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## **A short periconceptional exposure to maternal type-1 diabetes is sufficient to disrupt the fetoplacental phenotype in a rabbit model**

Delphine Rousseau-Ralliard, Anne Couturier-Tarrade, René Thieme, Roselyne Brat, Audrey Rolland, Pascal Boileau, Marie-Christine Aubrière, Nathalie Daniel, Michèle Dahirel, Emilie Derisoud, et al.

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**P2.25.**  
**EFFECTS OF TROPHOBLAST-DERIVED EXOSOMES PRODUCED UNDER HIGH AND LOW GLUCOSE CONDITIONS UPON ENDOMETRIAL EPITHELIAL CELL BEHAVIOR**

Rachel R. Zabel<sup>1</sup>, Leopold Böhm, Megdalena M. Rose, Diana M. Morales-Prieto, Ekkehard Schleussner, Udo R. Markert, Rodolfo R. Favaro. *University Hospital Jena, Jena, Germany*

**Objectives:** In the early stages of human pregnancy, trophoblast cells invade the endometrial stroma to develop the placenta. During this process they interact with many cell types, such as glandular epithelial cells. In this study, we examined the effects of trophoblast-derived extracellular vesicles (EVs) produced under high and low glucose conditions on endometrial epithelial cell metabolism, proliferation and gene expression.

**Methods:** HTR-8/SVneo trophoblast cells were cultivated in high (25 mM) or low (5.5 mM) glucose RPMI supplemented with 10% exosome-depleted (ED) FBS for 48 h. Subsequently, supernatants were collected and used for exosome isolation through ultracentrifugation. Exosome-enriched fractions were characterized by the presence of the exosome marker CD63 in dot-blots. Protein concentration was evaluated with microBCA. Ishikawa cells were treated for 4 or 48 h with 60 ng of the exosomal fraction in low glucose DMEM supplemented with 10% ED-FBS. Cells collected at 4 h were used for gene expression analysis by qPCR, whereas those collected at 48 h were tested for cell proliferation by FACS. The respective supernatants were used for evaluation of glucose consumption and lactate production.

**Results:** Ishikawa cells treated with trophoblast-derived exosomes had increased glucose consumption, lactate production and cell proliferation compared to non-treated cells. No differences were observed between exosomes obtained from high and low glucose conditions. No changes were observed in the expression of GLUT1, IL6, IL8 and cadherin-E between all groups.

**Conclusion:** Our results show that trophoblast cells communicate with endometrial epithelial cells through exosomes. Exosomes produced under both high and low glucose conditions similarly enhance epithelial cell metabolism and proliferation. Expression of other genes will be analyzed to investigate the mechanism by which EVs mediate their effects on epithelial cells.

**P2.26.**  
**A SHORT PERICONCEPTIONAL EXPOSURE TO MATERNAL TYPE-1 DIABETES IS SUFFICIENT TO DISRUPT THE FETO-PLACENTAL PHENOTYPE IN A RABBIT MODEL**

Delphine Rousseau-Ralliard<sup>1</sup>, Anne Couturier-Tarrade<sup>1</sup>, René Thieme<sup>2,3</sup>, Roselyne Brat<sup>1</sup>, Audrey Rolland<sup>1</sup>, Pascal Boileau<sup>4</sup>, Marie-Christine Aubrière<sup>1</sup>, Nathalie Daniel<sup>1</sup>, Michèle Dahirel<sup>1</sup>, Emilie Derisoud<sup>1</sup>, Natalie Fournier<sup>5</sup>, Maria Schindler<sup>2</sup>, Véronique Duranthon<sup>1</sup>, Bernd Fischer<sup>2</sup>, Anne Navarrete Santos<sup>2</sup>, Pascale Chavatte-Palmer<sup>1</sup>. <sup>1</sup>UMR BDR, INRA, ENVA, Université Paris Saclay, Jouy en Josas, France; <sup>2</sup>Department of Anatomy and Cell Biology, Martin Luther University Faculty of Medicine, Halle, Germany; <sup>3</sup>Department of Visceral, Transplant, Thoracic and Vascular Surgery, University Hospital Leipzig, Leipzig, Germany; <sup>4</sup>UVSQ (University of Versailles-Saint Quentin), Neonatal Medicine-CHIPS, Poissy, France; <sup>5</sup>European Georges Pompidou Hospital, Biochemistry Unit, Paris, France

**Objectives:** Tight metabolic control of type-1 diabetes is essential during gestation, but it could be crucial during the periconception period. Feto-placental consequences of maternal type-1 diabetes around the time of conception need to be explored.

**Methods:** Using a rabbit model, type-1 diabetes was induced by alloxan 7 days before mating. Glycemia was maintained at 15–20mmol/L with exogenous insulin injections to prevent ketoacidosis. At 4 days post-conception (dpc), embryos were collected from diabetic (D) or normoglycemic control (C) dams, respectively, and transferred into non-diabetic recipients. At 28dpc, D- and C-feto-placental units were collected for biometry, placental analyses and lipid profiles.

**Results:** D-fetuses were growth-retarded, hyperglycemic and dyslipidemic compared to C-fetuses. The efficiency of D-placentas was associated with an increased gene expression related to nutrient supply and lipid metabolism whereas volume density of fetal vessels decreased.

Fetal plasma, placental and fetal liver membranes had specific fatty acid signatures depending on embryonic origin. Tissues from D-fetuses contained more omega-6 polyunsaturated fatty acids. The concentrations of docosahexaenoic acid decreased while linoleic acid increased in the heart of D-fetuses.

**Conclusion:** This study demonstrates that a short exposure to maternal type-1 diabetes in the periconception window had programmed, adversely and durably, the fetal phenotype, through placental structural and molecular adaptations.

**P2.27.**  
**TARGETING THE DYSFUNCTIONAL PLACENTA: NOVEL PEPTIDES TO DELIVER DRUGS TO SPECIFIC UTEROPLACENTAL COMPARTMENTS**

Lewis Renshall<sup>1</sup>, Mark Wareing, Paul Brownbill, Frances Beards, Susan Greenwood, Edward Johnstone, Colin Sibley, John Aplin, Lynda Harris. *The University of Manchester, Manchester, United Kingdom*

**Objectives:** Placental dysfunction is the leading cause of fetal growth restriction and can be characterised by 1) inadequate remodelling of uteroplacental vasculature and 2) morphological and functional abnormalities in the syncytiotrophoblast. Patients may present with either or both of these pathologies. We hypothesised that (1) specific homing peptides could enable liposomes, potential vehicles for drug delivery, to be selectively targeted to either the syncytiotrophoblast or the vasculature and (2) empty peptide-decorated liposomes would have no deleterious effect on placental function.

**Methods:** Fluorophore-tagged homing peptides GAKRGDN (GAK) or CGPSSARAPC (GPS) were incubated with human term placental villous explants or myometrial arterial segments for 3 h then fluorescence localisation was carried out on cryosections. Empty peptide-decorated liposomes were prepared by the thin film method and added to explants for 48 h, to assess their effects on normal placental function. There were four treatments: PBS (control), GAK-liposomes (GAK-L), GPS-liposomes (GPS-L) and naked liposomes (N-L). Liposome uptake was assessed by fluorescence microscopy. Human chorionic gonadotropin (hCG) secretion was measured by ELISA. Proliferation and apoptosis were assessed by Ki67 and M30 immunostaining. Radiolabelled [<sup>14</sup>C]-methylaminoisobutyric (MeAIB) acid was used to assess the effect of peptide and liposomes on the rate of system A amino acid transport.

**Results:** GAK bound to the endothelium of myometrial spiral arteries whereas GPS accumulated in the syncytiotrophoblast. GPS-decorated (but not GAK-decorated) liposomes accumulated in the syncytiotrophoblast. hCG secretion at 48 h was similar in all groups (control 9.252 [4.618–10.66], N-L 7.461 [6.045–8.644], GAK-L 12.64 [5.616–17.55], GPS-L 7.871 [4.235–10.66] mIU hCG/mg protein; median+[IQR], n=3). Proliferation, apoptosis and Na<sup>+</sup>-dependent transport of [<sup>14</sup>C]-MeAIB were all unaffected by treatment.

**Conclusion:** Liposomes can be targeted to different uteroplacental compartments without detrimentally affecting placental function. Future work will test the ability of targeted liposomes to deliver site-specific therapeutics based on uteroplacental pathophysiological phenotype.

**P2.28.**  
**PLACENTAL ENDOCRINE IGF2 DEFICIENCY IMPAIRS INTRAUTERINE GROWTH WITH CONSEQUENCES FOR INSULIN SENSITIVITY AND ADIPOSIY IN ADULT OFFSPRING**

Hannah Ee Juen Yong<sup>1</sup>, Jorge Lopez-Tello<sup>1</sup>, Ionel Sandovici<sup>2,3</sup>, Miguel Constancia<sup>2,3</sup>, Amanda Sferruzzi-Perri<sup>1</sup>. <sup>1</sup>Centre for Trophoblast Research, University of Cambridge, Cambridge, United Kingdom; <sup>2</sup>Metabolic Research Laboratories, and MRC Metabolic Diseases Unit, Wellcome Trust-Medical Research Council Institute of Metabolic Science, University of Cambridge, Cambridge, United Kingdom; <sup>3</sup>Department of Obstetrics and Gynaecology, University of Cambridge, Cambridge, United Kingdom