis aries	XP_027827072.1	LRPAP1	42 kDa	ANOVA	0.047	6.68	7.09	7.34	7.19
40S ribosomal protein S16 isoform 1	Ovis aries	NP_010111.1	RPS16	16 kDa	ANOVA	0.047	7.18	7.7	7.53	7.77
mitochondrial glutathione S-transferase 1	Ovis aries	XP_00400867.1	MGST1	18 kDa	ANOVA	0.049	5.58	6.71	6.57	7.04
C1q-binding protein alpha chain isoform X1	Ovis aries	XP_012042366.2	LOC101119740	69 kDa	ANOVA	0.050	7.86	7.9	7.6	7.44
heme oxygenase 2	Ovis aries	XP_027817868.1	HMOX2	38 kDa	ANOVA	0.051	6.54	6	6.86	6.95
mannose-6-phosphate utilization defect 1 protein	Ovis aries	XP_004012714.2	MPDU1	27 kDa	ANOVA	0.051	6.4	6.87	6.97	7.27
endothelin-converting enzyme 1 isoform X1	Ovis aries	XP_027821363.1	ECE1	91 kDa	ANOVA	0.054	5.78	7.09	7.44	6.75
histone H1.3	Ovis aries	XP_011956523.2	LOC101109397	22 kDa	ANOVA	0.054	8.7	9.21	9.35	9.18
histone H1.2	Ovis aries	XP_004019136.2	H1-2	21 kDa	ANOVA	0.056	8.72	9.25	9.36	9.2
histone H1.5	Camelus dromedarius	XP_010973014.2	H1-5	23 kDa	ANOVA	0.058	8.51	9.14	9.18	9.08
peroxisomal bifunctional enzyme	Ovis aries	XP_027813339.1	EHHADH	80 kDa	ANOVA	0.059	6.58	6.95	6.61	5.97
matrix Gla protein	Ovis aries	XP_004006882.1	MGP	12 kDa	ANOVA	0.062	6.72	7.17	7.15	7.12
alpha-N-acetylglucosaminidase	Ovis aries	XP_027830301.1	NAGLU	82 kDa	ANOVA	0.063	7.11	7.55	7.66	7.78
zona pellucida sperm-binding protein 3	Ovis aries	XP_004021030.2	ZP3	47 kDa	ANOVA	0.063	6.56	6.96	7.3	6.29
complement component C8 alpha chain	Ovis aries	XP_027826446.1	C8A	44 kDa	ANOVA	0.067	6.67	7.14	Missing Value	6.74
complement C4-A-like	Bos indicus	XP_019840884.1	LOC109576672	173 kDa	ANOVA	0.067	8.44	8.49	8.25	8.33
acetolactate synthase-like protein	Ovis aries	XP_004008513.1	ILVBL	68 kDa	ANOVA	0.068	6.13	7.25	6.17	6.42
dehydrogenase/reductase SDR family member on chromosome X	Ovis aries	XP_027819102.1	DHRX5	37 kDa	ANOVA	0.070	6.03	6.56	6.5	6.67
lamin	Ovis aries	XP_027832136.1	LMNA	74 kDa	ANOVA	0.073	6.57	7.15	7.34	6.5
glutathione peroxidase 1	Ovis aries	XP_004018511.2	GPX1	23 kDa	ANOVA	0.075	Missing Value	6.48	6.41	6.11
glutathione peroxidase 7	Capra hircus	XP_017899689.1	GPX7	21 kDa	ANOVA	0.076	6.24	7.37	7.13	7.12
fibronectin isoform X11	Ovis aries	XP_027820957.1	FN1	249 kDa	ANOVA	0.078	9.41	9.86	9.47	9.16
peroxiredoxin-2	Ovis aries	NP_001159672.1	PRDX2	22 kDa	ANOVA	0.079	7.52	7.49	7.96	7.97
extended synaptotagmin-1 isoform X1	Ovis aries	XP_027823406.1	ESYT1	125 kDa	ANOVA	0.082	Missing Value	6.55	6.45	6.51
alpha-methylacyl-CoA racemase	Ovis aries	XP_004017112.2	AMACR	42 kDa	ANOVA	0.082	7.59	8.07	8.09	8.27
heterochromatin protein 1-binding protein 3 isoform X1	Ovis aries	XP_014949207.1	HP1BP3	61 kDa	ANOVA	0.084	6.68	7.38	6.89	6.53
melanoma inhibitory activity protein 3 isoform X1	Capra hircus	XP_017915670.1	MIA3	211 kDa	ANOVA	0.088	6.34	6.97	6.53	6.67
Fibronectin	Bos taurus	P07589.4	FN1	272 kDa	ANOVA	0.088	9.37	9.83	9.44	9.14
lysosome membrane protein 2	Ovis aries	XP_014951776.2	SCARB2	54 kDa	ANOVA	0.091	7.14	7.55	7.38	6.93
neuroplastin, partial	Ovis aries	XP_027827375.1	NPTN	43 kDa	ANOVA	0.094	Missing Value	6.61	6.68	6.42
60S ribosomal protein L22 isoform X2	Bos mutus	XP_014332763.1	RPL22	15 kDa	ANOVA	0.094	7.16	7.42	7.34	7.64
basement membrane-specific heparan sulfate proteoglycan core protein	Ovis aries	XP_027821348.1	HSPG2	469 kDa	ANOVA	0.095	7.6	8.19	7.6	7.54
endoplasmic reticulum metalloproteinase 1	Ovis aries	XP_004004415.2	ERMP1	100 kDa	ANOVA	0.096	Missing Value	6.45	6.12	6.04
histone H4-like, partial	Ovis aries	XP_014958099.2	LOC101102019	15 kDa	ANOVA	0.099	8.82	9.25	9.33	9.21
isocitrate dehydrogenase subunit alpha, mitochondrial	Vicugna pacos	XP_031547614.1	IDH3A	40 kDa	ANOVA	0.10	7.32	7.66	7.39	7.73
pentatricopeptide repeat-containing protein 1, mitochondrial-like	Bos indicus	XP_018465770.1	LOC109578103	83 kDa	ANOVA	0.10	7.15	7.46	7.49	7.67
ADP-dependent glucokinase isoform X1	Capra hircus	XP_017910165.1	ADPK	54 kDa	ANOVA	0.10	6.38	6.74	6.27	6.71
basigin-like isoform X1	Capra h									

protein disulfide-isomerase A6	Bos indicus	XP_019824917.1	LOC109565403	48 kDa	ANOVA	0.14	8.61	8.88	8.56	8.34
enoyl-CoA hydratase, mitochondrial	Capra hircus	XP_017896763.1	ECHS1	31 kDa	ANOVA	0.14	7.2	7.57	7.19	7.66
catenin alpha-1	Ovis aries	XP_004008890.1	CTNNA1	100 kDa	ANOVA	0.14	6.3	6.44	6.96	6.46
peroxisomal multifunctional enzyme type 2	Ovis aries	XP_004008734.2	HSD17B4	87 kDa	ANOVA	0.14	6.95	7.33	6.68	7.28
complement C1s subcomponent	Ovis aries	XP_004006966.1	C1S	78 kDa	ANOVA	0.14	6.44	6.4	6	6.07
membrane-associated progesterone receptor component 1	Ovis aries	NP_001295509.1	PGMRC1	22 kDa	ANOVA	0.14	7.75	7.95	7.98	8.23
2-iminobutanoate/2-iminopropanoate deaminase	Capra hircus	NP_001272642.1	RDA	14 kDa	ANOVA	0.14	5.81	6.32	6.19	6.72
cytochrome b5	Ovis aries	NP_001159665.1	CYB5A	15 kDa	ANOVA	0.14	7.33	7.6	7.35	7.72
mitochondrial-processing peptidase subunit alpha	Ovis aries	XP_027821975.1	PMPCA	58 kDa	ANOVA	0.15	6.14	6.13	6.3	6.21
dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1	Ovis aries	XP_027813657.1	RPN1	69 kDa	ANOVA	0.15	8.1	8.5	8.27	8.09
retinol dehydrogenase 11	Ovis aries	XP_012037274.1	RDH11	37 kDa	ANOVA	0.15	6.56	6.97	6.77	6.57
sarcoplasmic/endoplasmic reticulum calcium ATPase 2	Ovis aries	XP_011953174.1	ATP2A2	110 kDa	ANOVA	0.15	6.59	7.08	7.15	7.29
apoptosis-inducing factor 1, mitochondrial isoform X2	Ovis aries	XP_004022430.1	AIFM1	66 kDa	ANOVA	0.15	7.11	7.37	7.08	6.98
thioredoxin-dependent peroxide reductase, mitochondrial	Ovis aries	XP_004020276.3	PRDX3	28 kDa	ANOVA	0.15	7.45	7.73	7.63	7.92
complement component C6	Ovis aries	XP_004017065.2	C6	105 kDa	ANOVA	0.15	7.28	7.55	7.21	7.23
calreticulin	Ovis aries	XP_004008533.1	CALR	48 kDa	ANOVA	0.15	8.65	8.82	8.68	8.27
mannosyl-oligosaccharide glucosidase	Ovis aries	XP_004006147.4	MOGS	93 kDa	ANOVA	0.15	6.55	7.37	7.33	7.23
apolipoprotein E	Ovis aries	XP_027834259.1	APOE	36 kDa	ANOVA	0.16	6.72	7.52	6.68	6.91
lysosomal protective protein isoform X2	Ovis aries	XP_027833053.1	CTSA	54 kDa	ANOVA	0.16	6.43	6.57	6.53	6.91
dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 2 isoform X1	Ovis aries	XP_027832978.1	RPN2	71 kDa	ANOVA	0.16	8.39	8.72	8.31	8.18
ATP-binding cassette sub-family D member 1 isoform X1	Ovis aries	XP_027818719.1	ABCD1	82 kDa	ANOVA	0.16	6.63	7.19	7.03	7.01
short/branched chain specific acyl-CoA dehydrogenase, mitochondrial	Ovis aries	XP_027818210.1	ACADSB	47 kDa	ANOVA	0.16	6.89	7.05	6.35	6.61
cathepsin D	Ovis aries	XP_02783055.1	CTSD	45 kDa	ANOVA	0.16	6.97	7.44	7.78	7.24
40S ribosomal protein S27-like isoform X2	Bison bison	XP_010831802.1	LOC104983941	16 kDa	ANOVA	0.16	16.37	17.64	6.78	6.81
ATP synthase subunit O, mitochondrial	Capra hircus	XP_005674722.1	ATP5FO	23 kDa	ANOVA	0.16	7.44	7.76	7.67	7.85
phosphatidylethanolamine-binding protein 1	Ovis aries	XP_004017427.1	PFBP1	21 kDa	ANOVA	0.16	7.01	7.04	7.04	7.42
histone H2B type 1-N	Bos taurus	NP_001075211.1	H2BC15	14 kDa	ANOVA	0.16	9.05	9.39	9.4	9.31
60S ribosomal protein L13a	Camelus ferus	EPY89115.1	-	37 kDa	ANOVA	0.16	6.72	7.03	7.25	7.28
histone H2A type 1-A	Vicugna pacos	XP_031544014.1	LOC102537258	14 kDa	ANOVA	0.17	8.73	9.12	9.21	9.08
short palate, lung and nasal epithelium carcinoma-associated protein 2A-like	Ovis aries	XP_027832882.1	LOC114117619	28 kDa	ANOVA	0.17	9.34	9.44	9.11	9.34
plasma membrane calcium-transferring ATPase 4	Ovis aries	XP_027831983.1	ATP2B4	133 kDa	ANOVA	0.17	6.8	7.09	7.09	7.01
procollagen galactosyltransferase 1	Ovis aries	XP_027825246.1	COLGALT1	72 kDa	ANOVA	0.17	7.71	7.9	7.89	7.63
complement C4 isoform X1	Ovis aries	XP_027814604.1	LOC101123672	192 kDa	ANOVA	0.17	8.9	9.01	8.77	8.9
histone H2A type 1-A-like, partial	Camelus bactrianus	XP_010970234.1	LOC105082344	9 kDa	ANOVA	0.17	8.73	9.12	9.21	9.08
tissue alpha-L-fucosidase	Ovis aries	XP_004005173.2	FUCA1	54 kDa	ANOVA	0.17	6.87	7.24	6.97	6.84
pigment epithelium-derived factor isoform 1 precursor	Homo sapiens	NP_001316832.1	SERPINF1	46 kDa	ANOVA	0.17	6.43	6.5	6.72	6.93
coiled-coil domain-containing protein 134 precursor	Bos taurus	NP_001192755.1	CCDC134	26 kDa	ANOVA	0.17	5.9	6.89	6.74	6.78
INHA	Capra hircus	AEF40507.1	-	39 kDa	ANOVA	0.17	7.78	8.21	8	7.97
succinate dehydrogenase	Ovis aries	XP_027836013.1	SDHA	73 kDa	ANOVA	0.18	7.18	7.53	7.26	7.08
ER membrane protein complex subunit 1 isoform X2	Ovis aries	XP_027821434.1	EMC1	111 kDa	ANOVA	0.18	6.61	7.51	7.31	7.03
ATP-dependent 6-phosphofructokinase, liver type	Ovis aries	XP_027816853.1	PFKL	85 kDa	ANOVA	0.18	6.64	6.11	6.93	6.3
integrin beta-5 isoform X2	Ovis aries	XP_027812388.1	ITGB5	88 kDa	ANOVA	0.18	6.94	7.3	7.33	7.08
isobutyryl-CoA dehydrogenase, mitochondrial	Capra hircus	XP_017914891.1	ACAD8	45 kDa	ANOVA	0.18	6.88	6.99	6.84	7.02
vesicle-associated membrane protein-associated protein A isoform X1	Ovis aries	XP_014959144.1	VAPA	32 kDa	ANOVA	0.18	Missing Value	6.45	6.67	6.54
extracellular superoxide dismutase [Cu-Zn] isoform X1	Ovis aries	XP_014951904.2	SOD3	39 kDa	ANOVA	0.18	6.92	6.69	6.95	7.18
lamin-B1	Ovis aries	XP_004008711.1	LMNB1	66 kDa	ANOVA	0.18	7.71	8.04	7.94	7.47
tumor necrosis factor-inducible gene 6 protein	Ovis aries	XP_004004753.1	TNFAIP6	31 kDa	ANOVA	0.18	7.41	Missing Value	7.79	7.72
Ferredoxin-1	Ovis aries	P29330.2	FDX1	14 kDa	ANOVA	0.18	6.16	5.89	6.85	7.07
aromatase	Ovis aries	NP_001116472.1	CYP19	58 kDa	ANOVA	0.18	6.9	7.43	6.85	7.23
PRA1 family protein 2	Bos taurus	NP_001039474.1	PRAF2	19 kDa	ANOVA	0.18	6.06	6.62	6.54	7.06
TPA: keratin 6A-like	Bos taurus	DAA29993.1	-	63 kDa	ANOVA	0.18	7.78	7.81	7.81	8.13
protein disulfide-isomerase	Ovis aries	XP_027830078.1	PAHB	63 kDa	ANOVA	0.19	8.75	9.08	8.83	8.6
mitochondrial fission process protein 1 isoform X1	Capra hircus	XP_017916470.1	MTFP1	18 kDa	ANOVA	0.19	6.08	6.25	5.98	6.55
glutathione S-transferase P	Capra hircus	XP_017898539.1	LOC100861197	24 kDa	ANOVA	0.19	7.1	7.11	7.21	7.74
mitochondrial fission 1 protein isoform X2	Bos mutus	XP_014832815.1	FIS1	20 kDa	ANOVA	0.19	6.09	6.57	6.52	6.71
GPI transamidase component PIG-5	Bubalus bubalis	XP_006424254.1	PIG5	62 kDa	ANOVA	0.19	6.75	6.75	7.14	6.64
glutathione S-transferase A1-like	Ovis aries	XP_004018947.1	LOC101106720	25 kDa	ANOVA	0.19	7.96	8.18	8.29	8.41
nucleoside diphosphate kinase A 1	Ovis aries	XP_004012798.1	LOC101102072	17 kDa	ANOVA	0.19	6.09	6.34	6.46	6.95
peptidyl-prolyl cis-trans isomerase B	Ovis aries	XP_004010585.1	PIPB	24 kDa	ANOVA	0.19	8.26	8.47	8.52	8.57
NADH dehydrogenase 1 alpha subcomplex subunit 2	Bos taurus	NP_787009.1	NDUFA2	11 kDa	ANOVA	0.19	6.51	6.84	6.64	6.99
ORM1-like protein 3	Bos taurus	NP_001069835.1	ORMDL3	17 kDa	ANOVA	0.19	5.58	6.25	5.95	6.02
ELAV (embryonic lethal, abnormal vision, Drosophila)-like 1 (Hu antigen R), isoform CRA_b	Homo sapiens	EAW68950.1	-	50 kDa	ANOVA	0.19	6.8	6.74	7.07	7.13
mannan-binding lectin serine protease 2 isoform X2	Ovis aries	XP_027831448.1	MASP2	76 kDa	ANOVA	0.20	6.34	6.03	Missing Value	5.97
N-sulphoglucosamine sulphohydrolase	Capra hircus	XP_005694136.1	SGSH	57 kDa	ANOVA	0.20	6.05	6.77	6.64	6.83
ATP synthase subunit alpha, mitochondrial	Ovis aries	XP_004020569.1	ATP5F1A	60 kDa	ANOVA	0.20	8.64	8.91	8.62	8.4
fibrinogen beta chain	Ovis aries	XP_004017233.2	FBG	57 kDa	ANOVA	0.20	10.6	10.5	10.4	10.1
5'-nucleotidase	Ovis aries	XP_004011351.1	NTE	63 kDa	ANOVA	0.20	8.54	8.81	8.9	8.69
hepatitis A virus cellular receptor 1-like	Ovis aries	XP_004009061.1	LOC101111190	15 kDa	ANOVA	0.20	6.2	6.53	6.28	7.03
protein kish-A precursor	Bos taurus	NP_001107983.1	TMEM167A	8 kDa	ANOVA	0.20	5.8	5.96	6.01	6.28
glutathione S-transferase A1 isoform X1	Ovis aries	XP_027814130.1	GSTA1	25 kDa	ANOVA	0.21	8.17	8.56	8.55	8.75
60S ribosomal protein L14	Ovis aries	XP_027813337.1	RPL14	23 kDa	ANOVA	0.21	7.08	7.08	7.26	7.4
histone H2A type 3	Bos indicus	XP_019819308.1	LOC109561360	14 kDa	ANOVA	0.21	8.89	9.21	9.27	9.15
erlin-1	Ovis aries	XP_011958166.1	ERLN1	39 kDa	ANOVA	0.21	7.24	7.49	7.28	7.03
leucine-rich repeat-containing protein 59	Ovis aries	XP_004012816.1	LRRCS9	35 kDa	ANOVA	0.21	7.04	7.46	7.15	7.31
apolipoprotein F-like	Ovis aries	XP_004006628.2	LOC101107947	28 kDa	ANOVA	0.21	6.2	6.46	Missing Value	6.73
H2A histone family member X, partial	Muntiacus vaginalis	AXA12840.1	H2AX	11 kDa	ANOVA	0.21	8.86	9.17	9.22	9.09
heat shock protein gp96 precursor, partial	Homo sapiens	AAK74072.1	HSP90B1	90 kDa	ANOVA	0.21	8.84	9.29	9.19	8.82
Aldehyde dehydrogenase 7 family, member A1	Bos taurus	AAI05407.1	ALDH7A1	55 kDa	ANOVA	0.21	6.71	7.37	6.69	7.0
pigment epithelium-derived factor isoform X1	Ovis aries	XP_027829730.1	SERPINF1	44 kDa	ANOVA	0.22	7.26	7.01	7.21	7.41
transferrin receptor protein 2 isoform X1	Ovis aries	XP_027817323.1	TFR2	88 kDa	ANOVA	0.22	Missing Value	5.84	6.55	6.89
histone H2B 1/2-like	Bos indicus	XP_019823312.1	LOC109564212	9 kDa	ANOVA	0.22	8.84	9.09	9.11	9.06
histone H2B type 1-N-like	Bos indicus	XP_019821179.1	LOC109562588	16 kDa	ANOVA	0.22	8.85	9.1	9.12	9.07
histone H2B type 1-like	Bos indicus	XP_019808862.1	LOC109553226	11 kDa	ANOVA	0.22	8.97	9.26	9.3	9.3
neutral alpha-glucosidase AB isoform X2	Ovis aries	XP_011957423.2	GANAB	107 kDa	ANOVA	0.22	8.39	8.72	8.73	8.59
beta-2-glycoprotein 1 isoform X1	Capra hircus	XP_005694533.1	APOH	38 kDa	ANOVA	0.22	6.44	7.19	6.96	7.32
NADH dehydrogenase 1 alpha subcomplex subunit 11	Ovis aries	XP_004008632.1	NDUFA11	15 kDa	ANOVA	0.22	6.59	6.8	6.7	7.19
cytochrome c oxidase subunit 7A-related protein, mitochondrial	Ovis aries	XP_004006945.1	LOC101115694	13 kDa	ANOVA	0.22	6.34	6.73	6.69	6.86
clusterin	Ovis aries	XP_004008480.1	LOC101113728	51 kDa	ANOVA	0.22	7.89	8.27	8.14	8.7
ATP synthase subunit alpha, mitochondrial precursor	Bos taurus	NP_777109.1	ATP5F1A	60 kDa	ANOVA	0.22	8.6	8.87	8.59	8.39
protein disulfide-isomerase A3 precursor	Ovis aries	NP_001156517.1	PDI3A	57 kDa	ANOVA	0.22	8.86	9.21	9.06	8.7
vesicular integral-membrane protein VIP36 isoform X1	Ovis aries	XP_027825816.1	LMAN2	40 kDa	ANOVA	0.23	7.16	7.43	7.39	7.32
short-chain specific acyl-CoA dehydrogenase, mitochondrial	Ovis aries	XP_027812426.1	ACADS	45 kDa	ANOVA	0.23	6.78	7.28	6.91	7.01
nucleoside diphosphate kinase B	Capra hircus	XP_017920331.1	NME2	17 kDa	ANOVA	0.23	6.06	6.22	6.6	6.91
uncharacterized protein LOC102283318	Bos mutus	XP_014334962.1	LOC102283318	48 kDa	ANOVA	0.23	6.14	6.53	6.36	6.83
endoplasmic	Ovis aries	XP_012030315.1	HSP90B1	92 kDa	ANOVA	0.23	8.9	9.31	9.24	8.89
inter-alpha-trypsin inhibitor heavy chain H1	Ovis aries	XP_004018442.2	ITIH1	101 kDa	ANOVA	0.23	7.84	7.9	8.1	7.94
inter-alpha-trypsin inhibitor heavy chain H4 isoform X2	Ovis aries	XP_004018440.2	ITIH4	101 kDa	ANOVA	0.23	8.54	8.7	8.59	8.34
trifunctional enzyme subunit alpha, mitochondrial	Ovis aries	NP_001129962.1	HADHA	83 kDa	ANOVA	0.23	7.49	7.94	7.63	7.49
dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit DAD1	Bos taurus	NP_001029933.1	DAD1	12 kDa	ANOVA	0.23	7.15	7.57	7.39	7.64
60S acidic ribosomal protein P0	Bos taurus	NP_001012700.1	RPLP0	34 kDa	ANOVA	0.23	7.53	7.1	7.59	7.71
immunoglobulin lambda light chain constant region 2 allotypic variant IGLC2c, partial	Bos taurus	AEM05840.1	-	11 kDa	ANOVA	0.23	8.09	7.96	8.35	8.38
plasma protease C1 inhibitor	Ovis aries	XP_027835594.1	SERPINF1	52 kDa	ANOVA	0.24	8	8.07	7.91	8.09
ribosome-binding protein 1 isoform X3	Ovis aries	XP_027832521.1	RBP1	154 kDa	ANOVA	0.24	7.17	7.72	7.6	7.32
protein LYRIC isoform X1	Ovis aries	XP_027828995.1	MTDH	67 kDa	ANOVA	0.24	5.82	6.05	5.73	6.49
protein NipSnap homolog 3A	Ovis aries	XP_027819963.1	NIPSNAP3A	29 kDa	ANOVA	0.24	5.59	5.58	Missing Value	6.27
paraspöckle component 1 isoform X1	Bos taurus	XP_024855571.1	PSPC1	59 kDa	ANOVA	0.24	6.94	7.37	6.66	6.66
vitamin K-dependent protein C	Ovis aries	XP_014948797.2	PROC	54 kDa	ANOVA	0.24				

complement component C8 gamma chain isoform X1	Ovis aries	XP_027821902.1	C8G	30 kDa	ANOVA	0.27	7.3	7.31	6.95	7.27
ATP synthase subunit e, mitochondrial isoform X2	Bubalus bubalis	XP_025145348.1	ATP5ME	12 kDa	ANOVA	0.27	6.93	7.34	7.12	7.4
alpha-2-HS-glycoprotein	Odocoileus virginianus texanus	XP_020734476.1	AHG5	38 kDa	ANOVA	0.27	7.89	8.23	8.1	7.91
late histone H2B.L4-like	Bos indicus	XP_019822502.1	LOC109563569	14 kDa	ANOVA	0.27	8.42	8.86	8.89	8.98
hemoglobin subunit alpha-I/II	Bison bison bison	XP_010855734.1	LOC105001245	15 kDa	ANOVA	0.27	8.46	8.16	9.14	8.64
NAD(P) transhydrogenase, mitochondrial	Ovis aries	XP_0040117056.2	NNT	114 kDa	ANOVA	0.27	7.48	7.98	7.87	7.61
gap junction alpha-1 protein	Ovis aries	XP_00411208.1	GJA1	43 kDa	ANOVA	0.27	7.45	8.06	7.87	7.96
NADH dehydrogenase 1 beta subcomplex subunit 4	Ovis aries	XP_004003003.2	NDUF84	15 kDa	ANOVA	0.27	6.53	6.83	6.77	7.09
Hemoglobin subunit beta	Ovis aries	XP_02075.2	HBB	16 kDa	ANOVA	0.27	9.08	8.97	9.77	9.27
uroplakin-1b	Ovis aries	XP_011950373.1	UPK1B	30 kDa	ANOVA	0.28	6.72	6.67	6.27	Missing Value
procollagen-llysine-2-oxoglutarate 5-dioxygenase 1	Bubalus bubalis	XP_006076826.1	PIOD1	84 kDa	ANOVA	0.28	7.18	7.51	7.22	7.16
ribosome-binding protein 1	Bos mutus	XP_005904628.1	RBRP1	107 kDa	ANOVA	0.28	7.05	7.52	7.43	7.28
NADH dehydrogenase 1 beta subcomplex subunit 11, mitochondrial	Ovis aries	XP_004022189.1	NDUF811	17 kDa	ANOVA	0.28	5.82	6.18	5.79	6.52
primary amine oxidase, lung isozyme	Ovis aries	XP_004013452.2	LOC101113086	87 kDa	ANOVA	0.28	7.6	7.6	7.62	7.69
MICOS complex subunit MIC60 isoform X1	Ovis aries	XP_004005935.3	IMMT	84 kDa	ANOVA	0.28	7.33	7.74	7.62	7.46
leukocyte cell-derived chemotaxin-2 precursor	Bos taurus	NP_776805.1	LECT2	16 kDa	ANOVA	0.28	5.83	5.93	5.96	6.4
mitochondrial 2-oxoglutarate/malate carrier protein	Ovis aries	NP_001120745.1	SLC25A11	34 kDa	ANOVA	0.28	7.04	7.35	7.46	7.6
ras-related protein Rab-12	Bos taurus	NP_001095762.1	RAB12	27 kDa	ANOVA	0.28	7.07	7.19	7.33	7.48
fumarate hydratase, mitochondrial	Bos taurus	NP_001069271.1	FH	55 kDa	ANOVA	0.28	7.79	7.93	7.74	7.61
carbonic anhydrase 2	Ovis aries	XP_027829052.1	CA2	29 kDa	ANOVA	0.29	6.91	6.88	7.63	6.96
SUN domain-containing protein 2 isoform X1	Ovis aries	XP_027823918.1	SUN2	88 kDa	ANOVA	0.29	7	7.59	7.51	6.88
monoacylglycerol lipase ABHD6 isoform X1	Odocoileus virginianus texanus	XP_020743079.1	ABHD6	42 kDa	ANOVA	0.29	6.37	6.27	6.53	6.47
leucine-rich PPR motif-containing protein, mitochondrial	Ovis aries	XP_012493899.2	LPPRMC	158 kDa	ANOVA	0.29	6.63	6.39	Missing Value	6.12
glutamate dehydrogenase 1, mitochondrial	Bison bison bison	XP_010855690.1	GLUD1	62 kDa	ANOVA	0.29	5.63	6.02	6.22	6.22
cytochrome c oxidase assembly factor 3 homolog, mitochondrial	Capra hircus	XP_005699921.2	LOC102190454	12 kDa	ANOVA	0.29	5.94	6.33	Missing Value	6.53
estradiol 17-beta-dehydrogenase 11	Capra hircus	XP_005681936.2	HSD17B11	33 kDa	ANOVA	0.29	6.87	6.48	7.06	7.11
L-lactate dehydrogenase B chain	Capra hircus	XP_005680842.2	LDHB	36 kDa	ANOVA	0.29	6.42	7.24	7.47	7.62
NADH dehydrogenase 1 subunit C2	Ovis aries	XP_004019479.1	NDUFC2	14 kDa	ANOVA	0.29	6.87	7.18	7.07	7.29
ras-related protein Rab-11B	Bos taurus	NP_001030468.1	RAB11B	24 kDa	ANOVA	0.29	7.23	7.38	7.44	7.53
galactin-3-binding protein isoform X1	Ovis aries	XP_027830011.1	LGALS3BP	62 kDa	ANOVA	0.30	7.23	7.5	7.42	7.43
serpin A3-6	Capra hircus	XP_017921952.1	LOC102186111	46 kDa	ANOVA	0.30	8.42	8.49	8.16	8.46
U2 small nuclear ribonucleoprotein A'	Vicugna pacos	XP_006211551.1	SNRPA1	28 kDa	ANOVA	0.30	6.81	6.71	6.89	6.58
histone H3.1	Bos mutus	XP_005892274.1	LOC102280001	15 kDa	ANOVA	0.30	8.33	8.84	8.79	8.68
dehydrogenase/reductase SDR family member 1	Ovis aries	XP_004010348.1	DHRS1	34 kDa	ANOVA	0.30	6.03	6.42	Missing Value	6.37
starch-binding domain-containing protein 1	Ovis aries	XP_004009976.1	STBD1	36 kDa	ANOVA	0.30	6.96	6.88	7.03	7.18
cytochrome c oxidase subunit 5B, mitochondrial	Ovis aries	XP_004006204.1	LOC101110664	14 kDa	ANOVA	0.30	6.21	7.27	6.89	7.09
inhibitor of carbonic anhydrase-like isoform X2	Ovis aries	XP_004003380.2	LOC101117129	78 kDa	ANOVA	0.30	7.28	7.3	7.43	7.69
phosphoglycerate kinase 1	Ovis aries	NP_001135988.1	PGK1	45 kDa	ANOVA	0.30	7.08	7	7.48	7.65
translocin-associated protein subunit gamma	Bos taurus	NP_001070512.1	SSR3	21 kDa	ANOVA	0.30	6.72	7.04	6.7	6.97
antithrombin-III precursor	Ovis aries	NP_00100393.1	SERPINC1	52 kDa	ANOVA	0.30	8.19	8.17	8.06	8.13
Ig gamma-3 chain C region, partial	Bos mutus	ELR44890.1	-	33 kDa	ANOVA	0.30	8.67	8.35	9.22	8.85
histone H3	Homo sapiens	CABQ2546.1	H3C1	15 kDa	ANOVA	0.30	8.32	8.84	8.79	8.68
H3L-like histone, partial	Homo sapiens	AAQ96275.1	-	12 kDa	ANOVA	0.30	8.28	8.78	8.78	8.68
beta 2 glycoprotein I	Bos taurus	AB20668.1	-	36 kDa	ANOVA	0.30	6.47	7.22	7.04	7.34
dolichyl-diphosphooligosaccharide-protein glycosyltransferase subunit STT3B	Ovis aries	XP_027813742.1	STT3B	93 kDa	ANOVA	0.31	6.92	7.23	7.11	6.78
alpha-2-macroglobulin	Odocoileus virginianus texanus	XP_020760299.1	LOC110144654	155 kDa	ANOVA	0.31	8.23	8.21	8.06	8.02
procollagen-llysine-2-oxoglutarate 5-dioxygenase 2 isoform X1	Capra hircus	XP_017904680.1	PIOD2	88 kDa	ANOVA	0.31	7.15	7.15	7.17	6.9
fibulin-1 isoform X2	Capra hircus	XP_017904389.1	FBLN1	75 kDa	ANOVA	0.31	7.02	6.66	7.08	6.98
pterin-4-alpha-carbinolamine dehydratase 2 isoform X2	Ovis aries	XP_012039310.1	PCBD2	12 kDa	ANOVA	0.31	Missing Value	5.93	6.23	6.47
carboxypeptidase N subunit 2	Ovis aries	XP_004023454.3	CNP2	60 kDa	ANOVA	0.31	6.23	Missing Value	6.04	6.12
cytoskeleton-associated protein 4	Ovis aries	XP_004006741.2	CKAP4	65 kDa	ANOVA	0.31	8.62	8.97	8.66	8.58
UDP-glucose:glycoprotein glucosyltransferase 1 isoform X1	Ovis aries	XP_004004533.3	UGT1	178 kDa	ANOVA	0.31	7.46	7.78	7.73	7.42
delta(24)-sterol reductase	Ovis aries	XP_004002060.2	DHCR24	60 kDa	ANOVA	0.31	7.25	7.71	7.42	7.42
IDH3A	Cervus elaphus hippelaphus	OWK09169.1	-	53 kDa	ANOVA	0.31	7.48	7.55	7.45	7.65
immediate early response 3-interacting protein 1 precursor	Bos taurus	NP_001106799.1	IEK3IP1	9 kDa	ANOVA	0.31	6.06	6.3	6.21	6.58
ATP synthase membrane subunit DAP1, mitochondrial	Bos taurus	NP_001106789.1	ATP5MK	6 kDa	ANOVA	0.31	6.28	6.75	6.53	6.71
alpha-2-HS-glycoprotein precursor	Ovis aries	NP_001008802.1	AHSG	39 kDa	ANOVA	0.31	8.33	8.6	8.43	8.31
membrane-bound immunoglobulin gamma1 heavy chain constant region, partial	Bos taurus	ANNA6376.1	-	44 kDa	ANOVA	0.31	9.35	9.38	9.45	9.12
ADP/ATP translocase 2	Camelus dromedarius	XP_031302141.1	SLC25A5	33 kDa	ANOVA	0.32	8.28	8.48	8.47	8.38
annexin A6 isoform X2	Ovis aries	XP_027826224.1	ANXA6	75 kDa	ANOVA	0.32	7.03	7.65	7.42	7.52
integrin alpha-6 isoform X2	Capra hircus	XP_017920165.1	ITGA6	119 kDa	ANOVA	0.32	6.92	7.7	7.71	7.35
aspartyl/asparaginyl beta-hydroxylase isoform X1	Ovis aries	XP_012039134.2	ASPH	86 kDa	ANOVA	0.32	Missing Value	6.81	6.32	6.5
hypoxia up-regulated protein 1 isoform X1	Ovis aries	XP_011950949.2	HYOU1	111 kDa	ANOVA	0.32	7.91	8.25	8.33	8.17
pigment epithelium-derived factor	Capra hircus	XP_005693374.1	SERPINF1	46 kDa	ANOVA	0.32	7.15	7.02	7.15	7.37
diablo homolog, mitochondrial	Ovis aries	XP_004017389.3	DIABLO	31 kDa	ANOVA	0.32	5.85	6.26	6.43	6.57
annexin A6 isoform X1	Ovis aries	XP_004009036.1	ANXA6	76 kDa	ANOVA	0.32	7.03	7.65	7.71	7.52
isoamyl acetate-hydrolyzing esterase 1 homolog isoform X1	Ovis aries	XP_004005727.1	IAH1	28 kDa	ANOVA	0.32	6.23	6.15	6.83	6.53
hemoglobin subunit alpha	Ovis canadensis nelsoni	QLR83449.1	HBA-T1	15 kDa	ANOVA	0.32	8.83	8.68	9.5	8.99
mitochondrial pyruvate carrier 2	Bos taurus	NP_001180050.1	MPC2	14 kDa	ANOVA	0.32	6.04	6.32	6.31	6.57
hemoglobin subunit beta-C	Ovis aries	NP_001106896.1	HBB	16 kDa	ANOVA	0.32	8.78	8.68	9.43	8.94
D-dopa-chrome decarboxylase	Bos taurus	NP_001092620.1	DDT	13 kDa	ANOVA	0.32	5.67	5.76	5.71	6
alpha globin chain	Ovis aries	NP_00449760.1	-	15 kDa	ANOVA	0.32	8.84	8.67	9.49	9
alpha globin	Homo sapiens	CAA22749.1	-	14 kDa	ANOVA	0.32	7.33	7.51	8.17	7.76
similar to 60S ribosomal protein L7; similar to P18124 (PID:d133021)	Homo sapiens	AAD08846.1	-	29 kDa	ANOVA	0.32	6.95	7.33	7.21	7.41
DNA topoisomerase 1	Ovis aries	XP_027832995.1	TOP1	91 kDa	ANOVA	0.33	6.86	6.91	7.2	6.69
extracellular matrix protein 1 isoform X1	Ovis aries	XP_027830219.1	ECM1	61 kDa	ANOVA	0.33	7.57	8.12	7.8	7.64
mitochondrial proton/calcium exchanger protein isoform X1	Ovis aries	XP_027827113.1	LETM1	82 kDa	ANOVA	0.33	6.4	7.07	7.1	7.82
60S ribosomal protein L7a	Capra hircus	XP_017911629.1	RPL7A	30 kDa	ANOVA	0.33	7.59	7.76	7.73	6.86
alpha-2-antiplasmin isoform X1	Ovis aries	XP_012040849.2	SERPINF2	61 kDa	ANOVA	0.33	7.79	8.17	7.96	7.74
transmembrane 9 superfamily member 2	Ovis aries	XP_004012270.1	TM9SF2	76 kDa	ANOVA	0.33	Missing Value	6.31	6.46	6.51
cholesterol side-chain cleavage enzyme, mitochondrial precursor	Ovis aries	NP_001087258.1	CYP11A1	60 kDa	ANOVA	0.33	7.83	8.23	8.12	8.17
macrophage migration inhibitory factor	Bos taurus	NP_001028780.1	MIF	12 kDa	ANOVA	0.33	6.79	6.93	7.22	7.19
INH8	Capra hircus	AEP40509.1	-	48 kDa	ANOVA	0.33	6.88	7.2	6.77	6.97
mitochondrial malate dehydrogenase 2	Bos taurus	ABD77298.1	MDH2	30 kDa	ANOVA	0.33	8.42	8.67	8.51	8.62
cathepsin D [EC 3.4.23.5]	Bos taurus	AB26186.1	-	38 kDa	ANOVA	0.33	6.61	7.19	7.47	6.96
major vault protein	Ovis aries	XP_027817904.1	MVP	99 kDa	ANOVA	0.34	6.52	7.09	7.08	5.55
lanosterol synthase	Ovis aries	XP_027817929.1	LSS	83 kDa	ANOVA	0.34	Missing Value	7.09	6.71	6.6
BRI3-binding protein	Ovis aries	XP_02781202.1	BRI3BP	27 kDa	ANOVA	0.34	5.89	6.06	6.76	6.62
protein Nip5ap homolog 2 isoform X1	Ovis aries	XP_014959672.2	NIP5NAP2	34 kDa	ANOVA	0.34	5.96	6.7	6.45	6.52
CMP-N-acetylneuraminic-beta-galactoside-alpha-2,3-sialyltransferase 4 isoform X1	Ovis aries	XP_011956915.1	ST3GAL4	42 kDa	ANOVA	0.34	6.17	6.89	5.81	Missing Value
ribonuclease 4	Capra hircus	XP_005685456.1	LOC102176126	17 kDa	ANOVA	0.34	6.15	6.11	6.05	6.65
aldehyde dehydrogenase, mitochondrial	Ovis aries	XP_004017458.1	ALDH2	57 kDa	ANOVA	0.34	8.19	8.4	7.98	7.91
PIOD3	Cervus elaphus hippelaphus	OWK11025.1	-	104 kDa	ANOVA	0.34	7.21	7.68	7.46	7.33
immunoglobulin gamma 2 heavy chain constant region, partial	Capra hircus	ABQ51194.1	-	21 kDa	ANOVA	0.34	9.35	9.4	9.38	9.07
beta-1,4-galactosyltransferase 4	Ovis aries	XP_027836019.1	B4GALT4	40 kDa	ANOVA	0.35	6.57	6.38	6.95	6.81
transmembrane protein 43 isoform X1	Ovis aries	XP_027813625.1	TMEM43	47 kDa	ANOVA	0.35	7.02	7.18	7.34	7.05
polyubiquitin-C	Ovis aries	XP_027812205.1	UBC	95 kDa	ANOVA	0.35	8.28	8.57	8.51	8.55
NADH dehydrogenase [ubiquinone] iron-sulfur protein 6, mitochondrial isoform X2	Capra hircus	XP_017921207.1	NDUFS6	13 kDa	ANOVA	0.35	6.04	6.55	6.39	6.83
core histone macro-H2A.1	Bison bison bison	XP_010842926.1	LOC104991931	42 kDa	ANOVA	0.35	7.69	7.76	7.76	7.87
cytochrome b-c1 complex subunit 8	Bos taurus	NP_777230.1	UQCRC	10 kDa	ANOVA	0.35	6.19	6.5	6.27	6.41
alpha-1-macroglobulin-like	Ovis aries	XP_027823689.1	LOC101104482	163 kDa	ANOVA	0.36	6.22	6.94	Missing Value	6.28
probable ATP-dependent RNA helicase DDX31 isoform X1	Ovis aries	XP_027822037.1	DDX31	81 kDa	ANOVA	0.36	6.76	6.95	6.04	6.73
heat shock protein beta-1	Ovis aries	XP_027817273.1	HSPB1	22 kDa	ANOVA	0.36	7.91	7.74	8.04	8.23
very-long-chain (3R)-3-hydroxyacyl-CoA dehydratase 3 isoform X1	Bubalus bubalis	XP_025152097.1	HACD3	45 kDa	ANOVA	0.36	Missing Value	6.18	6.65	6.75
basigin	Bos indicus	XP_019820388.1	BSG	35 kDa	ANOVA	0.36	6.54	6.94	6.89	6.29
scaffold attachment factor B2 isoform X1	Capra hircus	XP_017906395.1	SFAF2	107 kDa	ANOVA	0.36	Missing Value	6.81	6.86	6.33
programmed cell death protein 6 isoform X1	Ovis aries	XP_014956838.2	PCDCE2	22 kDa	ANOVA	0.36	5.97	6.33	6.19	6.59

haptoglobin precursor	Bubalus bubalis	NP_001277908.1	HP	45 kDa	ANOVA	0,38	8,38	6,76	6,84	6,03
cholesterol side-chain cleavage enzyme, mitochondrial	Capra hircus	NP_001274503.1	CYP11A1	60 kDa	ANOVA	0,38	7,91	8,27	8,06	8,14
immunoglobulin kappa-2.1 light chain variable region, partial	Ovis aries	AA894900.1		13 kDa	ANOVA	0,38	7,18	6,94	7,46	7,04
serotransferrin	Ovis aries	XP_027816111.1	TF	77 kDa	ANOVA	0,39	9,24	9,26	9,45	9,33
fibronectin type III domain-containing protein 3B	Ovis aries	XP_014948036.2	FNDC3	133 kDa	ANOVA	0,39	Missing Value	6,69	6,1	6,27
serpin A3-8	Ovis aries	XP_011954394.2	LOC101119509	47 kDa	ANOVA	0,39	8,36	8,34	8,3	8,12
calnexin	Capra hircus	XP_005682095.1	CANX	68 kDa	ANOVA	0,39	7,99	8,33	8,26	8,13
histone H2A type 1-B/E	Bos taurus	NP_005202300.1	LOC524236	14 kDa	ANOVA	0,39	9,31	6,94	9,54	9,51
pyruvate carboxylase, mitochondrial	Ovis aries	XP_027815692.1	PC	130 kDa	ANOVA	0,40	7,74	8,09	7,89	7,64
lamin B2	Capra hircus	XP_017906266.1	LMNB2	70 kDa	ANOVA	0,40	7,02	7,53	7,48	7,22
glutathione S-transferase Mu 1-like	Capra hircus	XP_017901368.1	LOC108633298	26 kDa	ANOVA	0,40	6,82	6,38	6,66	6,94
prolyl 4-hydroxylase subunit alpha-1 isoform X2	Ovis aries	XP_004021508.1	PHA1A	61 kDa	ANOVA	0,40	7,58	7,47	7,54	7,08
protein SEC13 homolog	Ovis aries	XP_004018574.1	SEC13	35 kDa	ANOVA	0,40	6,48	6,3	6,12	6,46
dihydrodipicolinate succinyltransferase component of 2-oxoglutarate dehydrogenase	Ovis aries	XP_004010842.1	DLST	49 kDa	ANOVA	0,40	6,07	7,1	6,82	6,61
Core histone macro-H2A.2	Camelus dromedarius	KAB1271219.1	-	53 kDa	ANOVA	0,40	7,38	7,49	7,54	7,44
lactadherin	Ovis aries	XP_027812864.1	MFG8	48 kDa	ANOVA	0,41	8,63	8,51	8,83	8,56
nucleobindin-1	Capra hircus	XP_017918238.1	NUCB1	53 kDa	ANOVA	0,41	Missing Value	6,84	6,58	6,52
fructose-bisphosphate aldolase A	Vicugna pacos	XP_015092348.1	ALDOA	39 kDa	ANOVA	0,41	7,48	6,97	7,22	7,4
complement component C9	Ovis aries	XP_004017075.3	C9	62 kDa	ANOVA	0,41	7,92	8,19	7,95	7,91
60S ribosomal protein L18	Ovis aries	XP_004015402.1	RPL18	22 kDa	ANOVA	0,41	7,35	7,47	7,45	7,65
NADH dehydrogenase 1 beta subcomplex subunit 9 isoform X1	Ovis aries	XP_004011699.2	NDUF9	22 kDa	ANOVA	0,41	6,87	7,09	7,02	7,18
ALDH2	Cervus elaphus hippelaphus	OWK15140.1		58 kDa	ANOVA	0,41	8,12	8,3	7,88	7,82
ATP-dependent RNA helicase A	Bos taurus	NP_076461.1	HK9	142 kDa	ANOVA	0,41	7,44	7,75	7,68	7,68
gelsolin isoform X1	Ovis aries	XP_027819674.1	DSN	86 kDa	ANOVA	0,42	8,49	8,62	8,59	8,64
dihydrodipicolinate succinyltransferase component of pyruvate dehydrogenase complex	Ovis aries	XP_011950844.2	DLAT	69 kDa	ANOVA	0,42	6,45	6,79	6,65	6,53
complement factor I	Ovis aries	XP_004009671.1	CFI	69 kDa	ANOVA	0,42	7,25	6,93	7,08	7,31
Hexokinase-1	Bos taurus	P27595.1	HK1	103 kDa	ANOVA	0,42	6,57	7,2	6,9	6,98
histone H2A type 1-like	Bos indicus	XP_019841862.1	LOC109577385	14 kDa	ANOVA	0,43	9,39	9,6	9,54	9,54
cytochrome c oxidase subunit 4 isoform 1, mitochondrial	Capra hircus	XP_017917306.1	LOC102188434	20 kDa	ANOVA	0,43	6,51	7,18	6,25	7,41
HIG1 domain family member 1A, mitochondrial	Ovis aries	XP_011954842.1	HIGD1A	10 kDa	ANOVA	0,43	5,68	6,32	5,7	6,16
complement component C8 beta chain	Ovis aries	XP_004002065.2	C8B	66 kDa	ANOVA	0,43	7,23	7,51	7,22	7,29
Hemoglobin subunit beta-A	Bos javanicus	P04346.1		16 kDa	ANOVA	0,43	8,66	8,53	9,21	8,7
Ion protease homolog, mitochondrial	Ovis aries	XP_027825611.1	LONP1	107 kDa	ANOVA	0,44	7,43	7,71	7,57	7,4
V-type proton ATPase subunit G1	Ovis aries	XP_014948445.1	ATP6V1G1	14 kDa	ANOVA	0,44	5,65	5,94	5,86	5,97
acetyl-CoA acetyltransferase, mitochondrial	Ovis aries	XP_027834968.1	ACAT1	45 kDa	ANOVA	0,45	7,78	7,94	7,74	7,91
scaffold attachment factor B1 isoform X2	Ovis aries	XP_027825612.1	SAFB	180 kDa	ANOVA	0,45	6,59	7,38	7,24	6,69
delta-1-pyrroline-5-carboxylate dehydrogenase, mitochondrial	Ovis aries	XP_027821443.1	ALDH4A1	61 kDa	ANOVA	0,45	6,24	6,34	5,7	5,88
very-long-chain 3-oxoacyl-CoA reductase	Ovis aries	XP_004016470.1	HSD17B12	35 kDa	ANOVA	0,45	7,29	7,47	7,53	7,52
IDH3B protein, partial	Bos taurus	AAJ0453.1	IDH3B	42 kDa	ANOVA	0,45	6,76	7,09	7	7,18
protein sel-1 homolog 1	Ovis aries	XP_027827895.1	SEL1L	89 kDa	ANOVA	0,46	6,12	6,97	6,75	6,61
aconitate hydratase, mitochondrial	Ovis aries	XP_027823951.1	ACO2	85 kDa	ANOVA	0,46	7,77	8,2	7,96	7,84
serpin A3-5	Ovis aries	XP_027813163.1	LOC101115576	47 kDa	ANOVA	0,46	8,9	8,78	8,72	8,5
serpin H1	Bos indicus	XP_019830880.1	SERPINH1	46 kDa	ANOVA	0,46	9,27	9,46	9,42	9,29
nodal modulator 1	Ovis aries	XP_014959583.2	LOC101112427	134 kDa	ANOVA	0,46	6,75	7,42	7,08	7,11
poly(ADP-ribose) polymerase 1	Ovis aries	XP_012042537.2	PARP1	113 kDa	ANOVA	0,46	5,84	7,12	6,45	5,4
serpin A3-7-like	Ovis aries	XP_011963749.2	LOC101115576	47 kDa	ANOVA	0,46	8,39	8,32	8,27	8,21
3-hydroxyacyl-CoA dehydrogenase type-2	Ovis aries	XP_004022113.1	HSD17B10	27 kDa	ANOVA	0,46	8,03	8,17	7,98	8,29
ATP synthase subunit delta, mitochondrial	Ovis aries	XP_004008824.1	ATP5F1D	18 kDa	ANOVA	0,46	6,89	7,08	7,17	7,32
40S ribosomal protein S3 isoform 2	Homo sapiens	NP_001247435.1	RPS3	28 kDa	ANOVA	0,46	7,65	7,55	7,71	7,83
glyceraldehyde-3-phosphate dehydrogenase	Ovis aries	NP_001177319.1	GAPDH	36 kDa	ANOVA	0,46	8,39	7,99	8,43	8,49
SWI/SNF complex subunit SMARCC2	Camelus dromedarius	XP_031319512.1	SMARCC2	127 kDa	ANOVA	0,47	6,06	6,44	6,16	6,17
alpha-1B-glycoprotein	Ovis aries	XP_027834752.1	A1BG	54 kDa	ANOVA	0,47	8,36	8,51	8,39	8,43
persulfide dioxygenase ETHE1, mitochondrial isoform X1	Ovis aries	XP_027834207.1	ETHE1	28 kDa	ANOVA	0,47	7,4	7,6	7,46	7,58
ATPase family AAA domain-containing protein 3	Ovis aries	XP_027831599.1	LOC101105090	66 kDa	ANOVA	0,47	6,23	6,39	6,04	5,76
complement C5	Ovis aries	XP_004004015.2	LOC101121825	189 kDa	ANOVA	0,47	8,14	8,06	8,13	8,22
NADH dehydrogenase 1 alpha subcomplex subunit 12	Ovis aries	XP_012138660.1	NDUF12	17 kDa	ANOVA	0,47	6,24	6,47	6,39	6,57
mitochondrial carnitine/acylcarnitine carrier protein	Bos taurus	NP_001071404.1	SLC25A20	33 kDa	ANOVA	0,47	6,23	6,69	6,26	6,43
trifunctional enzyme subunit beta, mitochondrial	Equus asinus	XP_014699026.1	HADHB	51 kDa	ANOVA	0,48	6,92	7,12	6,6	6,59
mitochondrial amidoxime reducing component 2	Ovis aries	XP_012043312.3	MTAR2C	37 kDa	ANOVA	0,48	6,34	6,38	6,62	6,91
malate dehydrogenase, mitochondrial	Ovis aries	XP_004021309.2	MHD2	36 kDa	ANOVA	0,48	8,65	8,68	8,69	8,79
delta(3,5)-Delta(2,4)-dienoyl-CoA isomerase, mitochondrial	Ovis aries	XP_004015286.3	ECH1	36 kDa	ANOVA	0,48	6,55	6,67	Missing Value	6,43
mitochondrial import receptor subunit TOM22 homolog	Ovis aries	XP_004007043.2	TOMM22	15 kDa	ANOVA	0,48	6,51	6,72	6,22	6,93
sodium/potassium-transporting ATPase subunit alpha-1	Ovis aries	NP_001009360.1	ATP1A1	113 kDa	ANOVA	0,48	7,59	7,66	7,81	7,64
Vesicle-associated membrane protein 3, partial	Bos mutus	ELRS5847.1		11 kDa	ANOVA	0,48	6,65	6,93	6,68	6,74
60S acidic ribosomal protein P2	Ovis aries	XP_019820217.1	RPLP2	13 kDa	ANOVA	0,49	6,79	6,92	6,83	7,11
zinc transporter ZIP14 isoform X1	Ovis aries	XP_014948594.1	SLC39A14	54 kDa	ANOVA	0,49	Missing Value	6,78	6,12	Missing Value
immunoglobulin kappa light chain constant region, partial	Ovis aries	AAJ45094.1		12 kDa	ANOVA	0,49	8,81	8,86	9,04	8,83
complement C3	Ovis aries	XP_027825575.1	C3	188 kDa	ANOVA	0,50	9,46	9,47	9,4	9,45
eukaryotic translation initiation factor 3 subunit B	Ovis aries	XP_027817731.1	EIF3B	89 kDa	ANOVA	0,50	Missing Value	6,6	Missing Value	6,36
Serine/threonine-protein phosphatase PGAMS, mitochondrial isoform X1	Ovis aries	XP_027812156.1	PGAM5	32 kDa	ANOVA	0,50	6,29	6,4	6,35	5,91
endoplasmic reticulum aminopeptidase 1 isoform X1	Ovis aries	XP_01204380.2	ERAP1	113 kDa	ANOVA	0,50	6,93	7,52	7,41	7,19
aspartate aminotransferase, mitochondrial	Ovis aries	XP_004015091.1	GOT2	48 kDa	ANOVA	0,50	8,01	8,23	8,05	8,08
26S proteasome non-ATPase regulatory subunit 12	Ovis aries	XP_004013087.1	PSMD12	53 kDa	ANOVA	0,50	Missing Value	5,98	Missing Value	6,03
2,4-dienoyl-CoA reductase, mitochondrial isoform X1	Ovis aries	XP_004011896.3	DECR1	35 kDa	ANOVA	0,50	Missing Value	6,78	6,25	5,98
acyl-CoA-binding protein	Ovis aries	XP_004004799.1	DBI	10 kDa	ANOVA	0,50	6,24	6,78	6,73	6,79
coatomer subunit alpha isoform X1	Ovis aries	XP_004002719.1	COPA	139 kDa	ANOVA	0,50	6,92	6,52	6,95	6,9
endoplasmic reticulum resident protein 29 precursor	Ovis aries	NP_001119826.1	ERP29	29 kDa	ANOVA	0,50	7,58	7,77	7,68	7,56
proteasome subunit alpha type-1	Bos taurus	NP_001030387.1	PSMA1	30 kDa	ANOVA	0,50	6,2	Missing Value	6,15	6,46
stearyl-CoA desaturase	Ovis aries	ACN86166.1	SCD	42 kDa	ANOVA	0,50	6,2	6,11	Missing Value	Missing Value
lipocalin/cytosolic fatty-acid binding domain-containing protein	Capra hircus	XP_017899981.1	LOC102183974	22 kDa	ANOVA	0,51	7,12	6,94	6,58	6,88
cytochrome b-c1 complex subunit 1, mitochondrial	Ovis aries	XP_011955483.2	LOC101110095	53 kDa	ANOVA	0,51	6,99	7,33	7,11	7,15
zona pellucida sperm-binding protein 2	Ovis aries	XP_004020876.3	ZP2	80 kDa	ANOVA	0,51	6,51	6,69	6,65	5,67
protein YIF1A isoform X2	Ovis aries	XP_004019740.1	YIF1A	32 kDa	ANOVA	0,51	5,39	6,32	6,32	6,37
60S ribosomal protein L6	Ovis aries	XP_004017428.1	LOC101109212	33 kDa	ANOVA	0,51	7,62	7,46	7,7	7,8
cathespin B precursor	Ovis aries	NP_001295516.1	CTSB	37 kDa	ANOVA	0,51	6,61	6,48	6,5	6,95
inorganic pyrophosphatase 2, mitochondrial isoform X1	Bos taurus	XP_005207716.1	PPA2	39 kDa	ANOVA	0,52	6,67	6,64	6,69	6,86
complement factor B	Ovis aries	XP_004018376.1	CFB	88 kDa	ANOVA	0,52	7,8	7,81	8,01	7,94
NADH dehydrogenase 1 alpha subcomplex subunit 13	Ovis aries	XP_004008949.1	NDUF13	17 kDa	ANOVA	0,52	Missing Value	6,38	6,58	6,19
splicing factor proline/glutamine-rich (polypyrimidine tract binding protein associated), isoform X1	Homo sapiens	EAJ07433.1	SFPQ	68 kDa	ANOVA	0,52	7,95	8,29	8,24	7,93
scavenger receptor class B member 1 isoform X1	Ovis aries	XP_027812206.1	SCARB1	58 kDa	ANOVA	0,53	Missing Value	Missing Value	7,15	6,97
Ig lambda chain variable region, partial	Bos taurus	QH43021.1	-	12 kDa	ANOVA	0,53	6,42	5,51	6,07	6,29
oligosaccharyltransferase complex subunit OSTC	Bos taurus	NP_001070560.1	OSTC	17 kDa	ANOVA	0,53	6,47	6,58	6,52	6,79
immunoglobulin gamma-1 chain, partial	Ovis aries	CAA49451.1		52 kDa	ANOVA	0,53	9,69	9,65	9,74	9,45
3-hydroxyacyl-CoA dehydrogenase type-2-like	Camelus ferus	XP_032330258.1	LOC102511542	28 kDa	ANOVA	0,54	7,37	7,5	7,33	7,64
renin receptor	Capra hircus	XP_017899412.1	ATP6P2	39 kDa	ANOVA	0,54	5,69	5,76	Missing Value	Missing Value
electron transfer flavoprotein subunit alpha, mitochondrial	Bubalus bubalis	XP_006044468.1	ETFA	35 kDa	ANOVA	0,54	7,8	7,93	7,84	7,93
26S proteasome non-ATPase regulatory subunit 13 isoform X2	Ovis aries	XP_004019791.1								

alpha-2-macroglobulin isoform X3	Ovis aries	XP_012030836.2	LOC101122940	164 kDa	ANOVA	0.59	8.5	8.45	8.39	8.28
4F2 cell-surface antigen heavy chain C3	Ovis aries	XP_004019669.2	SLC3A2	63 kDa	ANOVA	0.59	6.38	6.46	6.18	5.97
	Cervus elaphus hippelaphus	OWK12416.1	-	164 kDa	ANOVA	0.59	9.08	9.09	9.02	9.01
40S ribosomal protein S18	Camelus dromedarius	KAB127869.1	-	8 kDa	ANOVA	0.59	6.11	6.21	6.2	6.46
RNA-binding protein 3 isoform X1	Odocoileus virginianus texanus	XP_020756899.1	RBM3	18 kDa	ANOVA	0.60	6.48	6.7	6.72	7.1
glia-derived nexin	Ovis aries	XP_004005018.1	SERPINE2	44 kDa	ANOVA	0.60	8.29	8.22	8.4	8.32
dnaI homolog subfamily C member 10	Ovis aries	XP_004004576.2	DNAC10	91 kDa	ANOVA	0.60	5.72	6.8	6.48	5.88
transferrin receptor protein 4	Ovis aries	XP_004003050.1	TFR4	86 kDa	ANOVA	0.60	6.73	6.84	6.81	6.73
rab GDP dissociation inhibitor alpha	Ovis aries	NP_001155341.1	GD1I	51 kDa	ANOVA	0.60	6.47	6.58	6.1	6.46
isocitrate dehydrogenase 3 (NAD+) gamma isoform a precursor	Bos taurus	AA46424.1	IDH3G	43 kDa	ANOVA	0.60	7.17	7.25	7.03	7.21
phosphotyrosine phosphatidylinositol inorganic pyrophosphate phosphatase isoform X1	Ovis aries	XP_027816306.1	LHPP	29 kDa	ANOVA	0.61	5.55	5.35	Missing Value	5.54
serpin A3-8 isoform X1	Bos indicus	XP_019838879.1	LOC109575332	52 kDa	ANOVA	0.61	8.17	8.12	8.06	7.97
succinate-CoA ligase GDP-forming] subunit beta, mitochondrial	Ovis aries	XP_004018389.2	SUCLG2	47 kDa	ANOVA	0.61	7.16	7.3	7.14	7.35
protein transport protein Sec23A	Ovis aries	XP_004017955.1	SEC23A	86 kDa	ANOVA	0.61	Missing Value	6.84	6.41	6.46
serine protease HTRA2, mitochondrial	Ovis aries	XP_004006156.2	HTRA2	49 kDa	ANOVA	0.61	6.36	6.61	6.34	6.27
U2 small nuclear ribonucleoprotein B'	Bos taurus	NP_001179481.1	SNRPB2	25 kDa	ANOVA	0.61	6.33	6.44	6.69	6.73
e2rin	Ovis aries	XP_027828426.1	EZR	69 kDa	ANOVA	0.62	6.73	6.85	7.16	6.96
serpin A3-1	Ovis aries	XP_027813161.1	LOC101116892	46 kDa	ANOVA	0.62	8.87	8.89	8.75	8.65
insulin-like growth factor-binding protein complex acle labile subunit	Capra hircus	XP_017896378.1	IGFALS	66 kDa	ANOVA	0.62	6	6.57	Missing Value	6.49
CDP-diacylglycerol-inositol 3-phosphatidylinositol transferase	Ovis aries	XP_004020942.1	CDIPT	24 kDa	ANOVA	0.62	5.5	5.72	5.83	5.97
hydroxysteroid dehydrogenase-like protein 2	Ovis aries	XP_004004059.1	HSD1L2	45 kDa	ANOVA	0.62	6.86	6.84	6.79	6.86
estradiol 17-beta-dehydrogenase 1	Ovis aries	XP_027830302.1	HSD17B1	34 kDa	ANOVA	0.63	7.9	7.82	7.74	7.9
FN1L4 domain-containing protein 2	Capra hircus	XP_01921255.1	LOC108658411	16 kDa	ANOVA	0.63	5.99	6.04	6.32	6.33
valacyclovir hydrolase isoform X2	Ovis aries	XP_004019198.3	BPHL	33 kDa	ANOVA	0.63	6.44	6.55	6.41	6.48
histone H1x	Ovis aries	XP_004018603.2	LOC101106288	22 kDa	ANOVA	0.63	7.65	7.9	7.85	7.72
F-actin-capping protein subunit alpha-1	Ovis aries	XP_004002380.1	CAPZA1	33 kDa	ANOVA	0.63	6.57	6.71	6.87	6.81
immunoglobulin lambda chain variable region, partial	Capra hircus	AA45027.1	25 kDa	ANOVA	0.63	9.32	9.15	9.42	9.34	
immunoglobulin light chain variable region, partial	Bos taurus	AA866576.1	11 kDa	ANOVA	0.63	7.88	7.8	7.94	7.93	
T-complex protein 1 subunit delta	Ovis aries	XP_014948768.2	LOC105608622	58 kDa	ANOVA	0.64	6.94	7.29	6.93	6.84
beta-2-glycoprotein 1	Ovis aries	XP_004013204.2	APOH	38 kDa	ANOVA	0.64	7.8	7.83	7.84	7.55
dihydropyridyl dehydrogenase, mitochondrial	Ovis aries	XP_004007902.1	DLSD	54 kDa	ANOVA	0.64	7	7.43	7.12	7.09
prostaglandin reductase 1	Ovis aries	XP_004004063.1	PTGR1	36 kDa	ANOVA	0.64	7.04	6.75	7.02	7.28
NADH dehydrogenase 1 beta subcomplex subunit 6	Ovis aries	NP_001172052.1	NDUF86	16 kDa	ANOVA	0.64	6.45	6.77	6.63	6.59
immunoglobulin mu heavy chain variable region, partial	Capra hircus	ABX90000.1	16 kDa	ANOVA	0.64	6.33	6.41	5.96	Missing Value	
fibrinogen gamma chain isoform X1	Ovis aries	XP_011952709.1	FGG	50 kDa	ANOVA	0.65	10.5	10.5	10.5	10.4
kininogen-1 isoform X2	Capra hircus	XP_005675214.1	KNG1	49 kDa	ANOVA	0.65	7.31	7.56	7.36	7.29
leucine-rich alpha-2-glycoprotein	Ovis aries	XP_004008643.2	LRG1	38 kDa	ANOVA	0.65	6.68	6.31	6.52	6.78
C-reactive protein	Ovis aries	XP_004002700.1	LOC101115495	25 kDa	ANOVA	0.65	7.65	7.49	7.58	7.83
serrate RNA effector molecule homolog isoform X1	Ovis aries	XP_027817707.1	SRRF	101 kDa	ANOVA	0.66	Missing Value	Missing Value	6.34	6.5
signal recognition particle receptor subunit beta	Ovis aries	XP_027815116.1	SRPB	32 kDa	ANOVA	0.66	6.86	7.1	6.9	7.09
thioredoxin domain-containing protein 5	Ovis aries	XP_027814397.1	TXNDC5	54 kDa	ANOVA	0.66	7.5	7.7	7.6	7.45
T-complex protein 1 subunit alpha	Ovis aries	XP_004011485.1	TCP1	60 kDa	ANOVA	0.66	6.59	6.94	6.96	6.9
yimentin	Ovis aries	AB948145.1	VIM	54 kDa	ANOVA	0.66	9.03	9.28	9.1	9
alpha-1,6-mannosylglycoprotein 6-beta-N-acetylglucosaminyltransferase A	Ovis aries	XP_027820820.1	MGAT5	84 kDa	ANOVA	0.67	Missing Value	6.02	6.26	Missing Value
transmembrane protein 256	Ovis aries	XP_004012698.2	TMEM256	12 kDa	ANOVA	0.67	6.34	6.54	6.62	6.8
NADH dehydrogenase 1 alpha subcomplex subunit 5	Ovis aries	XP_004005022.1	LOC101114379	13 kDa	ANOVA	0.67	6.04	6.61	6.45	6.67
TPA: RNA binding motif protein 25	Bos taurus	DA425145.1	RBM25	115 kDa	ANOVA	0.67	5.8	6.02	6.24	5.95
bifunctional epoxide hydrolase 2	Ovis aries	XP_027820104.1	EPHX2	63 kDa	ANOVA	0.68	7.64	7.67	7.48	7.4
phosphate carrier protein, mitochondrial	Odocoileus virginianus texanus	XP_020765880.1	SLC25A3	40 kDa	ANOVA	0.68	7.63	7.82	7.38	7.78
78 kDa glucose-regulated protein	Odocoileus virginianus texanus	XP_020730015.1	HSPA5	72 kDa	ANOVA	0.68	9.28	9.48	9.37	9.34
transmembrane protein 56	Bos mutus	XP_005908781.1	LOC102271207	30 kDa	ANOVA	0.68	5.58	6.35	Missing Value	Missing Value
cytochrome b-c1 complex subunit 2, mitochondrial	Ovis aries	XP_004020879.1	LOC101102527	48 kDa	ANOVA	0.68	7.79	8	7.9	7.89
Putative ATP-dependent RNA helicase DDX17, partial	Bos mutus	ELRS3727.1	80 kDa	ANOVA	0.68	6.74	7.06	7.12	7.11	
alpha S1 casein	Bos taurus	ACG63494.1	CSN151	24 kDa	ANOVA	0.68	5.76	5.69	5.98	5.86
Enoyl Coenzyme A hydratase, short chain, 1, mitochondrial	Bos taurus	AA109666.1	ECHS1	31 kDa	ANOVA	0.68	7.36	7.63	7.33	7.5
immunoglobulin lambda-delta light chain variable region, partial	Ovis aries	AA894913.1	12 kDa	ANOVA	0.68	6.98	6.94	6.58	7.15	
alpha-2-macroglobulin-like	Vicugna pacos	XP_031526388.1	LOC102530085	165 kDa	ANOVA	0.69	6.78	7.79	7.7	7.57
C4b-binding protein alpha chain-like	Ovis aries	XP_027831945.1	LOC101114456	66 kDa	ANOVA	0.69	6.7	6.99	6.82	7.09
keratin, type I cytoskeletal 19	Ovis aries	XP_027830330.1	KRT19	44 kDa	ANOVA	0.69	6.8	6.38	Missing Value	6.25
citrate synthase, mitochondrial-like	Bos indicus x Bos taurus	XP_027408687.1	LOC113896665	57 kDa	ANOVA	0.69	7.69	7.86	7.68	7.67
sodium/potassium-transporting ATPase subunit beta-1	Capra hircus	XP_005690673.1	ATP1B1	35 kDa	ANOVA	0.69	Missing Value	6.98	6.68	6.62
endoplasmic reticulum chaperone BIP	Ovis aries	XP_004005686.1	HSPA5	72 kDa	ANOVA	0.69	9.3	9.5	9.39	9.37
adenylate kinase 2, mitochondrial isoform X2	Ovis aries	XP_004005056.2	AK2	26 kDa	ANOVA	0.69	7.41	7.48	7.58	7.38
3-hydroxyisobutyryl-CoA hydrolase, mitochondrial isoform X1	Ovis aries	XP_004004547.1	HIBC8	43 kDa	ANOVA	0.69	6.45	6.62	6.36	6.22
vitamin K-dependent protein 5	Ovis aries	XP_004002896.2	PROS1	75 kDa	ANOVA	0.69	6.63	6.63	6.79	6.76
prohibitin-2	Bos taurus	NP_001039663.1	PHB2	33 kDa	ANOVA	0.69	7.91	8.02	8.01	7.92
thrombospondin-1, partial	Bos taurus	CA661682.1	25 kDa	ANOVA	0.69	6.02	Missing Value	6.2	6.71	
heat shock 70kDa protein 5 isoform 1	Cervus elaphus	ACT46910.1	HSPA5	67 kDa	ANOVA	0.69	9.22	9.42	9.25	9.25
HSPA5	Homo sapiens	AAF13605.1	HSPA5	71 kDa	ANOVA	0.69	9.25	9.44	9.34	9.32
glucosylceramidase	Odocoileus virginianus texanus	XP_020768044.1	GBA1	60 kDa	ANOVA	0.70	6.32	6.88	5.96	6.25
nucleosome assembly protein 1-like 4 isoform X1	Capra hircus	XP_017899439.1	NAP1L4	44 kDa	ANOVA	0.70	6.2	6.12	6	5.74
nucleotide exchange factor SIL1 isoform X1	Ovis aries	NP_012033970.1	SIL1	55 kDa	ANOVA	0.70	5.96	6.15	Missing Value	Missing Value
serine/threonine-protein phosphatase PPI-beta catalytic subunit	Bos taurus	NP_001023825.1	PPP1CB	37 kDa	ANOVA	0.70	6.62	6.39	6.46	6.67
serine/threonine phosphatase 1 gamma, partial	Homo sapiens	BA482664.1	PPP1CC	34 kDa	ANOVA	0.70	6.69	6.39	6.46	6.67
NADH-cytochrome b5 reductase 3 isoform X2	Camelus dromedarius	XP_031319240.1	LOC105091873	29 kDa	ANOVA	0.71	6.6	6.75	6.67	6.67
emerin	Ovis aries	XP_027818905.1	EMD	30 kDa	ANOVA	0.71	5.99	6.05	5.52	5.8
serum paraoxonase/arylesterase 2	Capra hircus	XP_017902886.1	PON2	39 kDa	ANOVA	0.71	6.63	6.83	6.76	6.69
ornithine aminotransferase, mitochondrial	Ovis aries	XP_014958975.2	OAT	48 kDa	ANOVA	0.71	7.43	7.23	7.46	7.44
methylsterol monooxygenase 1	Ovis aries	XP_014959632.1	MSMO1	35 kDa	ANOVA	0.71	6.87	6.83	6.76	7.09
nucleolar protein 58 isoform X1	Bos mutus	XP_014336459.1	NOP58	62 kDa	ANOVA	0.71	6.09	6.46	6.35	6.1
AP-2 complex subunit alpha-2, partial	Bison bison bison	XP_010861897.1	AP2A2	87 kDa	ANOVA	0.71	6.31	6.36	6.51	6.25
serum albumin	Capra hircus	XP_005681801.1	ALB	69 kDa	ANOVA	0.71	10.4	10.6	10.6	10.4
tripeptidyl-peptidase 1	Ovis aries	XP_004016255.1	TPP1	62 kDa	ANOVA	0.71	Missing Value	6.4	6.56	5.91
reticulocalbin-3	Ovis aries	XP_004015422.2	RCN3	38 kDa	ANOVA	0.71	6.68	6.84	6.59	6.44
cytochrome c oxidase subunit NDUF4A	Ovis aries	XP_004007802.1	NDUF4A	9 kDa	ANOVA	0.71	7.09	7.17	7.31	7.3
secretory carrier-associated membrane protein 3	Ovis aries	XP_004002634.2	SCAMP3	38 kDa	ANOVA	0.71	6.41	6.71	6.6	6.55
protein disulfide-isomerase A5 precursor	Ovis aries	NP_001156518.1	PDIAS	60 kDa	ANOVA	0.71	6.48	6.68	6.43	Missing Value
WJACA ribonucleoprotein complex subunit DKC1	Ovis aries	NP_001135985.1	DKC1	57 kDa	ANOVA	0.71	5.95	6.67	Missing Value	Missing Value
NADP-dependent malic enzyme	Ovis aries	NP_001128692.1	ME1	64 kDa	ANOVA	0.71	Missing Value	6.55	Missing Value	Missing Value
dipeptidyl peptidase 2	Ovis aries	XP_027821880.1	DPPI2	54 kDa	ANOVA	0.72	Missing Value	6.51	Missing Value	5.9
complement component 1 Q subcomponent-binding protein, mitochondrial	Ovis aries	XP_004012638.2	C1QB	30 kDa	ANOVA	0.72	7.16	7.24	7.27	7.01
protein HP-20 homolog	Ovis aries	XP_004006762.2	LOC101119895	21 kDa	ANOVA	0.72	7.11	7.01	7.01	7.29
TIMP-1 protein, partial	Bos taurus	AAD30303.1	-	19 kDa	ANOVA	0.72	6.63	Missing Value	6.73	6.6
immunoglobulin alpha heavy chain, partial	Ovis aries	AC64980.1	50 kDa	ANOVA	0.72	6.69	6.82	6.28	6.53	
cAMP-dependent protein kinase type II-beta regulatory subunit	Ovis aries	XP_027824390.1	PRKAR2B	46 kDa	ANOVA	0.72	6.73	6.96	6.73	6.94
NAD-dependent protein deacetylase sirtuin-5, mitochondrial	Capra hircus	XP_017894704.1	SIRT5	34 kDa	ANOVA	0.73	6.19	6.36	6.06	6.3
thyroid hormone receptor-associated protein 3 isoform X1	Ovis aries	XP_004001852.1	THRAP3	109 kDa	ANOVA	0.73	6.48	6.61	6.96	6.84
alpha-1-antitrypsin transcript variant 1	Ovis aries	AF171068.1	SERPINA1	46 kDa	ANOVA	0.73	8.65	8.7	8.58	8.62
protein canopy homolog 3	Bos indicus	XP_019841754.1	CNPY3	31 kDa	ANOVA	0.74	6.19	6.48	6.2	6.34
ran GTPase-activating protein 1	Ovis aries	XP_012031089.2	RANGAP1	63 kDa	ANOVA	0.74	6.22	6.37	6.25	Missing Value
ATP synthase subunit gamma, mitochondrial isoform X1	Ovis aries	XP_004014229.1	ATP5F1C	33 kDa	ANOVA	0.74	7.89	7.94	7.93	7.85
Hemoglobin subunit alpha-1/2	Odocoileus virginianus virginianus	P01972.1	-	13 kDa	ANOVA	0.74	6.89	7.49	7.86	6.9
acyl-coenzyme A thioesterase 13-like	Ovis aries	XP_027814416.1	LOC114109597	16 kDa	ANOVA	0.75	5.32	5.8	5.81	5.06
probable global transcription activator SNF2L11 isoform X1	Ovis aries	XP_014960538.2	SMARCA1	125 kDa	ANOVA	0.75	Missing Value	Missing Value	6.32	Missing Value
staphylococcal nuclease domain-containing protein 1	Bison bison bison	XP_010830022.1	SNF1	102 kDa	ANOVA	0.75	6.81	6.96	7.1	6.87
albumin precursor	Ovis aries	NP_001093976.1	ALB	69 kDa	ANOVA	0.75	10.5	10.7	10.6	10.5
immunoglobulin V lambda chain, partial	Ovis aries	AA895457.1	-	12 kDa	ANOVA	0.75	8.01	7.94	8.04	8.02
heterogeneous nuclear ribonucleoprotein U	Odocoileus virginianus texanus	XP_020770929.1	HNRNPU	91 kDa	ANOVA	0.76	7.79	7.9	7.81</	

torsin-1A-interacting protein 2	Ovis aries	XP_004013887.2	LOC101122123	52 kDa	ANOVA	0.78	6.03	6.34	6.25	6.17
proteasome subunit beta type-5	Ovis aries	XP_004010385.1	PSM85	29 kDa	ANOVA	0.78	Missing Value	6.08	5.72	6.35
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10, mitochondrial isoform X1	Ovis aries	XP_004001808.2	NDUFA10	40 kDa	ANOVA	0.78	7.3	7.16	7.11	7.02
catechol O-methyltransferase	Ovis aries	XP_027812737.1	COMT	30 kDa	ANOVA	0.79	6.74	6.72	6.5	6.74
serpin A3-5 isoform X1	Capra hircus	XP_017921950.1	LOC102174166	52 kDa	ANOVA	0.79	8.53	8.52	8.38	8.44
medium-chain specific acyl-CoA dehydrogenase, mitochondrial	Capra hircus	XP_017910046.1	LOC102190925	37 kDa	ANOVA	0.79	6.27	6.43	6.23	6.38
hexokinase-2	Ovis aries	XP_00494962.2	HK2	102 kDa	ANOVA	0.79	Missing Value	Missing Value	6.47	Missing Value
proteasome activator complex subunit 2 isoform X2	Capra hircus	XP_005685286.1	PSM62	27 kDa	ANOVA	0.79	6.61	5.63	6.13	6.49
isocitrate dehydrogenase	Ovis aries	XP_004018103.4	IDH2	51 kDa	ANOVA	0.79	7.38	7.46	7.2	7.43
GPI-anchor transamidase	Ovis aries	XP_004002140.1	PIGK	45 kDa	ANOVA	0.79	6.49	6.56	6.51	6.36
ER membrane protein complex subunit 4	Bos taurus	NP_001029719.1	EMC4	20 kDa	ANOVA	0.79	Missing Value	5.91	Missing Value	5.93
immunoglobulin lambda 1 light chain, partial	Homo sapiens	ABU90640.1		23 kDa	ANOVA	0.79	9.01	9.09	9.14	8.93
cell cycle and apoptosis regulator protein 2 isoform X4	Ovis aries	XP_027820136.1	CCAR2	102 kDa	ANOVA	0.80	6.24	Missing Value	6.34	6.23
T-complex protein 1 subunit epsilon isoform X2	Bos mutus	XP_014348469.1	CCT5	56 kDa	ANOVA	0.80	6.9	6.84	6.85	6.53
NSFL1 cofactor p47 isoform X1	Ovis aries	XP_004014502.1	NSFL1C	41 kDa	ANOVA	0.80	6.21	6.5	Missing Value	6.24
prothrombin precursor	Ovis aries	NP_001159667.1	F2	70 kDa	ANOVA	0.80	7.8	7.74	7.76	7.9
stathmin 1	Homo sapiens	BAG70133.1	STMN1	17 kDa	ANOVA	0.80	5.99	6.22	6.31	6.37
peroxiredoxin-5	Ovis aries	AGA19346.1	PRDX5	17 kDa	ANOVA	0.80	Missing Value	6.2	Missing Value	6.09
dehydrogenase/reductase SDR family member 7B isoform X1	Ovis aries	XP_027830550.1	DHRS7B	39 kDa	ANOVA	0.81	5.78	6.09	6.4	6.08
primary amine oxidase, liver isozyme	Ovis aries	XP_027830273.1	LOC101112834	91 kDa	ANOVA	0.81	7.74	7.7	7.77	7.85
haloacid dehalogenase-like hydrolase domain-containing 5 isoform X1	Ovis aries	XP_027823864.1	HDH05	44 kDa	ANOVA	0.81	6.34	6.42	6.14	6.31
cytoplasmic dynein 1 heavy chain 1	Ovis aries	XP_027813216.1	DYNC1H1	532 kDa	ANOVA	0.81	Missing Value	Missing Value	Missing Value	5.9
interleukin enhancer-binding factor 3 isoform X1	Capra hircus	XP_017906357.1	ILF3	95 kDa	ANOVA	0.81	6.52	6.59	6.82	6.48
ruvB-like 1	Bison bison bison	XP_010831132.1	RUVB1	50 kDa	ANOVA	0.81	Missing Value	6.81	Missing Value	6.24
N-acetylmuramoyl-L-alanine amidase	Capra hircus	XP_005682280.2	PGLYRP2	64 kDa	ANOVA	0.81	6.26	Missing Value	6.17	Missing Value
complement C1q subcomponent subunit 1 isoform X1	Ovis aries	XP_004005191.2	C1QA	34 kDa	ANOVA	0.81	7.25	7.23	7.39	6.97
U6 snRNA-associated Sm-like protein Lsm3	Bos taurus	NP_001032564.1	LMS3	12 kDa	ANOVA	0.81	5.79	5.75	5.82	5.84
malate dehydrogenase, cytoplasmic isoform MDH1	Bos taurus	NP_001029800.1	MDH1	36 kDa	ANOVA	0.81	6.74	6.55	6.48	6.82
guanine nucleotide-binding protein subunit alpha-13	Ovis aries	XP_014954475.2	GNAI3	44 kDa	ANOVA	0.82	6.64	6.83	6.77	6.76
catalase isoform X1	Ovis aries	XP_004016445.1	CAT	60 kDa	ANOVA	0.82	7.3	7.48	7.22	7.19
rho GDP-dissociation inhibitor 1	Bos taurus	NP_788823.1	ARHGDI1A	23 kDa	ANOVA	0.82	6.6	6.75	6.56	6.8
nuclear mitotic apparatus protein 1 isoform X1	Ovis aries	XP_027835270.1	NUMA1	237 kDa	ANOVA	0.83	Missing Value	6.5	Missing Value	Missing Value
small integral membrane protein 1	Ovis aries	XP_027831530.1	SMIM1	9 kDa	ANOVA	0.83	Missing Value	6.18	5.61	6.09
complement C3-like	Equus caballus	XP_023500356.1	LOC100060505	186 kDa	ANOVA	0.83	8.51	8.46	8.54	8.5
nucleolin	Bos mutus	XP_014336327.1	LOC102278736	113 kDa	ANOVA	0.83	6.85	7.04	7.06	6.68
annexin A5	Ovis aries	XP_012034784.2	ANXA5	36 kDa	ANOVA	0.83	7.34	7.28	7.38	7.45
plasma serine protease inhibitor	Ovis aries	XP_004018025.1	SERPINA5	45 kDa	ANOVA	0.83	6.69	6.92	6.81	6.86
heat shock 70kDa protein 5 [glucose-regulated protein, 78kDa], isoform CRA_b	Homo sapiens	EAWR6721.1	-	51 kDa	ANOVA	0.83	9.08	9.24	9.05	9.1
CD14 antigen	Ovis aries	ABP95759.1	-	40 kDa	ANOVA	0.83	6.1	6.64	6.05	Missing Value
glutathione peroxidase 3	Ovis aries	XP_014951639.1	GPX3	26 kDa	ANOVA	0.84	6.91	7.03	Missing Value	6.23
MICOS complex subunit MIC13 isoform X1	Ovis aries	XP_012033429.2	MICOS13	15 kDa	ANOVA	0.84	5.66	Missing Value	5.83	6.46
multifunctional methyltransferase subunit TRM112-like protein	Ovis aries	XP_004019703.2	TRMT112	14 kDa	ANOVA	0.84	6.21	6.23	6.07	6.15
OCA1 domain-containing protein 1 isoform X1	Ovis aries	XP_004009869.1	OCA1D1	28 kDa	ANOVA	0.84	Missing Value	6.27	Missing Value	Missing Value
endoplasmic reticulum resident protein 44	Ovis aries	XP_004004270.1	ERP44	47 kDa	ANOVA	0.84	7.69	7.8	7.82	7.63
regulator complex protein LAMTOR3	Bos taurus	NP_001069450.1	LAMTOR3	14 kDa	ANOVA	0.84	5.87	6.14	6.09	6.1
RNA-binding protein 12B	Bos taurus	NP_027829033.1	RBM12B	116 kDa	ANOVA	0.85	Missing Value	6.42	Missing Value	Missing Value
coatamer subunit gamma-1	Ovis aries	XP_027813655.1	COPG1	97 kDa	ANOVA	0.85	6.79	6.73	6.99	6.9
ADP-ribose pyrophosphatase, mitochondrial	Capra hircus	XP_005681938.1	NUDT9	39 kDa	ANOVA	0.85	Missing Value	5.93	6.33	6.14
hemopexin	Ovis aries	XP_004016259.1	HPX	52 kDa	ANOVA	0.85	8.56	8.31	8.53	8.42
Parathyromin	Bos taurus	P08814.2	PTMS	11 kDa	ANOVA	0.85	5.48	Missing Value	Missing Value	5.77
serpin A3-6 precursor	Bos taurus	NP_001139774.1	SERPINA3-6	46 kDa	ANOVA	0.85	8.3	8.18	8.3	8.15
beta-2-microglobulin	Ovis aries	ABP37878.1	-	14 kDa	ANOVA	0.85	6.65	6.77	Missing Value	6.99
transaldolase	Ovis aries	XP_027815783.1	TALDO1	38 kDa	ANOVA	0.86	6.06	6.3	6.36	6.53
heat shock protein 75 kDa, mitochondrial	Ovis aries	XP_014959538.2	TRAP1	79 kDa	ANOVA	0.86	7.54	7.77	7.68	7.54
deoxyribonuclease-1-like 1, partial	Ovis aries	XP_004027203.3	DNAse1L1	36 kDa	ANOVA	0.86	6.08	6.16	Missing Value	Missing Value
cytochrome b-c1 complex subunit Rieske, mitochondrial	Ovis aries	XP_004004904.1	LOC101113001	30 kDa	ANOVA	0.86	Missing Value	6.46	Missing Value	6.46
adipocyte plasma membrane-associated protein	Ovis aries	XP_004018356.2	APMAP	46 kDa	ANOVA	0.86	7.82	7.95	7.82	7.73
cytochrome c oxidase assembly factor 1 homolog	Bos taurus	NP_001029428.1	COA1	15 kDa	ANOVA	0.86	Missing Value	5.88	Missing Value	6.32
succinate-CoA ligase [ADP-forming] subunit beta, mitochondrial	Ovis aries	XP_027829360.1	SUCLA2	51 kDa	ANOVA	0.87	Missing Value	6.72	6.1	6.23
nicotin isoform X1	Ovis aries	XP_027825701.1	NCLN	63 kDa	ANOVA	0.87	6.46	6.67	6.41	6.18
3-ketoacyl-CoA thiolase, mitochondrial isoform X2	Ovis aries	XP_027816604.1	ACAA2	42 kDa	ANOVA	0.87	7.36	7.33	7.14	7.22
phosphoglucomutase-2 isoform X1	Ovis aries	XP_014951922.2	PGM2	69 kDa	ANOVA	0.87	6.17	6.49	Missing Value	6.53
colled-coil domain-containing protein 167	Capra hircus	XP_005696338.3	CCDC167	13 kDa	ANOVA	0.87	4.89	5.52	5.31	5.52
glucose-6-phosphate isomerase	Ovis aries	XP_004015200.2	GPI	63 kDa	ANOVA	0.87	6.54	6.8	6.24	6.61
elongation factor Ts, mitochondrial	Ovis aries	XP_004006563.1	TSFM	37 kDa	ANOVA	0.87	6.41	6.12	5.73	6.11
CB1 cannabinoid receptor-interacting protein 1	Bos taurus	NP_001069651.1	CNRP1	19 kDa	ANOVA	0.87	Missing Value	5.83	Missing Value	6.08
protein ABHD11	Bos taurus	NP_001029544.1	ABHD11	34 kDa	ANOVA	0.87	6.7	6.67	6.47	6.49
ATP synthase F(0) complex subunit B1, mitochondrial	Bos indicus	XP_019812404.1	ATP5PB	29 kDa	ANOVA	0.88	7.2	7.1	7.01	7.38
UF0568 protein C14orf166 homolog	Capra hircus	XP_017909833.1	RTRAF	28 kDa	ANOVA	0.88	6.49	Missing Value	Missing Value	6.18
coatomer subunit beta'	Ovis aries	XP_004003349.1	COPB2	102 kDa	ANOVA	0.88	6.5	6.7	6.93	6.8
septin-11	Bos taurus	NP_001075916.1	SEPTIN11	49 kDa	ANOVA	0.88	Missing Value	6.37	Missing Value	5.78
elongation factor 3-delta	Ovis aries	NP_001008449.1	EEF1D	31 kDa	ANOVA	0.88	7.35	7.38	7.42	7.42
sorting and assembly machinery component 50 homolog	Bos mutus	XP_005909618.1	SAMM50	58 kDa	ANOVA	0.89	Missing Value	6.37	Missing Value	Missing Value
elongation factor 1-gamma	Capra hircus	XP_005699833.1	EEF1G	50 kDa	ANOVA	0.89	6.98	7.19	7.09	7.15
serine hydroxymethyltransferase, mitochondrial isoform X1	Capra hircus	XP_005680363.1	SHMT2	55 kDa	ANOVA	0.89	6.59	6.95	6.67	6.15
probable glutathione peroxidase 8 isoform X1	Ovis aries	XP_004017038.1	GPX8	24 kDa	ANOVA	0.89	5.76	6.15	5.9	Missing Value
monofunctional C1-tetrahydrofolate synthase, mitochondrial	Ovis aries	XP_004011460.2	MTHFD1L	105 kDa	ANOVA	0.89	5.86	6.2	6.06	Missing Value
hydroxyacyl-coenzyme A dehydrogenase, mitochondrial	Ovis aries	XP_004009686.1	HADH	34 kDa	ANOVA	0.89	6.68	6.71	6.69	6.54
immunoglobulin lambda-delta light chain variable region, partial	Ovis aries	AA894911.1		12 kDa	ANOVA	0.89	6.84	6.56	6.94	6.65
wolframin	Ovis aries	XP_027826972.1	WFS1	100 kDa	ANOVA	0.90	Missing Value	Missing Value	6.35	Missing Value
major facilitator superfamily domain-containing protein 10 isoform X1	Capra hircus	XP_017905340.1	MFSD10	62 kDa	ANOVA	0.90	Missing Value	5.72	5.9	5.76
B-cell receptor-associated protein 31	Capra hircus	XP_017900268.1	BCAP31	28 kDa	ANOVA	0.90	Missing Value	6.07	5.59	6.23
aldose reductase	Ovis aries	XP_004008126.1	AKR1B1	36 kDa	ANOVA	0.90	6.81	6.46	6.71	6.91
eukaryotic translation initiation factor 3 subunit L isoform X1	Ovis aries	XP_004007031.1	EIF3L	67 kDa	ANOVA	0.90	Missing Value	6.1	Missing Value	6.03
Aldo-keto reductase family 1 member B1	Bos taurus	P16116.2		36 kDa	ANOVA	0.90	6.94	6.61	6.51	6.58
nucleolin isoform X1	Ovis aries	XP_027821112.1	NCL	79 kDa	ANOVA	0.91	7.33	7.16	7.57	7.41
serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform-like	Bos indicus x Bos taurus	XP_017869991.1	LOC113875586	65 kDa	ANOVA	0.91	6.5	6.54	6.36	6.61
cytochrome b5 type B isoform X1	Ovis aries	XP_014956001.1	LOC101121621	16 kDa	ANOVA	0.91	7.44	7.39	7.44	7.16
MICOS complex subunit MIC26 isoform X1	Ovis aries	XP_011961801.1	APOD	23 kDa	ANOVA	0.91	6.1	6.17	6.14	6.25
NADH dehydrogenase 1 alpha subcomplex subunit 9, mitochondrial	Capra hircus	XP_005681037.1	NDUF9A	43 kDa	ANOVA	0.91	7.16	7.07	7.02	7.1
transketolase	Ovis aries	XP_004018433.1	TKT	68 kDa	ANOVA	0.91	6.82	6.8	6.6	6.77
TPA: FUS interacting protein [serine-arginine rich] 1-like	Bos taurus	DA418755.1	FUSIP1	31 kDa	ANOVA	0.91	6.68	6.9	6.95	6.95
ras related v-ral simian leukemia viral oncogene homolog A, partial	Bos taurus	ABF57337.1	RALA	21 kDa	ANOVA	0.91	Missing Value	6.22	6.01	5.89
immunoglobulin heavy chain precursor, partial	Ovis aries	AA52601.1		13 kDa	ANOVA	0.91	6.83	6.29	6.66	6.63
solute carrier family 12 member 7 isoform X1	Ovis aries	XP_027835994.1	SLC12A7	119 kDa	ANOVA	0.92	Missing Value	6.28	Missing Value	Missing Value
dolichol-phosphate mannosyltransferase subunit 1	Ovis aries	XP_027833130.1	DPM1	30 kDa	ANOVA	0.92	6.98	6.88	7.01	6.93
zinc-alpha-2-glycoprotein	Ovis aries	XP_011960249.3	AZGP1	36 kDa	ANOVA	0.92	6.04	6.25	Missing Value	6.83
peptidyl-tRNA hydrolase 2, mitochondrial	O									

annexin A4	Ovis aries	XP_004005861.1	ANXA4	36 kDa	ANOVA	0.95	7.65	7.49	7.62	7.43
2-amino-3-ketobutyrate coenzyme A ligase, mitochondrial	Camelus ferus	EPY88370.1	-	62 kDa	ANOVA	0.95	6.56	6.57	6.55	6.61
7-dehydrocholesterol reductase	Ovis aries	XP_027815288.1	DHCR7	54 kDa	ANOVA	0.96	7.06	7	6.94	6.89
serpin A3-1 isoform X1	Bos indicus	XP_019838877.1	LOC109575331	51 kDa	ANOVA	0.96	8.27	8.2	8.28	8.15
protein ABHD11 isoform X2	Ovis aries	XP_004021301.4	ABHD11	33 kDa	ANOVA	0.96	7.31	7.26	7.29	7.31
enoyl-CoA delta isomerase 1, mitochondrial isoform X2	Ovis aries	XP_004020766.1	EC11	33 kDa	ANOVA	0.96	6.45	6.01	5.76	6.09
glutamine-tRNA ligase	Ovis aries	XP_004018515.2	QARS1	87 kDa	ANOVA	0.96	Missing Value	6.55	5.84	Missing Value
inositol-3-phosphate synthase 1	Bos taurus	NP_001039497.1	ITSNA1	61 kDa	ANOVA	0.96	5.98	5.96	Missing Value	5.1
complement component C3d, partial	Ovis aries	XP_014338681.1	ATP13A1	140 kDa	ANOVA	0.97	6.07	6.13	5.72	5.95
manganese-transporting ATPase 13A1	Bos mutus	XP_012038601.1	PLG	90 kDa	ANOVA	0.97	8	8.13	8.1	8.02
plasmalogen isoform X1	Ovis aries	XP_005891545.1	COQ5	38 kDa	ANOVA	0.97	Missing Value	6.1	Missing Value	Missing Value
2-methoxy-6-polypropenyl-1,4-benzoquinol methylase, mitochondrial	Bos mutus	XP_004022278.1	APOL	29 kDa	ANOVA	0.97	Missing Value	Missing Value	6.13	5.67
MICOS complex subunit MIC27	Ovis aries	XP_004020914.1	E1FC3	105 kDa	ANOVA	0.97	6.33	Missing Value	6.02	5.76
eukaryotic translation initiation factor 3 subunit C	Ovis aries	XP_004018415.1	SLMAP	97 kDa	ANOVA	0.97	Missing Value	Missing Value	Missing Value	6.21
sarcolemmal membrane-associated protein isoform X2	Ovis aries	XP_004006893.1	HEBP1	21 kDa	ANOVA	0.97	5.87	5.7	5.8	6.41
heme-binding protein 1	Ovis aries	XP_004004017.2	PSMD5	56 kDa	ANOVA	0.97	Missing Value	5.93	Missing Value	5.36
26S proteasome non-ATPase regulatory subunit 5	Ovis aries	XP_027829425.1	B3GLCT	56 kDa	ANOVA	0.98	6.01	5.83	Missing Value	Missing Value
beta-1,3-glucosyltransferase	Ovis aries	XP_027826981.1	STX18	30 kDa	ANOVA	0.98	6.09	5.52	5.9	5.47
syntaxin-18 isoform X2	Ovis aries	XP_027821040.1	ACS13	80 kDa	ANOVA	0.98	6.33	Missing Value	Missing Value	5.74
long-chain-fatty-acyl-CoA ligase 3	Ovis aries	XP_027815774.1	CHD11	46 kDa	ANOVA	0.98	6.85	7.03	6.91	7.08
chitinase domain-containing protein 1	Odocoileus virginianus texanus	XP_020756519.1	LOC110141932	48 kDa	ANOVA	0.98	Missing Value	6.08	6.15	6.04
heterogeneous nuclear ribonucleoprotein H-like	Capra hircus	XP_01292321.1	LOC102179426	50 kDa	ANOVA	0.98	8.06	7.92	7.95	7.8
tubulin alpha-1C chain	Ovis aries	XP_01204955.2	LOC10117269	66 kDa	ANOVA	0.98	Missing Value	Missing Value	Missing Value	6.81
craniofacial development protein 2	Ovis aries	XP_012005634.3	MECR	40 kDa	ANOVA	0.98	6.1	6.1	Missing Value	Missing Value
enoyl-[acyl-carrier-protein] reductase, mitochondrial isoform X2	Ovis aries	XP_011960575.2	ANXA7	50 kDa	ANOVA	0.98	Missing Value	6.44	Missing Value	5.92
annexin A7	Bos taurus	XP_005227728.1	SR4	19 kDa	ANOVA	0.98	7.65	7.63	7.54	7.62
translocan-associated protein subunit delta isoform X1	Ovis aries	XP_004010328.1	PKM	58 kDa	ANOVA	0.98	7.28	7.11	7.42	7.13
pyruvate kinase PKM isoform X2	Ovis aries	XP_004007077.1	POLDIP3	46 kDa	ANOVA	0.98	6.06	6.12	Missing Value	Missing Value
polymerase delta-interacting protein 3 isoform X1	Ovis aries	XP_004005800.1	PREB	46 kDa	ANOVA	0.98	Missing Value	Missing Value	5.92	5.73
prolactin regulatory element-binding protein isoform X1	Ovis aries	XP_004002637.2	FDP5	40 kDa	ANOVA	0.98	Missing Value	6.56	6.02	Missing Value
farnesyl pyrophosphate synthase	Ovis aries	NP_001138656.1	SLRP	12 kDa	ANOVA	0.98	5.46	5.68	5.62	Missing Value
SRA stem-loop-interacting RNA-binding protein, mitochondrial	Bos taurus	AAD33073.1	ENO1	47 kDa	ANOVA	0.98	7.99	7.68	7.84	7.69
alpha enolase	Ovis aries	XP_027826816.1	SAC1C	93 kDa	ANOVA	0.99	5.94	6	Missing Value	Missing Value
multifunctional protein ADE2 isoform X2	Ovis aries	XP_027813542.1	PAACM11	61 kDa	ANOVA	0.99	6.05	6.24	Missing Value	6.16
phosphatidylinositol phosphatase SA1 isoform X2	Odocoileus virginianus texanus	XP_020727988.1	IVD	53 kDa	ANOVA	0.99	Missing Value	Missing Value	Missing Value	6.67
isovaleryl-CoA dehydrogenase, mitochondrial isoform X2	Bos indicus	XP_019831842.1	PRDX6	25 kDa	ANOVA	0.99	6.71	6.42	6.48	6.52
peroxiredoxin-6	Ovis aries	XP_004022354.1	SF4	52 kDa	ANOVA	0.99	6.21	6.54	6.36	5.94
coagulation factor IX	Ovis aries	XP_012014303.2	FLC4A1	104 kDa	ANOVA	0.99	6.17	Missing Value	7.28	6.23
band 3 anion transport protein	Ovis aries	XP_004008300.1	LUM4	39 kDa	ANOVA	0.99	Missing Value	Missing Value	Missing Value	5.98
lumican	Ovis aries	XP_004003178.1	NDUF85	22 kDa	ANOVA	0.99	Missing Value	5.74	5.59	Missing Value
NADH dehydrogenase 1 beta subcomplex subunit 5, mitochondrial isoform X1	Ovis aries	NP_001263383.1	DDX21	87 kDa	ANOVA	0.99	Missing Value	Missing Value	Missing Value	5.98
nuclear RNA helicase 2	Ovis aries	NP_001119815.1	HEXA	60 kDa	ANOVA	0.99	6.11	6.13	Missing Value	Missing Value
beta-hexosaminidase subunit alpha precursor	Ovis aries	NP_001033711.1	ACLY	121 kDa	ANOVA	0.99	6.3	5.99	6.35	6.4
ATP-citrate synthase	Camelus ferus	EPY87691.1	-	91 kDa	ANOVA	0.99	Missing Value	Missing Value	Missing Value	6.61
glutamine-fructose-6-phosphate aminotransferase [isomerizing] 2	Homo sapiens	AAD33872.1	-	36 kDa	ANOVA	0.99	7.56	7.26	7.42	7.19
alpha-tubulin, partial	Ovis aries	XP_004022186.1	UBA1	118 kDa	ANOVA	1.00	Missing Value	6.75	6.34	6.28
ubiquitin-like modifier-activating enzyme 1	Ovis aries	XP_004018542.2	LOC101112427	19 kDa	ANOVA	1.00	Missing Value	Missing Value	5.72	Missing Value
cathelicidin-7	Ovis aries	XP_004015361.3	TOMM40	38 kDa	ANOVA	1.00	7.17	7.04	6.97	6.94
mitochondrial import receptor subunit TOM40 homolog	Ovis aries	XP_004013914.2	COLGALT2	73 kDa	ANOVA	1.00	Missing Value	6.54	6.13	6.35
procollagen galactosyltransferase 2	Ovis aries	XP_004013652.2	EPRS1	170 kDa	ANOVA	1.00	5.92	Missing Value	Missing Value	Missing Value
bifunctional glutamate/proline-tRNA ligase	Ovis aries	XP_004003269.2	PTX3	42 kDa	ANOVA	1.00	Missing Value	Missing Value	6.49	6.2
pentraxin-related protein PTX3	Ovis aries	NP_001123961.1	TAPPB	48 kDa	ANOVA	1.00	6	Missing Value	Missing Value	6.07
tapasin precursor	Ovis aries	XP_027835128.1	OAF	31 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
out at first protein homolog	Ovis aries	XP_027835651.1	LOC110141877	69 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
liver carboxylesterase-like	Ovis aries	XP_02783601.1	PTRM1	116 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
presenence protease, mitochondrial	Ovis aries	XP_02783718.1	TOR1AIP1	62 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
forixin-1A-interacting protein 1 isoform X1	Ovis aries	XP_027831601.1	WVA1	44 kDa	ANOVA	--	Missing Value	6.67	Missing Value	Missing Value
von Willebrand factor A domain-containing protein 1	Ovis aries	XP_027831367.1	PTGFRN	100 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
prostaglandin F2 receptor negative regulator	Ovis aries	XP_027830326.1	CERS2	45 kDa	ANOVA	--	Missing Value	6.53	Missing Value	Missing Value
ceramide synthase 2	Ovis aries	XP_027830105.1	FASN	274 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
fatty acid synthase	Ovis aries	XP_027830043.1	GAA	105 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	6.51
lysosomal alpha-glucosidase	Ovis aries	XP_027829492.1	PHGDH	56 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
D-3-phosphoglycerate dehydrogenase	Ovis aries	XP_027828737.1	MCMA4	94 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
DNA replication licensing factor MCM4	Ovis aries	XP_027824359.1	LOC101115115	53 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
platelet glycoprotein 4	Ovis aries	XP_027823724.1	EMG1	29 kDa	ANOVA	--	5.73	Missing Value	Missing Value	Missing Value
ribosomal RNA small subunit methyltransferase NEP1 isoform X1	Ovis aries	XP_027822531.1	TGOLN2	36 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
trans-Golgi network integral membrane protein 2	Ovis aries	XP_027822120.1	CRAT	71 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
carnitine O-acetyltransferase isoform X2	Ovis aries	XP_027821966.1	SEC16A	250 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
protein transport protein Sec16A isoform X1	Ovis aries	XP_027818922.1	HMG8B	23 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
high mobility group protein B3	Ovis aries	XP_027818540.1	AGS4H1	45 kDa	ANOVA	--	Missing Value	Missing Value	5.8	Missing Value
acyl ceramidase	Ovis aries	XP_027817520.1	MCMT7	81 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
DNA replication licensing factor MCM7 isoform X1	Ovis aries	XP_027816165.1	PAP52	70 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
bifunctional 3'-phosphoadenosine 5'-phosphosulfate synthase 2	Ovis aries	XP_027815764.1	RNH1	52 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
ribonuclease inhibitor isoform X1	Ovis aries	XP_027815397.1	LOC10560471	15 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
serum amyloid A protein-like	Ovis aries	XP_027814691.1	LOC106990117	43 kDa	ANOVA	--	Missing Value	6.07	Missing Value	Missing Value
BOLA class I histocompatibility antigen, alpha chain BL3-7-like isoform X4	Ovis aries	XP_027813689.1	ALDH1L1	99 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
cytosolic 10-formyltetrahydrofolate dehydrogenase	Ovis aries	XP_027813448.1	LOC101106719	196 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
laminin subunit beta-2 isoform X1	Ovis aries	XP_027812996.1	SEMA7A	75 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	6.24
semaphorin-7A	Ovis aries	XP_027812644.1	LOC101118990	27 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
glutathione S-transferase theta-3 isoform X3	Ovis aries	XP_027812608.1	SELENOM	16 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
selenoprotein M	Ovis aries	XP_027812464.1	SART3	109 kDa	ANOVA	--	Missing Value	6.68	Missing Value	Missing Value
protein NipSnap homolog 1 isoform X1	Ovis aries	XP_025147744.1	ESY72	107 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
squamous cell carcinoma antigen recognized by T-cells 3 isoform X2	Bubalus bubalis	XP_025134345.1	SNRNP40	43 kDa	ANOVA	--	Missing Value	Missing Value	5.88	Missing Value
extended synaptotagmin-2	Bubalus bubalis	XP_024848786.1	ANKA1	25 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
US small nuclear ribonucleoprotein 40 kDa protein isoform X1	Bos taurus	XP_02071954.1	ANKA1	39 kDa	ANOVA	--	Missing Value	6.23	Missing Value	Missing Value
alpha-S2-casein isoform X2	Odocoileus virginianus texanus	XP_019841967.1	TMX3	45 kDa	ANOVA	--	Missing Value	Missing Value	6.21	Missing Value
annexin A1	Bos indicus	XP_019834274.1	KARS1	71 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
histone H3.3C-like	Bos indicus	XP_019811827.1	TIMM8A	11 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
protein disulfide-isomerase TMX3	Bos indicus	XP_017920430.1	CBX1	25 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
lysine-tRNA ligase isoform X1	Capra hircus	XP_017917916.1	BLVRB	22 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
mitochondrial import inner membrane translocase subunit Tim8 A	Capra hircus	XP_017904043.1	PH3	80 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
chromobox protein homolog 1 isoform X1	Capra hircus	XP_017903215.1	LOC102183766	55 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
flavin reductase (NADPH)	Capra hircus	XP_017899991.1	PHPT1	14 kDa	ANOVA	--	Missing Value	5.87	Missing Value	Missing Value
prolyl 3-hydroxylase 3	Capra hircus	XP_017895343.1	SEPTIN2	41 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	5.87
keratin, type II cuticular Hb1	Capra hircus	XP_015096108.2	TMEM263	22 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	5.72
phosphohistidine phosphatase	Capra hircus	XP_014956364.2	PGR	96 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	6.29
septin-2	Vicugna pacos	XP_014954428.2	ACOX1	75 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
transmembrane protein 263	Ovis aries	XP_014954042.2	CPD	153 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
progesterone receptor isoform X1	Ovis aries	XP_014953991.2	MYO1D	116 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
peroxisomal acyl-coenzyme A oxidase 1 isoform X1	Ovis aries	XP_014952596.2	STNE2	799 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
carboxypeptidase D	Ovis aries	XP_014952070.2	ITN1	157 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	5.9
unconventional myosin-Id isoform X2	Ovis aries	XP_014952070.2	SEC31A	134 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	6.22
nesprin-2	Ovis aries	XP_014949854.1	RANBP2	340 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
kinectin isoform X1	Ovis aries	XP_013828650.2	SERPINA14	50 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
protein transport protein Sec31A isoform X1	Capra hircus	XP_013824066.2	LOC102184534	16 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	6.08
E3 SUMO-protein ligase RanBP2 isoform X1	Ovis aries	XP_012045061.1	GALNS	58 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
serpin peptidase inhibitor, clade A (alpha-1 antitrypsinase, antitrypsin), member 14 isoform 3	Ovis aries	XP_012041854.2	RNF213	591 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
cystatin-C	Ovis aries	XP_012035568.2	USO1	109 kDa	ANOVA	--	Missing Value	Missing Value	6.22	Missing Value
N-acetylgalactosamine-6-sulfatase isoform X3	Ovis aries	XP_012034241.2	MRLP22	18 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
E3 ubiquitin-protein ligase RNF213 isoform X1	Ovis aries	XP_011960734.1	SEC24C	121 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
general vesicular transport factor p115 isoform X1	Ovis aries	XP_011956976.2	FOLH1B	85 kDa	ANOVA	--	Missing Value	6.1	Missing Value	Missing Value
39S ribosomal protein L22, mitochondrial isoform X3	Ovis aries	XP_010965265.1	LOC105078415	41 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	5.87
protein transport protein Sec24C isoform X1	Camelus bactrianus	XP_010853328.1	AGK	50 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
glutamate carboxypeptid										

SUMO-activating enzyme subunit 1 isoform X1	Ovis aries	XP_004015383.1	SAE1	38 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
DRGK domain-containing protein 1	Ovis aries	XP_004014421.1	DRGK1	36 kDa	ANOVA	--	Missing Value	5.73	Missing Value	Missing Value
acyl-CoA synthetase family member 2, mitochondrial	Ovis aries	XP_004012812.2	ACSF2	68 kDa	ANOVA	--	Missing Value	Missing Value	5.92	Missing Value
perlestin isoform X1	Ovis aries	XP_004012160.2	POSTN	93 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
NHL repeat-containing protein 3	Ovis aries	XP_004012147.1	NHLRC3	39 kDa	ANOVA	--	Missing Value	6.35	Missing Value	Missing Value
protein PRRC1	Ovis aries	XP_004008706.1	PRRC1	46 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
ATP-dependent Clp protease proteolytic subunit, mitochondrial	Ovis aries	XP_004008625.1	CLPP	30 kDa	ANOVA	--	Missing Value	6.43	Missing Value	Missing Value
biliverdin reductase A	Ovis aries	XP_004008040.1	BLVRA	34 kDa	ANOVA	--	Missing Value	6.15	Missing Value	Missing Value
ATP-dependent 6-phosphofructokinase, muscle type	Ovis aries	XP_004006455.2	PFKM	94 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
premylcytosteine oxidase 1	Ovis aries	XP_004005853.2	PCYOX1	57 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
disintegrin and metalloproteinase domain-containing protein 17	Ovis aries	XP_004005725.1	ADAM17	93 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
protein lilegquad 3	Ovis aries	XP_004004971.1	TMBIM1	34 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
aldehyde oxidase	Ovis aries	XP_004004859.2	AOX1	148 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
nucleoporin NUP35	Ovis aries	XP_004004571.1	NUP35	35 kDa	ANOVA	--	Missing Value	5.91	Missing Value	Missing Value
fructose-1,6-bisphosphatase 1	Ovis aries	XP_004004141.1	FBP1	37 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	6.02
apolipoprotein A-II	Ovis aries	XP_004002742.1	APOA2	11 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	6.35
MHC class I molecule, partial	Ovis aries	SPC50556.1	-	40 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
anti-SARS-CoV-2 immunoglobulin light chain variable region, partial	Homo sapiens	QKK35531.1	-	12 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
Cytochrome P450C17	Ovis aries	Q29497.2	CYP17A1	57 kDa	ANOVA	--	Missing Value	5.67	Missing Value	Missing Value
Serum amyloid A protein	Ovis aries	P42819.1	SAA	13 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
Follicle-stimulating hormone receptor	Homo sapiens	P23945.3	FSHR	78 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
Superoxide dismutase [Cu-Zn]	Ovis aries	P09670.2	SOD1	16 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
Hemoglobin subunit beta-C(NA)	Ammotragus lervia	PQ2080.1	-	12 kDa	ANOVA	--	4.83	Missing Value	Missing Value	Missing Value
TRAP1, partial	Cervus elaphus hippelaphus	OWK11054.1	-	31 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
proteolipid protein 2	Bos taurus	NP_976239.1	PLP2	17 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
refoldin subunit 5	Bos taurus	NP_771157.1	PFNO5	17 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	5.74
adiponectin precursor	Ovis aries	NP_001295494.1	ADIPOQ	26 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
IgG receptor FcRn large subunit p51 precursor	Ovis aries	NP_001116875.1	FCGR2	39 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
mitochondrial import receptor subunit TOM6 homolog	Bos taurus	NP_001107190.1	TOMM6	8 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
delta(14)-sterol reductase LBR	Bos taurus	NP_001093790.1	LBR	71 kDa	ANOVA	--	Missing Value	5.8	Missing Value	Missing Value
refoldin subunit 1	Bos taurus	NP_001071530.1	PFDN1	14 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	5.81
syntaxin-7	Bos taurus	NP_001071332.1	STX7	30 kDa	ANOVA	--	Missing Value	6.16	Missing Value	Missing Value
protein FMC1 homolog	Bos taurus	NP_001070465.1	FMCL1	13 kDa	ANOVA	--	Missing Value	5.82	Missing Value	Missing Value
calcineurin B homologous protein 1	Bos taurus	NP_001069044.1	CHP1	22 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
glycogen phosphorylase, liver form	Bos taurus	NP_001068671.1	PYGL	97 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
mitochondrial import inner membrane translocase subunit Tim17-B	Bos taurus	NP_001039953.1	TIMM17B	18 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	6
minor histocompatibility antigen H13	Bos taurus	NP_001039589.2	HM13	42 kDa	ANOVA	--	5.97	5.95	Missing Value	Missing Value
regulator complex protein LAMTOR2	Bos taurus	NP_001029963.1	LAMTOR2	14 kDa	ANOVA	--	5.63	Missing Value	Missing Value	Missing Value
signal peptidase complex subunit 1	Bos taurus	NP_001029576.1	SPCS1	12 kDa	ANOVA	--	Missing Value	Missing Value	6.16	Missing Value
nuclear envelope phosphatase-regulatory subunit 1	Bos taurus	NP_001029475.1	CNEP1R1	14 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
lipid droplet-regulating VLDL assembly factor AUP1	Bos taurus	NP_001015555.1	AUP1	46 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
DNA replication licensing factor MCM3	Bos taurus	NP_001013604.2	MCM3	91 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
DNA replication licensing factor MCM6	Camelus ferus	EPY87703.1	-	136 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
Ig kappa chain V-II region RPM1 6410 precursor-like protein	Camelus ferus	EPY82054.1	-	40 kDa	ANOVA	--	Missing Value	Missing Value	6.21	Missing Value
tRNA-splicing ligase RtcB-like protein	Camelus ferus	EPY77446.1	-	98 kDa	ANOVA	--	5.76	Missing Value	Missing Value	Missing Value
Aspartate aminotransferase, cytoplasmic, partial	Bos mutus	ELR59015.1	-	47 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
TPA: CAP1 protein-like	Bos taurus	DAA23999.1	-	51 kDa	ANOVA	--	Missing Value	Missing Value	6.19	Missing Value
TPA: polybromo 1 isoform 2	Bos taurus	DAA17006.1	PB1	185 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
TPA: ER lumen protein retaining receptor 2	Bos taurus	DAA15085.1	KDEL2	24 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
solute carrier family 27 member 2, partial	Bos taurus	AKG52548.1	SLC27A2	63 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
DnaJ (Hsp40) homolog, subfamily C, member 3	Bos taurus	AAI26581.1	DNAJC3	58 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value
Derlin	Bos taurus	AAI02072.1	DERL2	13 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	6.28
Immunoglobulin kappa-1 light chain variable region, partial	Ovis aries	AAB94899.1	-	13 kDa	ANOVA	--	Missing Value	Missing Value	Missing Value	Missing Value

Table S2

List of differentially abundant proteins according to the diet and the dose of bisphenol S after global ANOVA analysis and chi square test

Heatmap Cluster	Protein Name	Species	Accession Number	Gene Name	Molecular Weight	Test	p-Value (ANOVA or Chi-square)	in R0 (detection rate %)	in R50 (detection rate %)	in WFO (detection rate %)	in WF50 (detection rate %)
C1	cadherin-6 isoform X2	Bos taurus	XP_024837107.1	CDH6	80 kDa	Chi-square	0.012	N.D. (0%)	7.55 (25%)	7.43 (25%)	7.75 (75%)
C1	bis(5'-adenosyl)-triphosphatase isoform X1	Ovis aries	XP_011954617.2	FHIT	17 kDa	Chi-square	0.012	N.D. (0%)	6.5 (50%)	5.76 (25%)	7.3 (100%)
C1	beta-glucuronidase	Ovis aries	XP_027817734.1	GUSB	74 kDa	Chi-square	0.002	N.D. (0%)	6.88 (100%)	6.18 (50%)	6.6 (100%)
C1	sulfhydryl oxidase 2 isoform X1	Capra hircus	XP_017911573.1	LOC102189594	87 kDa	Chi-square	0.003	N.D. (0%)	7.21 (75%)	6.25 (25%)	6.34 (100%)
C1	splicing factor 3B subunit 5	Bos taurus	NP_001020521.1	SF3B5	10 kDa	Chi-square	0.028	N.D. (0%)	6.56 (75%)	6.62 (75%)	6.57 (75%)
C1	vesicle-associated membrane protein-associated protein B/C	Capra hircus	XP_017913111.1	VAPB	27 kDa	ANOVA	0,00037	6.54	7.36	7.38	7.52
C1	transthyretin precursor	Ovis aries	NP_001009800.1	TTR	16 kDa	ANOVA	0,0028	8.27	8.44	8.39	8.8
C1	pre-B-cell leukemia transcription factor-interacting protein 1 isoform X1	Ovis aries	XP_027831619.1	PBXIP1	90 kDa	ANOVA	0,0056	6.24	6.74	7.13	7.13
C1	ITIH2, partial	elaphus hippe	OWK03472.1	-	103 kDa	ANOVA	0,0057	7.15	7.31	7.9	7.88
C1	ras-related protein Rab-5C	Bos taurus	NP_001029915.1	RAB5C	23 kDa	ANOVA	0,0076	6.42	6.89	6.99	6.99
C1	complement C1q subcomponent subunit C	Ovis aries	XP_027820684.1	C1QC	94 kDa	ANOVA	0,0085	Missing Value	7.26	7.21	6.94
C1	vitronectin isoform X1	Ovis aries	XP_027831040.1	VTN	54 kDa	ANOVA	0,011	7.92	8.17	8.06	8.22
C1	vitronectin	Capra hircus	XP_005693309.1	VTN	54 kDa	ANOVA	0,011	7.91	8.15	8.05	8.17
C1	TPA: inter-alpha globulin inhibitor H2 polypeptide	Bos taurus	DAA23635.1	ITIH2	106 kDa	ANOVA	0,011	7.48	7.58	8.08	8.05
C1	ras-related protein Rab-5A isoform X1	Ovis aries	XP_014947086.1	RAB5A	24 kDa	ANOVA	0,012	6.37	6.71	6.87	6.81
C1	ras-related protein Rab-5B	Bos taurus	NP_001193120.1	RAB5B	24 kDa	ANOVA	0,017	6.37	6.71	6.86	6.88
C1	glutamine amidotransferase-like class 1 domain-containing protein 3A, mitochondr	Ovis aries	NP_001156032.1	GATD3	29 kDa	ANOVA	0,017	6.27	6.82	6.75	6.91
C1	palmitoyl-protein thioesterase 1	Ovis aries	XP_004001885.2	PPT1	34 kDa	ANOVA	0,018	6.46	6.95	6.9	6.8
C1	receptor expression-enhancing protein 5	Ovis aries	XP_014952182.2	REEP5	21 kDa	ANOVA	0,019	6.2	6.97	6.99	7.19
C1	inter-alpha-trypsin inhibitor heavy chain H2	Ovis aries	XP_004014227.2	ITIH2	106 kDa	ANOVA	0,020	7.58	7.61	8.18	8.1
C1	non-specific lipid-transfer protein isoform X2	ndicus x Bos t	XP_027393023.1	SCP2	52 kDa	ANOVA	0,030	5.85	6.53	6.69	6.94
C1	histidine-rich glycoprotein	Ovis aries	XP_004003109.3	HRG	62 kDa	ANOVA	0,031	7.45	7.7	7.12	7.63
C1	immunoglobulin superfamily DCC subclass member 4	Ovis aries	XP_027827301.1	IGDCC4	134 kDa	ANOVA	0,034	Missing Value	6.58	6.25	6.51
C1	dynein light chain 1, cytoplasmic-like	Bos indicus	XP_019812000.1	LOC109555509	10 kDa	ANOVA	0,037	6.41	6.84	6.83	6.85
C1	NADH dehydrogenase 1 alpha subcomplex subunit 7	Ovis aries	XP_004008614.1	NDUFA7	13 kDa	ANOVA	0,037	5.49	6.16	6.19	6.59
C1	NADPH-cytochrome P450 reductase isoform X1	Ovis aries	XP_027817441.1	LOC101115252	87 kDa	ANOVA	0,038	6.82	7.51	7.5	7.36
C1	electron transfer flavoprotein subunit beta isoform X2	us virginianus	XP_020755939.1	ETFB	28 kDa	ANOVA	0,038	7.21	7.7	7.73	7.78
C1	electron transfer flavoprotein subunit beta isoform X1	Ovis aries	XP_004015435.3	ETFB	28 kDa	ANOVA	0,038	7.21	7.7	7.73	7.78
C1	ras-related protein Rab-8A	Bos taurus	NP_001098951.1	RAB8A	24 kDa	ANOVA	0,041	7.09	7.33	7.52	7.68
C1	glutaredoxin-related protein 5, mitochondrial	Ovis aries	XP_004018030.1	GLRX5	17 kDa	ANOVA	0,046	6.54	7.05	6.95	7.25
C1	vitronectin precursor	Bos taurus	NP_001030222.1	VTN	54 kDa	ANOVA	0,046	7.71	7.92	7.72	7.8
C1	alpha-2-macroglobulin receptor-associated protein isoform X2	Ovis aries	XP_027827072.1	LRPAP1	42 kDa	ANOVA	0,047	6.68	7.09	7.34	7.19
C1	40S ribosomal protein S16 isoform 1	Homo sapiens	NP_001011.1	RPS16	16 kDa	ANOVA	0,047	7.18	7.4	7.53	7.77
C1	microsomal glutathione S-transferase 1	Ovis aries	XP_004006867.1	MGST1	18 kDa	ANOVA	0,049	5.58	6.71	6.57	7.04
C2	aflatoxin B1 aldehyde reductase member 2	Ovis aries	XP_027821430.1	AKR7A2	41 kDa	Chi-square	0.007	6.76 (25%)	7.03 (100%)	N.D. (0%)	7.21 (100%)
C2	squalene synthase isoform X2	Ovis aries	XP_004004500.1	FDFT1	48 kDa	Chi-square	0.012	6.56 (25%)	6.63 (100%)	N.D. (0%)	6.59 (50%)
C2	inactive hydroxysteroid dehydrogenase-like protein 1	Bos taurus	NP_001092341.1	HSDL1	37 kDa	Chi-square	0.003	6.17 (75%)	6.21 (100%)	N.D. (0%)	6.76 (75%)
C2	SLC35A4 upstream open reading frame protein	ubalus bubali	XP_025148374.1	LOC112586898	11 kDa	Chi-square	0.012	5.41 (25%)	6.44 (75%)	N.D. (0%)	6.76 (75%)
C2	transportin-2 isoform X4	Ovis aries	XP_027825368.1	TNPO2	103 kDa	Chi-square	0.003	6.32 (25%)	6.44 (75%)	N.D. (0%)	6.82 (100%)
C2	nucleoprotein TPR	Capra hircus	XP_005691036.2	TPR	275 kDa	Chi-square	0.012	6.39 (25%)	6.87 (75%)	N.D. (0%)	6.02 (75%)
C3	dermcidin isoform 1 preproprotein	Homo sapiens	NP_444513.1	DCD	11 kDa	Chi-square	0.046	5.47 (50%)	N.D. (0%)	5.94 (25%)	6.41 (75%)
C3	complement factor H-related protein 2	Ovis aries	XP_004013976.1	LOC101123223	31 kDa	Chi-square	0.028	6.45 (50%)	N.D. (0%)	6.05 (25%)	7.15 (75%)
C3	apolipoprotein A-I	Ovis aries	XP_011950887.2	APOA1	30 kDa	ANOVA	0,0019	9.1	9.11	9.13	9.53
C3	tetranectin precursor	Bos taurus	NP_001039677.1	CLEC3B	22 kDa	ANOVA	0,022	7.07	7.13	6.97	7.47
C3	protein AMBP isoform X2	Capra hircus	XP_005684398.1	AMBP	39 kDa	ANOVA	0,033	6.97	7.07	7.14	7.53
C4	nicastatin isoform X2	Ovis aries	XP_012039753.2	NCSTN	67 kDa	Chi-square	0.028	6.58 (50%)	6.8 (75%)	6.68 (75%)	N.D. (0%)
C4	prolyl 4-hydroxylase subunit alpha-2 isoform X1	Ovis aries	XP_004008688.1	P4HA2	61 kDa	Chi-square	0.005	7.09 (75%)	6.8 (100%)	7.13 (100%)	N.D. (0%)
C4	reticulon-4 isoform X1	Capra hircus	XP_017910740.1	RTN4	130 kDa	Chi-square	0.028	N.D. (0%)	7.14 (75%)	7.05 (75%)	6.16 (50%)
C4	thiosulfate sulfurtransferase	Ovis aries	XP_014950344.2	TST	33 kDa	Chi-square	0.003	6.99 (75%)	6.91 (100%)	5.87 (25%)	N.D. (0%)
C4	lipopolysaccharide-binding protein	Ovis aries	XP_004014615.1	LBP	53 kDa	ANOVA	0,0012	7.28	7.9	7.14	6.69
C4	long-chain fatty acid transport protein 1	Ovis aries	XP_027825247.1	SLC27A1	71 kDa	ANOVA	0,0066	6.6	7.16	6.59	6.52
C4	immunoglobulin heavy chain variable region, partial	Ovis aries	CAD45049.1	-	12 kDa	ANOVA	0,022	7.35	7.64	7.36	6.92
C4	glucosidase 2 subunit beta	Ovis aries	XP_027825495.1	PRKCSH	60 kDa	ANOVA	0,023	7.22	7.94	7.91	7.53
C4	zona pellucida sperm-binding protein 4	Ovis aries	XP_027818021.1	ZP4	59 kDa	ANOVA	0,025	6.72	7.08	7.07	Missing Value
C4	protein ERGIC-53 isoform X1	Ovis aries	XP_014959285.2	LMAN1	58 kDa	ANOVA	0,025	6.51	7.36	7.04	6.54
C4	GDP-fucose protein O-fucosyltransferase 2 isoform X1	Ovis aries	XP_027816944.1	POFUT2	50 kDa	ANOVA	0,030	7.06	7.49	6.97	6.94
C4	complement component C7	Ovis aries	XP_004017066.2	C7	93 kDa	ANOVA	0,039	7.65	7.78	7.31	7.55
C4	Ig mu chain C region membrane-bound form, partial	Ovis aries	XP_027813089.1	LOC101113211	54 kDa	ANOVA	0,040	7.82	7.79	7.79	7.41
C4	C4b-binding protein alpha chain isoform X1	Ovis aries	XP_012042366.2	LOC101119740	69 kDa	ANOVA	0,050	7.86	7.9	7.6	7.44

Table S2

List of differentially abundant proteins between 0 and 50 µg/kg/day of BP in restricted (R) ewes

Protein Name	Species	Accession Number	Gene Symbol	Molecular Weight	ANOVA				Chi-square	Average	
					p-value	Log2 Fold change corrected R50:R0	Corrected fold-change R50:R0	Corrected fold-change R0:R50	p-value	R0 (detection rate %)	R50 (detection rate %)
afatoxin B1 aldehyde reductase member 2	Ovis aries	XP_027821430.1	AKR7A2	41 kDa	-	-	-	-	0.007	6.76 (25%)	7.03 (100%)
beta-glucuronidase	Ovis aries	XP_027817734.1	GUSB	74 kDa	-	-	-	-	0.00194577	N.D. (0%)	6.88 (100%)
inactive hydroxysteroid dehydrogenase-like protein 1	Bos taurus	NP_001092341.1	HSDL1	37 kDa	-	-	-	-	0.003	6.17 (75%)	6.21 (100%)
complement factor H-related protein 2	Ovis aries	XP_004013976.1	LOC101123223	31 kDa	-	-	-	-	0.028	6.45 (50%)	N.D. (0%)
sulfhydryl oxidase 2 isoform X1	Capra hircus	XP_017911573.1	LOC102189594	87 kDa	-	-	-	-	0.003	N.D. (0%)	7.21 (75%)
SLC35A4 upstream open reading frame protein	Bubalus bubalis	XP_025148374.1	LOC112586898	11 kDa	-	-	-	-	0.012	5.41 (25%)	6.44 (75%)
reticulon-4 isoform X1	Capra hircus	XP_017910740.1	RTN4	130 kDa	-	-	-	-	0.028	N.D. (0%)	7.14 (75%)
splicing factor 3B subunit 5	Bos taurus	NP_001020521.1	SF3B5	10 kDa	-	-	-	-	0.028	N.D. (0%)	6.56 (75%)
transportin-2 isoform X4	Ovis aries	XP_027825368.1	TNPO2	103 kDa	-	-	-	-	0.003	6.32 (25%)	6.44 (75%)
nucleoprotein TPR	Capra hircus	XP_005691036.2	TPR	275 kDa	-	-	-	-	0.012	6.39 (25%)	6.87 (75%)
complement C1q subcomponent subunit C	Ovis aries	XP_027820684.1	C1QC	94 kDa	0.012	Reference Missing	-	-	-	6.44	7.32
gap junction alpha-1 protein	Ovis aries	XP_004011208.1	GJA1	43 kDa	0.041	2.06	4.17	0.24	-	7.60	8.10
glutaredoxin-related protein 5, mitochondrial	Ovis aries	XP_004018030.1	GLRX5	17 kDa	0.034	1.84	3.58	0.28	-	6.48	7.12
PREDICTED: glutathione peroxidase 7	Capra hircus	XP_017899689.1	GPX7	21 kDa	0.031	3.96	15.56	0.06	-	6.49	7.28
acetylactate synthase-like protein	Ovis aries	XP_004008513.1	ILVBL	68 kDa	0.044	3.95	15.45	0.06	-	6.36	7.11
Inhibin alpha chain	Capra hircus	AEP40507.1	INHA	39 kDa	0.0089	1.43	2.69	0.37	-	7.90	8.25
clusterin	Ovis aries	XP_004004480.1	LOC101113728	51 kDa	0.047	1.33	2.51	0.40	-	8.00	8.32
NADPH--cytochrome P450 reductase isoform X1	Ovis aries	XP_027817441.1	LOC101115252	87 kDa	0.028	2.33	5.03	0.20	-	6.99	7.64
PREDICTED: LOW QUALITY PROTEIN: ADP-ribosylation factor 4-like, partial	Bos mutus	XP_014337480.1	LOC102268931	29 kDa	0.03	2.91	7.52	0.13	-	5.53	6.39
matrix Gla protein	Ovis aries	XP_004006882.1	MGP	12 kDa	0.018	1.58	2.99	0.33	-	6.81	7.24
microsomal glutathione S-transferase 1	Ovis aries	XP_004006867.1	MGST1	18 kDa	0.025	4.06	16.68	0.06	-	5.84	6.71
mannose-P-dolichol utilization defect 1 protein	Ovis aries	XP_004012714.2	MPDU1	27 kDa	0.015	1.8	3.48	0.29	-	6.33	6.94
ORM1-like protein 3	Bos taurus	NP_001069835.1	ORMDL3	17 kDa	0.02	2.43	5.39	0.19	-	5.54	6.10
GDP-fucose protein O-fucosyltransferase 2 isoform X1	Ovis aries	XP_027816944.1	POFUT2	50 kDa	0.045	1.51	2.85	0.35	-	7.02	7.49
palmitoyl-protein thioesterase 1	Ovis aries	XP_004001885.2	PPT1	34 kDa	0.019	1.69	3.23	0.31	-	6.60	6.94
PRA1 family protein 2	Bos taurus	NP_001039474.1	PRAF2	19 kDa	0.023	2.04	4.11	0.24	-	6.13	6.76
ras-related protein Rab-5A isoform X1	Ovis aries	XP_014947086.1	RAB5A	24 kDa	0.026	1.29	2.45	0.41	-	6.47	6.81
ras-related protein Rab-5B	Bos taurus	NP_001193120.1	RAB5B	24 kDa	0.027	1.29	2.45	0.41	-	6.48	6.81
ras-related protein Rab-5C	Bos taurus	NP_001029915.1	RAB5C	23 kDa	0.029	1.63	3.10	0.32	-	6.53	6.95
retinol dehydrogenase 11	Ovis aries	XP_012037274.1	RDH11	37 kDa	0.019	1.37	2.58	0.39	-	6.54	6.97
LOW QUALITY PROTEIN: long-chain fatty acid transport protein 1	Ovis aries	XP_027825247.1	SLC27A1	71 kDa	0.026	1.92	3.78	0.26	-	6.52	7.17
thioredoxin-related transmembrane protein 1	Ovis aries	XP_004010572.2	TMX1	32 kDa	0.026	1.21	2.31	0.43	-	6.48	6.93
PREDICTED: vesicle-associated membrane protein-associated protein B/C	Capra hircus	XP_017913111.1	VAPB	27 kDa	0.0093	3	8.00	0.13	-	6.69	7.37
PREDICTED: vitamin K epoxide reductase complex subunit 1 isoform X1	Capra hircus	XP_017895520.1	VKORC1	18 kDa	0.04	1.42	2.68	0.37	-	6.04	6.47

Table S2

List of differentially abundant proteins between 0 and 50 µg/kg/day of BP in well-fed (WF) ewes

Protein Name	Species	Accession Number	Gene Symbol	Molecular Weight	ANOVA		Corrected fold-change WF50:WF0	Corrected fold-change WF0:WF50	Chi-square p-value	Average	
					p-value	Log2 Fold change corrected WF50:WF0				WF0 (detection rate %)	WF50 (detection rate %)
aflatoxin B1 aldehyde reductase member 2	Ovis aries	XP_027821430.1	AKR7A2	41 kDa	-	-	-	-	0.007	N.D. (0%)	7.21 (100%)
beta-glucuronidase	Ovis aries	XP_027817734.1	GUSB	74 kDa	-	-	-	-	0.002	6.18 (50%)	6.6 (100%)
inactive hydroxysteroid dehydrogenase-like protein 1	Bos taurus	NP_001092341.1	HSDL1	37 kDa	-	-	-	-	0.003	N.D. (0%)	6.76 (75%)
sulfhydryl oxidase 2 isoform X1	Capra hircus	XP_017911573.1	LOC102189594	87 kDa	-	-	-	-	0.003	6.25 (25%)	6.34 (100%)
SLC35A4 upstream open reading frame protein	Bubalus bubalis	XP_025148374.1	LOC112586898	11 kDa	-	-	-	-	0.012	N.D. (0%)	6.76 (75%)
nicastrin isoform X2	Ovis aries	XP_012039753.2	NCSTN	67 kDa	-	-	-	-	0.028	6.68 (75%)	N.D. (0%)
prolyl 4-hydroxylase subunit alpha-2 isoform X1	Ovis aries	XP_004008688.1	P4HA2	61 kDa	-	-	-	-	0.005	7.13 (100%)	N.D. (0%)
transportin-2 isoform X4	Ovis aries	XP_027825368.1	TNPO2	103 kDa	-	-	-	-	0.003	N.D. (0%)	6.82 (100%)
nucleoprotein TPR	Capra hircus	XP_005691036.2	TPR	275 kDa	-	-	-	-	0.012	N.D. (0%)	6.02 (75%)
DNA-(apurinic or apyrimidinic site) lyase	Ovis aries	XP_004010439.2	APEX1	36 kDa	0.021	1	2.00	0.5	-	6.20	6.55
apolipoprotein A-I	Ovis aries	XP_011950887.2	APOA1	30 kDa	0.021	1.23	2.35	0.43	-	9.07	9.47
apolipoprotein A-IV	Ovis aries	XP_004016096.1	APOA4	43 kDa	0.045	1.85	3.61	0.28	-	7.84	8.35
branched-chain-amino-acid aminotransferase, mitochondrial isoform X1	Ovis aries	XP_027834382.1	BCAT2	45 kDa	0.024	1.74	3.34	0.30	-	7.35	7.74
tetranectin precursor	Bos taurus	NP_001039677.1	CLEC3B	22 kDa	0.025	1.63	3.10	0.32	-	6.90	7.40
endothelin-converting enzyme 1 isoform X1	Ovis aries	XP_027821363.1	ECE1	91 kDa	0.049	-2.37	0.19	5.17	-	7.43	6.94
histidine-rich glycoprotein	Ovis aries	XP_004003109.3	HRG	62 kDa	0.022	1.7	3.25	0.31	-	7.16	7.63
lipopolysaccharide-binding protein	Ovis aries	XP_004014615.1	LBP	53 kDa	0.029	-1.55	0.34	2.93	-	7.17	6.59
lamin	Ovis aries	XP_027832136.1	LMNA	74 kDa	0.0094	-2.82	0.14	7.06	-	7.32	6.62
lamin-B1	Ovis aries	XP_004008711.1	LMNB1	66 kDa	0.049	-1.57	0.34	2.97	-	7.84	7.45
glutathione S-transferase P	Capra hircus	XP_017898539.1	LOC100861197	24 kDa	0.022	1.73	3.32	0.30	-	7.23	7.61
protein disulfide-isomerase A4	Ovis aries	XP_027824715.1	PDIA4	73 kDa	0.043	-1.32	0.40	2.50	-	8.25	7.91
TPA: profilin 1-like	Bos taurus	DAA33226.1	PFN1	15 kDa	0.038	1.88	3.68	0.27	-	6.21	6.87
retinol-binding protein 4	Ovis aries	XP_027815955.1	RBP4	23 kDa	0.035	2.75	6.73	0.15	-	6.87	7.47
SUN domain-containing protein 2 isoform X1	Ovis aries	XP_027823918.1	SUN2	88 kDa	0.046	-2.15	0.23	4.44	-	7.44	6.94
transthyretin precursor	Ovis aries	NP_001009800.1	TTR	16 kDa	0.04	1.3	2.46	0.41	-	8.36	8.78
zona pellucida sperm-binding protein 3	Ovis aries	XP_004021030.2	ZP3	47 kDa	0.021	-3.43	0.09	10.78	-	7.20	6.69

Table S2

List of differentially abundant proteins between restricted (R) and well-fed (WF) ewes exposed to 0 µg/kg/day of BP in well-fed ewes (overabundant in R0 than WF0)

Protein Name	Species	Accession Number	Gene Symbol	Molecular Weight	R0 vs S0		Corrected fold-change WF0:R0	Corrected fold-change R0:WF0	Chi-square	Average	
					p-value	Log2 Fold change WF0:R0				p-value	R0 (detection rate %)
aflatoxin B1 aldehyde reductase member 2	Ovis aries	XP_027821430.1	AKR7A2	41 kDa	-	-	-	-	0.007	6.76 (25%)	N.D. (0%)
cadherin-6 isoform X2	Bos taurus	XP_024837107.1	CDH6	80 kDa	-	-	-	-	0.012	N.D. (0%)	7.43 (25%)
dermcidin isoform 1 preproprotein	Homo sapiens	NP_444513.1	DCD	11 kDa	-	-	-	-	0.046	5.47 (50%)	5.94 (25%)
squalene synthase isoform X2	Ovis aries	XP_004004500.1	FDFT1	48 kDa	-	-	-	-	0.012	6.56 (25%)	N.D. (0%)
bis(5'-adenosyl)-triphosphatase isoform X1	Ovis aries	XP_011954617.2	FHIT	17 kDa	-	-	-	-	0.012	N.D. (0%)	5.76 (25%)
reticulon-4 isoform X1	Capra hircus	XP_017910740.1	RTN4	130 kDa	-	-	-	-	0.028	N.D. (0%)	7.05 (75%)
splicing factor 3B subunit 5	Bos taurus	NP_001020521.1	SF3B5	10 kDa	-	-	-	-	0.028	N.D. (0%)	6.62 (75%)
thiosulfate sulfurtransferase	Ovis aries	XP_014950344.2	TST	33 kDa	-	-	-	-	0.003	6.99 (75%)	5.87 (25%)
alpha globin chain	Ovis aries	CAA49750.1	-	15 kDa	0.033	2.25	4.76	0.21	-	8.87	9.62
alpha globin	Homo sapiens	CAA23749.1	-	14 kDa	0.029	2.9	7.46	0.13	-	7.42	7.95
ITIH2, partial	Cervus elaphus hippelaphus	OWK03472.1	-	103 kDa	0.015	2.54	5.82	0.17	-	7.35	7.95
apolipoprotein D	Ovis aries	XP_004003075.1	APOD	24 kDa	0.027	-1	0.50	2.00	-	6.86	6.73
electron transfer flavoprotein subunit beta isoform X1	Ovis aries	XP_004015435.3	ETFB	28 kDa	0.047	1.73	3.32	0.30	-	7.27	7.79
Adrenodoxin	Ovis aries	P29330.2	FDX1	14 kDa	0.017	2.41	5.31	0.19	-	6.20	6.93
glutaredoxin-related protein 5, mitochondrial	Ovis aries	XP_004018030.1	GLRX5	17 kDa	0.029	1.4	2.64	0.38	-	6.51	7.04
histone H1.2	Ovis aries	XP_004019136.2	H1-2	21 kDa	0.045	2.19	4.56	0.22	-	8.74	9.46
histone H1.5	Camelus dromedarius	XP_010973014.2	H1-5	23 kDa	0.048	2.27	4.82	0.21	-	8.56	9.30
hemoglobin subunit alpha	Ovis canadensis nelsoni	QLJ83449.1	HBA-T1	15 kDa	0.03	2.32	4.99	0.20	-	8.87	9.62
Hemoglobin subunit beta	Ovis aries	P02075.2	HBB	16 kDa	0.023	2.39	5.24	0.19	-	9.11	9.89
inter-alpha-trypsin inhibitor heavy chain H2	Ovis aries	XP_004014227.2	ITIH2	106 kDa	0.017	2.01	4.03	0.25	-	7.70	8.19
Kininogen-1	Bos taurus	P01044.1	KNG1	69 kDa	0.019	1.01	2.01	0.50	-	6.99	7.33
histone H1.3	Ovis aries	XP_011956523.2	LOC101109397	22 kDa	0.042	2.19	4.56	0.22	-	8.72	9.44
alpha-2-macroglobulin receptor-associated protein isoform X2	Ovis aries	XP_027827072.1	LRPAP1	42 kDa	0.014	2.2	4.59	0.22	-	6.71	7.41
matrix Gla protein	Ovis aries	XP_004006882.1	MGP	12 kDa	0.0031	1.47	2.77	0.36	-	6.80	7.09
mannose-P-dolichol utilization defect 1 protein	Ovis aries	XP_004012714.2	MPDU1	27 kDa	0.026	2.02	4.06	0.25	-	6.38	6.93
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 7	Ovis aries	XP_004008614.1	NDUFA7	13 kDa	0.028	2.48	5.58	0.18	-	5.76	6.29
pre-B-cell leukemia transcription factor-interacting protein 1 isoform X1	Ovis aries	XP_027831619.1	PBXIP1	90 kDa	0.019	3.04	8.22	0.12	-	6.30	7.10
palmitoyl-protein thioesterase 1	Ovis aries	XP_004001885.2	PPT1	34 kDa	0.022	1.51	2.85	0.35	-	6.61	6.95
peroxiredoxin-2	Ovis aries	NP_001159672.1	PRDX2	22 kDa	0.0076	1.46	2.75	0.36	-	7.50	8.02
glucosidase 2 subunit beta	Ovis aries	XP_027825495.1	PRKCSH	60 kDa	0.028	2.37	5.17	0.19	-	7.37	8.02
ras-related protein Rab-5B	Bos taurus	NP_001193120.1	RAB5B	24 kDa	0.0045	1.69	3.23	0.31	-	6.49	6.93
ras-related protein Rab-5C	Bos taurus	NP_001029915.1	RAB5C	23 kDa	0.0091	1.94	3.84	0.26	-	6.54	7.07
receptor expression-enhancing protein 5	Ovis aries	XP_014952182.2	REEP5	21 kDa	0.023	2.73	6.63	0.15	-	6.23	7.02
transmembrane protein 256	Ovis aries	XP_004012698.2	TMEM256	12 kDa	0.039	1.01	2.01	0.50	-	6.25	6.67
vesicle-associated membrane protein-associated protein B/C	Capra hircus	XP_017913111.1	VAPB	27 kDa	0.0057	2.92	7.57	0.13	-	6.71	7.46
zona pellucida sperm-binding protein 3	Ovis aries	XP_004021030.2	ZP3	47 kDa	0.011	2.5	5.66	0.18	-	6.75	7.27
Hemoglobin subunit beta-A	Bos javanicus	P04346.1	-	16 kDa	0.029	1.89	3.71	0.27	-	8.74	9.35

Table S2

List of differentially abundant proteins between restricted (R) and well-fed (WF) ewes exposed to 50 µg/kg/day of BP in well-fed ewes (overabundant in R50 than WF50)

Protein Name	Species	Accession Number	Gene Symbol	Molecular Weight	R50 vs WF50				Chi-square	Average	
					p-value	Log2 Fold change WF50:R50	Corrected fold-change WF50:R50	Corrected fold-change R50:WF50		p-value	R50 (detection rate %)
cadherin-6 isoform X2	Bos taurus	XP_024837107.1	CDH6	80 kDa	-	-	-	-	0.012	7.55 (25%)	7.75 (75%)
dermcidin isoform 1 preproprotein	Homo sapiens	NP_444513.1	DCD	11 kDa	-	-	-	-	0.046	N.D. (0%)	6.41 (75%)
squalene synthase isoform X2	Ovis aries	XP_004004500.1	FDFT1	48 kDa	-	-	-	-	0.012	6.63 (100%)	6.59 (50%)
bis(5'-adenosyl)-triphosphatase isoform X1	Ovis aries	XP_011954617.2	FHIT	17 kDa	-	-	-	-	0.012	6.5 (50%)	7.3 (100%)
complement factor H-related protein 2	Ovis aries	XP_004013976.1	LOC101123223	31 kDa	-	-	-	-	0.028	N.D. (0%)	7.15 (75%)
nicastrin isoform X2	Ovis aries	XP_012039753.2	NCSTN	67 kDa	-	-	-	-	0.028	6.8 (75%)	N.D. (0%)
prolyl 4-hydroxylase subunit alpha-2 isoform X1	Ovis aries	XP_004008688.1	P4HA2	61 kDa	-	-	-	-	0.005	6.8 (100%)	N.D. (0%)
thiosulfate sulfurtransferase	Ovis aries	XP_014950344.2	TST	33 kDa	-	-	-	-	0.003	6.91 (100%)	N.D. (0%)
PREDICTED: ADP-dependent glucokinase isoform X1	Capra hircus	XP_017910167.1	ADPGK	54 kDa	0.0057	-3.27	0.10	9.65	-	7.04	6.30
aldehyde dehydrogenase, mitochondrial	Ovis aries	XP_004017458.1	ALDH2	57 kDa	0.043	-1.53	0.35	2.89	-	8.24	7.87
apolipoprotein A-I	Ovis aries	XP_011950887.2	APOA1	30 kDa	0.0075	1.31	2.48	0.40	-	8.93	9.38
ATP synthase subunit alpha, mitochondrial	Ovis aries	XP_004020569.1	ATP5F1A	60 kDa	0.022	-1.59	0.33	3.01	-	8.75	8.36
ATP synthase subunit beta, mitochondrial	Ovis aries	XP_004006621.1	ATP5F1B	56 kDa	0.016	-1.45	0.37	2.73	-	8.96	8.55
branched-chain-amino-acid aminotransferase, mitochondrial isoform X1	Ovis aries	XP_027834382.1	BCAT2	45 kDa	0.042	1.99	3.97	0.25	-	7.11	7.67
complement C1s subcomponent	Ovis aries	XP_004006966.1	C1S	78 kDa	0.017	-1.12	0.46	2.17	-	6.32	6.00
calreticulin	Ovis aries	XP_004008533.1	CALR	48 kDa	0.026	-1.79	0.29	3.46	-	8.65	8.10
dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa subunit	Ovis aries	XP_004005208.2	DDOST	49 kDa	0.0058	-1.25	0.42	2.38	-	8.17	7.79
peroxisomal bifunctional enzyme	Ovis aries	XP_027813339.1	EHHADH	80 kDa	0.023	-3.28	0.10	9.71	-	6.81	6.21
NADPH:adrenodoxin oxidoreductase, mitochondrial	Ovis aries	XP_027829849.1	FDXR	54 kDa	0.05	-1.34	0.40	2.53	-	7.57	7.08
fibrinogen beta chain	Ovis aries	XP_004017233.2	FGB	57 kDa	0.013	-1.18	0.44	2.27	-	10.29	9.95
fumarate hydratase, mitochondrial	Bos taurus	NP_001069271.1	FH	55 kDa	0.031	-1.04	0.49	2.06	-	7.74	7.53
fibronectin isoform X11	Ovis aries	XP_027820957.1	FN1	249 kDa	0.014	-2.22	0.21	4.66	-	9.65	9.14
heterochromatin protein 1-binding protein 3 isoform X1	Ovis aries	XP_014949207.1	HP1BP3	61 kDa	0.0043	-2.83	0.14	7.11	-	7.14	6.60
basement membrane-specific heparan sulfate proteoglycan core protein	Ovis aries	XP_027821348.1	HSPG2	469 kDa	0.014	-2.18	0.22	4.53	-	8.10	7.45
acetolactate synthase-like protein	Ovis aries	XP_004008513.1	ILVBL	68 kDa	0.037	-2.79	0.14	6.92	-	6.97	6.40
lipopolysaccharide-binding protein	Ovis aries	XP_004014615.1	LBP	53 kDa	0.00095	-4.02	0.06	16.22	-	7.79	6.54
protein ERGIC-53 isoform X1	Ovis aries	XP_014959285.2	LMAN1	58 kDa	0.018	-2.76	0.15	6.77	-	7.26	6.49
lamin-B1	Ovis aries	XP_004008711.1	LMNB1	66 kDa	0.022	-1.83	0.28	3.56	-	7.89	7.38
Ig mu chain C region membrane-bound form, partial	Ovis aries	XP_027813089.1	LOC101113211	54 kDa	0.043	-1.23	0.43	2.35	-	7.68	7.38
inhibitor of carbonic anhydrase-like isoform X2	Ovis aries	XP_004003380.2	LOC101117129	78 kDa	0.034	1.28	2.43	0.41	-	7.18	7.59
PREDICTED: protein disulfide-isomerase A6	Bos indicus	XP_019824917.1	LOC109565403	48 kDa	0.015	-1.66	0.32	3.16	-	8.63	8.23
lysophospholipid acyltransferase 5	Ovis aries	XP_027823723.1	LPCAT3	56 kDa	0.035	-1.85	0.28	3.61	-	6.33	6.13
protein NipSnap homolog 3A	Ovis aries	XP_027819963.1	NIPSNAP3A	29 kDa	0.0043	-1.07	0.48	2.10	-	6.52	6.21
protein disulfide-isomerase	Ovis aries	XP_027830078.1	P4HB	63 kDa	0.035	-1.54	0.34	2.91	-	8.88	8.48
GPI transamidase component PIG-T isoform X1	Ovis aries	XP_027833042.1	PIGT	74 kDa	0.036	-1.96	0.26	3.89	-	6.68	5.96
GDP-fucose protein O-fucosyltransferase 2 isoform X1	Ovis aries	XP_027816944.1	POFUT2	50 kDa	0.016	-1.84	0.28	3.58	-	7.33	6.89
retinol-binding protein 4	Ovis aries	XP_027815955.1	RBP4	23 kDa	0.045	1.55	2.93	0.34	-	6.96	7.40
PREDICTED: reticulocalbin-2 isoform X2	Capra hircus	XP_017921860.1	RCN2	36 kDa	0.00022	-2.95	0.13	7.73	-	7.09	6.30
dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1	Ovis aries	XP_027813657.1	RPN1	69 kDa	0.038	-1.36	0.39	2.57	-	8.33	8.05
dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 2 isoform X1	Ovis aries	XP_027832978.1	RPN2	71 kDa	0.0099	-1.73	0.30	3.32	-	8.49	8.04
calcium-binding mitochondrial carrier protein Aralar2 isoform X1	Ovis aries	XP_004007792.1	SLC25A13	74 kDa	0.04	-2.14	0.23	4.41	-	6.90	6.31
long-chain fatty acid transport protein 1	Ovis aries	XP_027825247.1	SLC27A1	71 kDa	0.0026	-2.18	0.22	4.53	-	7.04	6.48
CMP-N-acetylneuraminase-beta-galactosamide-alpha-2,3-sialyltransferase 4 isoform X1	Ovis aries	XP_011956915.1	ST3GAL4	42 kDa	0.025	Missing Value	-	-	-	6.81	5.77
SUN domain-containing protein 2 isoform X1	Ovis aries	XP_027823918.1	SUN2	88 kDa	0.025	-2.39	0.19	5.24	-	7.55	6.88
mitochondrial import receptor subunit TOM70	Ovis aries	XP_004002928.1	TOMM70	68 kDa	0.024	-2.32	0.20	4.99	-	6.67	6.20
transthyretin precursor	Ovis aries	NP_001009800.1	TTR	16 kDa	0.043	1.13	2.19	0.46	-	8.33	8.69
immunoglobulin lambda light chain constant region 2 allotypic variant IGLC2c, partial	Bos taurus	AEM05840.1	-	11 kDa	0.017	1.34	2.53	0.40	-	7.85	8.21
immunoglobulin heavy chain variable region, partial	Ovis aries	CAD45049.1	-	12 kDa	0.013	-2.28	0.21	4.86	-	7.41	6.97

Table S3

List of differentially abundant proteins according to the diet and the dose of bisphenol S after chi-square test

Protein Name	Species	Accession Number	Gene Symbol	Molecular Weight	in R0 (detection rate %)	in R50 (detection rate %)	in WF0 (detection rate %)	in WF50 (detection rate %)	Dose effect p-value (chi-square)	Diet effect p-value (chi- square)	R0 vs R50 p-value (chi-square)	WF0 vs WF50 p-value (chi-square)	R0 vs WF0 p-value (chi- square)	R50 vs WF50 p-value (chi-square)
aflatoxin B1 aldehyde reductase member 2	Ovis aries	XP_027821430.1	AKR7A2	41 kDa	6.76 (25%)	7.03 (100%)	N.D. (0%)	7.21 (100%)	0.007	0.106	0.285	0.005	0.028	-
cadherin-6 isoform X2	Bos taurus	XP_024837107.1	CDH6	80 kDa	N.D. (0%)	7.55 (25%)	7.43 (25%)	7.75 (75%)	0.614	0.012	0.285	1.000	0.028	0.157
dermcidin isoform 1 preproprotein	Homo sapiens	NP_444513.1	DCD	11 kDa	5.47 (50%)	N.D. (0%)	5.94 (25%)	6.41 (75%)	0.317	0.046	0.102	1.000	-	-
squalene synthase isoform X2	Ovis aries	XP_004004500.1	FDFT1	48 kDa	6.56 (25%)	6.63 (100%)	N.D. (0%)	6.59 (50%)	0.131	0.012	0.285	0.102	0.028	0.102
bis(5'-adenosyl)-triphosphatase isoform X1	Ovis aries	XP_011954617.2	FHIT	17 kDa	N.D. (0%)	6.5 (50%)	5.76 (25%)	7.3 (100%)	0.131	0.012	0.102	0.285	0.028	0.102
beta-glucuronidase	Ovis aries	XP_027817734.1	GUSB	74 kDa	N.D. (0%)	6.88 (100%)	6.18 (50%)	6.6 (100%)	0.002	0.302	0.005	0.102	0.102	-
inactive hydroxysteroid dehydrogenase-like protein 1	Bos taurus	NP_001092341.1	HSDL1	37 kDa	6.17 (75%)	6.21 (100%)	N.D. (0%)	6.76 (75%)	0.003	0.248	0.028	0.028	0.285	0.285
complement factor H-related protein 2	Ovis aries	XP_004013976.1	LOC101123223	31 kDa	6.45 (50%)	N.D. (0%)	6.05 (25%)	7.15 (75%)	0.614	0.614	0.028	0.157	-	-
sulfhydryl oxidase 2 isoform X1	Capra hircus	XP_017911573.1	LOC102189594	87 kDa	N.D. (0%)	7.21 (75%)	6.25 (25%)	6.34 (100%)	0.003	0.317	0.028	0.028	0.028	0.285
SLC35A4 upstream open reading frame protein	Bubalus bubalis	XP_025148374.1	LOC112586898	11 kDa	5.41 (25%)	6.44 (75%)	N.D. (0%)	6.76 (75%)	0.012	0.614	0.157	0.028	-	-
nicastrin isoform X2	Ovis aries	XP_012039753.2	NCSTN	67 kDa	6.58 (50%)	6.8 (75%)	6.68 (75%)	N.D. (0%)	0.317	0.317	0.465	0.028	0.465	0.028
prolyl 4-hydroxylase subunit alpha-2 isoform X1	Ovis aries	XP_004008688.1	P4HA2	61 kDa	7.09 (75%)	6.8 (100%)	7.13 (100%)	N.D. (0%)	0.106	0.106	0.285	0.005	0.285	0.005
reticulon-4 isoform X1	Capra hircus	XP_017910740.1	RTN4	130 kDa	N.D. (0%)	7.14 (75%)	7.05 (75%)	6.16 (50%)	0.317	0.317	0.028	0.465	0.028	0.465
splicing factor 3B subunit 5	Bos taurus	NP_001020521.1	SF3B5	10 kDa	N.D. (0%)	6.56 (75%)	6.62 (75%)	6.57 (75%)	0.131	0.131	0.028	1.000	0.028	1.000
transportin-2 isoform X4	Ovis aries	XP_027825368.1	TNPO2	103 kDa	6.32 (25%)	6.44 (75%)	N.D. (0%)	6.82 (100%)	0.003	1.000	0.157	0.005	0.285	0.285
nucleoprotein TPR	Capra hircus	XP_005691036.2	TPR	275 kDa	6.39 (25%)	6.87 (75%)	N.D. (0%)	6.02 (75%)	0.012	0.614	0.157	0.028	0.285	1.000
thiosulfate sulfurtransferase	Ovis aries	XP_014950344.2	TST	33 kDa	6.99 (75%)	6.91 (100%)	5.87 (25%)	N.D. (0%)	1.000	0.003	0.285	0.285	0.157	0.005