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1 Sperm interactions with the female reproductive tract: a key for successful 2 fertilization in mammals

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8 Abstract

9 Sperm migration through the female genital tract is not a quiet journey. Uterine contractions quickly
10 operate a drastic selection, leading to a very restrictive number of sperm reaching the top of uterine
11 horns and finally, provided the presence of key molecules on sperm, the oviduct, where fertilization
12 takes place. During hours and sometimes days before fertilization, subpopulations of spermatozoa
13 interact with dynamic and region-specific maternal components, including soluble proteins,
14 extracellular vesicles and epithelial cells lining the lumen of the female tract. Interactions with
15 uterine and oviductal cells play important roles for sperm survival as they modulate the maternal
16 immune response and allow a transient storage before ovulation. The body of work reported here
17 highlights the importance of sperm interactions with proteins originated from both the uterine and
18 oviductal fluids, as well as hormonal signals around the time of ovulation for sperm acquisition of
19 fertilizing competence.

20 **Keywords:** Spermatozoa; oviduct; uterus; utero-tubal junction; interaction; protein; progesterone;
21 extracellular vesicle; exosome.

22 1. Introduction

23 Ejaculated mammalian spermatozoa are not able to fertilize the oocyte; this ability is acquired
24 following a series of molecular and physiological changes, collectively known as capacitation, which
25 are accomplished during the transit of spermatozoa through the female genital tract. In addition to
26 sperm acquisition of fertilizing competence, the maternal environment operates a dramatic sperm
27 selection, resulting in a very low sperm:egg ratio in the site of fertilization (Hino et al., 2016). The
28 maternal environment allows also long-term survival of a subpopulation of spermatozoa up to the
29 time of ovulation. These crucial steps preceding fertilization imply sperm interactions with the
30 complex and dynamic fluids present in the female reproductive tract and with epithelial cells lining
31 its lumen, in addition to flows induced by muscular contractions of the female genital tract.
32 Fertilization can occur in vitro, thus in the absence of these interactions, but the female tract may
33 increase the efficiency and quality of fertilization. To illustrate, the rate of polyspermy and the
34 incidence of chromosomal abnormalities in early embryos are generally much lower in vivo than
35 under in vitro conditions (Coy and Aviles, 2010; Viuff et al., 2000; Viuff et al., 2001). Therefore, the
36 mechanisms involved in sperm interactions with somatic cells and region-specific secretions in vivo
37 are of particular importance for the understanding of factors determining male and female fertility,
38 but also for the improvement of assisted reproductive technologies (ART) and for better
39 evaluation/prediction of male fertility in human and farm animals.
40 The objective of this review is to provide an update on the effects of interactions in the uterus, utero-
41 tubal junction (UTJ) and the oviduct (known as the fallopian tube in human) on sperm physiology,
42 with emphasis on the oviduct where fertilization takes place. Physical and biochemical interactions
43 of spermatozoa in the cervix have been recently reviewed (Fair et al., 2019; Rickard et al., 2019) and

44 were not included. In each region starting from the uterus, effects of interaction with secreted fluids,
45 including extracellular vesicles, and luminal epithelial cells on sperm will be considered separately.
46 Special attention will be given to sperm-interacting proteins identified in female secretions that
47 modulate sperm physiology. However, details on the reorganization of specific sperm surface
48 microdomains and proteins during capacitation were excluded as they are well described elsewhere
49 (Baker, 2016; Brohi and Huo, 2017; Gadella, 2017). The changes induced by sperm interactions on
50 female tract gene expression were also considered out of the scope of the present review. All
51 mammals will be considered with a particular interest in farm animals, in which large amounts of
52 data on sperm interactions were acquired thanks to the availability of the biological material and due
53 to the economic importance of such research area for animal breeding and livestock production.

54

55 **2. Sperm interactions with the uterus**

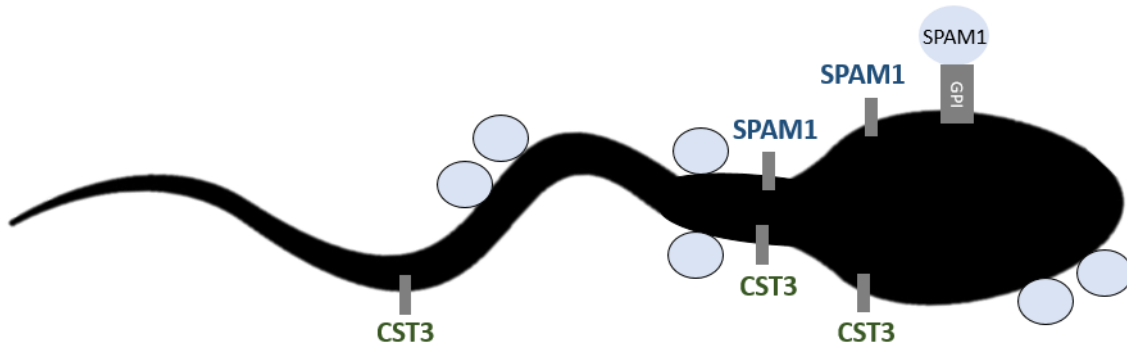
56 The migration of spermatozoa through the uterus is associated with sperm interactions with the
57 uterine fluid (UF) and with uterine (or endometrial) epithelial cells (UECs), each mediated by
58 specific components and triggering different effects on sperm.

59 ***2.1. Sperm interactions with uterine fluid and extracellular vesicles***

60 Changes in sperm physiology in contact with uterine fluid have been poorly investigated compared
61 with oviductal fluid, and data lack consistency. Incubation of sperm with UF maintained higher
62 sperm motility over time compared with untreated controls in cattle (Abe et al., 1995a) and human
63 (Chirinos et al., 2017). Furthermore, a significant increase in protein tyrosine phosphorylation, a
64 marker of sperm capacitation, without impact on sperm viability was observed when human sperm
65 were incubated for 3 h with uterine flushing from women at the time of ovulation (Chirinos et al.,
66 2017). However, adverse effects of UF on motility, viability and acrosome integrity of ejaculated
67 boar sperm were observed in less than 2 h *in vitro* (Luongo et al., 2019). The negative effects of UF
68 were reduced in the presence of seminal plasma, leading to the hypothesis that proteins in the
69 seminal plasma have a protective effect against uterine attack by coating sperm surface (Luongo et
70 al., 2019).

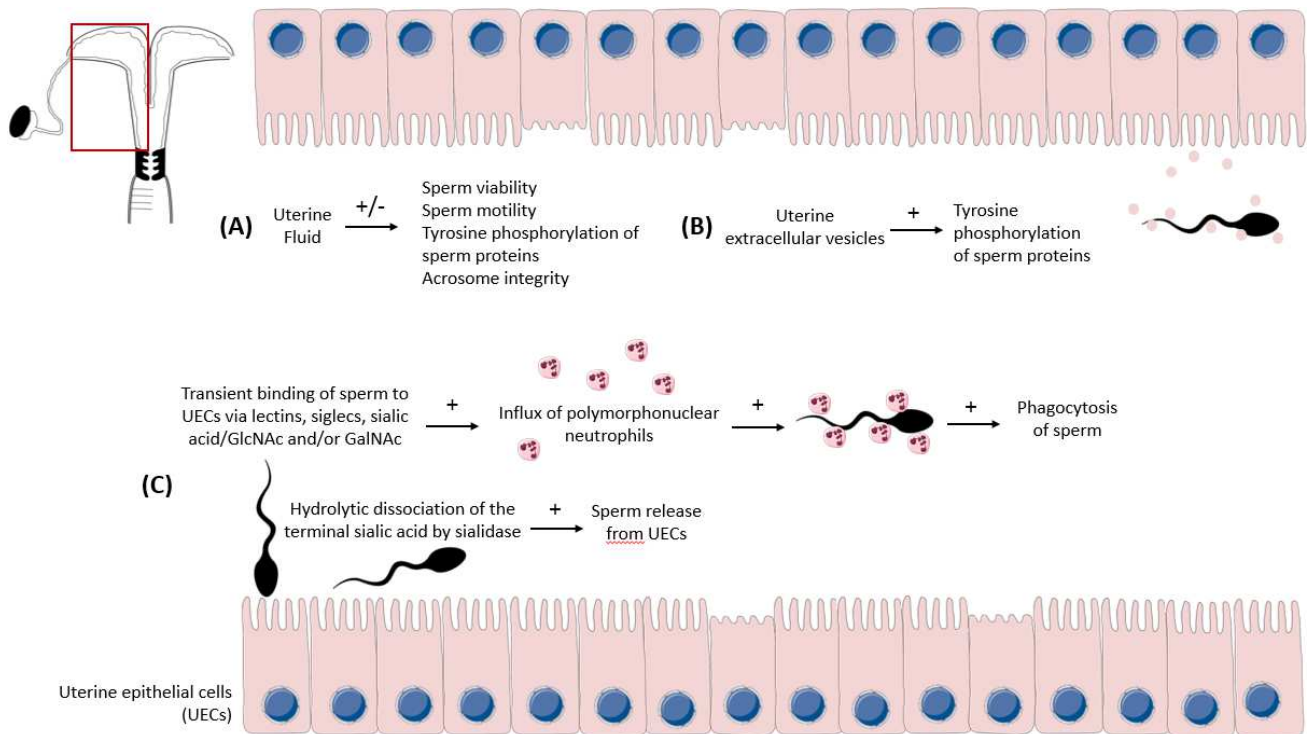
71 A comprehensive analysis of proteins present in the UF is now available in some mammals including
72 cattle (Gegenfurtner et al., 2020), horses (Maloney et al., 2019) and humans (Kasvandik et al., 2020).
73 However, specific proteins involved in sperm-UF interactions are poorly known (Figure 1). Sperm
74 Adhesion Molecule 1 (SPAM1 or PH-20 hyaluronidase), a well conserved sperm surface
75 hyaluronidase involved in fertilization, is secreted in the male genital tract and already present at the
76 surface of ejaculated spermatozoa (Martin-DeLeon, 2006). SPAM1 was also identified in the uterine
77 and oviductal fluids of female mice in the absence of semen (Griffiths et al., 2008a). SPAM1 from
78 estrous UF was shown to associate with sperm of *Spam1*-null and wild-type mouse, predominantly to
79 the acrosome and the mid-piece of the flagella (Griffiths et al., 2008a) (Figure 1). Incubation of
80 murine sperm with UF increased their ability to bind to hyaluronic acid, a compound abundantly
81 secreted by cumulus cells surrounding the oocyte, and this effect was inhibited when spermatozoa
82 were exposed to SPAM1 antiserum (Griffiths et al., 2008a). However, sperm lacking SPAM1 can
83 fertilize murine oocytes under *in vitro* conditions, although with lower ability to disperse cumulus
84 cells (Baba et al., 2002), suggesting that SPAM1 is not essential for *in vitro* fertilization in mice. But
85 it is possible that the requirements for successful fertilization *in vivo* are different than *in vitro* and
86 uterine SPAM1 may be required *in vivo*. Recently, cystatin-C (CST3), a cysteine protease inhibitor
87 highly present in the human cervix, endometrium and UF near ovulation, was shown to interact with
88 human sperm at the post-acrosomal head region and mid and principal piece of the tail (Lee et al.,
89 2018). *In vitro*, recombinant CST3 enhanced sperm motility but inhibited the efflux of cholesterol

90 from the sperm plasma membrane, an initiating step of sperm capacitation, and the subsequent
91 increase in sperm protein tyrosine phosphorylation (Lee et al., 2018). It was suggested that CST3
92 may prevent precocious capacitation, thus preserving sperm fertilizing ability before reaching the
93 oviduct.
94



95
96 **Figure 1. Identification and localization of uterine proteins and extracellular vesicles**
97 **interacting with spermatozoa.** Sperm Adhesion Molecule 1 (SPAM1) interacts with mouse sperm
98 acrosome and midpiece (Griffiths et al., 2008a). Cystatin-C (CST3) interacts with sperm post-acrosomal
99 region, midpiece and tail of human sperm (Lee et al., 2018). Uterine extracellular vesicles (EVs, in blue)
100 interact with sperm head, acrosome, midpiece and tail in mice (Griffiths et al., 2008b), human (Franchi et al.,
101 2016) and pigs (Alcantara-Neto et al., 2020a). Murine uterine EVs deliver SPAM1 to sperm, possibly via
102 glycosylphosphatidylinositol (GPI)-linked mechanisms (Griffiths et al., 2008b).

103 Extracellular vesicles in the female reproductive tract secretions have raised attention due to their
104 potential role in modulating sperm function (Figure 2). Exosomes (40-100 nm) and microvesicles
105 (100-1000 nm), collectively known as extracellular vesicles (EVs), are able to transfer a complex
106 selection of molecules from one cell to another in a high variety of biological fluids (Yanez-Mo et
107 al., 2015). While the involvement of EVs from epididymis (or epididymosomes) in sperm maturation
108 is well established (Sullivan, 2016), few data are available on the molecular content and on the roles
109 of uterine EVs, also known as uterosomes, on sperm physiology. The first report of the existence of
110 uterine nanovesicles was made in 2008 in mice (Griffiths et al., 2008b). Since then, uterine EVs have
111 been reported in several mammals including sheep (Burns et al., 2014), cattle (Qiao et al., 2018) and
112 women (Franchi et al., 2016). Sperm analyzed after incubation with fluorescently labeled isolated
113 uterine EVs revealed interactions with the acrosome and the midpiece of murine sperm (Griffiths et
114 al., 2008b) (Figure 1). Association of uterine EVs with human sperm head and tail was observed
115 after only 15 minutes of incubation and reported to increase tyrosine phosphorylation of sperm
116 proteins (Franchi et al., 2016). Murine spermatozoa were able to acquire SPAM1 during incubation
117 with uterine EVs, suggesting vesicular docking to sperm via glycosylphosphatidylinositol (GPI)-
118 linked mechanisms (Griffiths et al., 2008b). Recent data on sperm interaction with oviductal EVs
119 support the idea that EVs carry proteins that are important for sperm maturation during their transit
120 through the female reproductive tract (Alcântara-Neto et al., 2019; Alcântara-Neto et al., 2020b;
121 Ferraz et al., 2019; Franchi et al., 2020) (see below).
122



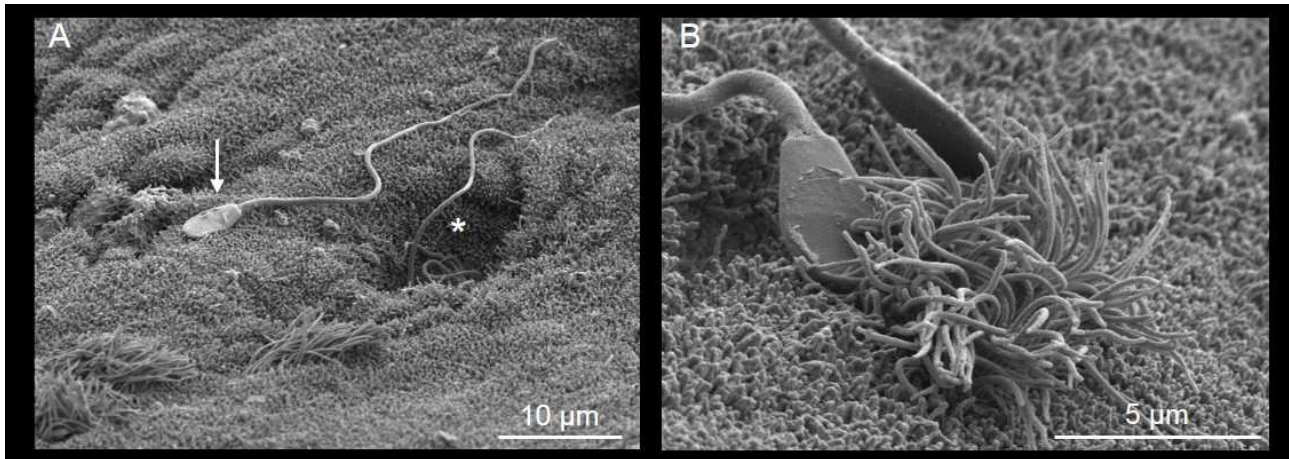
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124 **Figure 2. Summarized effects of interactions with the uterus on sperm physiology.** Sperm interact
 125 with uterine fluid (A), uterine extracellular vesicles (B) and uterine epithelial cells (UEC, C). Sperm-UEC
 126 interactions imply sialic acid-binding immunoglobulin-like lectins (Siglecs) as well as sialic acids, N-acetyl-
 127 glucosamine (GlcNAc), N-acetylgalactosamines (GalNAc) potentially present on both sperm and endometrial
 128 surfaces. See the text for corresponding references.

129

130 **2.2. Sperm interaction with uterine epithelial cells and effects on local inflammatory response**

131 Sperm interaction with UECs is linked to the integrity of sperm plasma membrane (Figure 3). Most
 132 of the spermatozoa bound to the sow's endometrium showed normal ultrastructure, intact plasma
 133 membrane and high mitochondrial membrane potential whereas most of the spermatozoa collected in
 134 the uterine lumen had damaged membranes (Rath et al., 2008; Rodriguez-Martinez et al., 1990;
 135 Taylor et al., 2008). *In vitro* experiments of incubation of boar spermatozoa with porcine UECs in
 136 the presence of lectins indicate that sperm binding to UECs is mediated by N-acetyl-glucosamine
 137 (GlcNAc)/sialic acid and/or N-Acetylgalactosamine (GalNAc) moieties with corresponding lectins
 138 (Bergmann et al., 2012; Bergmann et al., 2013). Moreover, sperm sialic acids may interact with
 139 endometrial sialic acid-binding immunoglobulin-like lectins (Siglecs) detected at the endometrial
 140 surface in mice and women (Teclé et al., 2019). It was proposed that sperm binding may be transient
 141 with sperm detachment regulated by sialidase (Figure 2). The sialidase might be liberated with
 142 follicular fluid at the time of ovulation and reach the uterine cavity where spermatozoa are released
 143 by hydrolytic dissociation of the terminal sialic acids (Rath et al., 2016).



144

145 **Figure 3. Scanning electron microscopy (SEM) images of dog sperm interacting with uterine**
 146 **epithelial cells *in vivo*.** Uterine epithelial cells at the luminal surface (A, white arrow) and in uterine gland
 147 (A, asterisk). B: higher magnification showing sperm heads with intact plasma membrane interacting with
 148 cilia at the UEC luminal surface. Source: K. Reynaud.

149 Sperm binding to UECs induces transient endometrial inflammation followed by the entry of
 150 polymorphonuclear neutrophils (PMNs) in the lumen and their binding to spermatozoa (Schjenken
 151 and Robertson, 2014). One possible role of PMN binding to spermatozoa is to eliminate by
 152 phagocytosis the spermatozoa not previously removed by uterine contractions. Scanning electron
 153 microscopy of bovine endometrial explants incubated with spermatozoa revealed the presence of
 154 spermatozoa in the uterine glands along with PMNs (Akthar et al., 2019). Spermatozoa induce an
 155 acute inflammatory response and upregulation of mRNA expression of IL8 and TLR2 in endometrial
 156 explants (Akthar et al., 2019). *In vitro* models of sperm interaction with bovine UECs showed that
 157 sperm binding triggers innate immunity with induction of a pro-inflammatory response (Elweza et
 158 al., 2018) through the Toll-like receptor 2/4 (TLR2/4) signaling pathway (Ezz et al., 2019). In the
 159 horse, the influx of PMNs into the uterine lumen was previously shown to be triggered via
 160 complement activation (Troedsson et al., 1998). Another mechanism of sperm elimination in the
 161 uterus is the formation of neutrophils extracellular traps (NETs), previously described for bacteria
 162 elimination (Brinkmann et al., 2004), which ensnare spermatozoa and hinder their motility. Sperm
 163 entrapment by NETs has been reported in horses (Alghamdi and Foster, 2005), cattle (Alghamdi et
 164 al., 2009; Fichtner et al., 2020) and humans (Zambrano et al., 2016). Spermatozoa might also be
 165 eliminated in the oviduct as PMNs were detected in the oviductal fluid of cyclic cows (Marey et al.,
 166 2014) and buffaloes (Yousef et al., 2019). However, *in vitro* data indicate that bovine oviduct
 167 epithelial cells around estrus secrete factors, including PGE₂, that suppress the phagocytic behavior
 168 of PMNs toward sperm but not toward bacteria (Marey et al., 2014; Marey et al., 2019; Yousef et al.,
 169 2019).

170 The site of sperm deposition, vagina or uterus, and therefore the absence or presence of seminal
 171 plasma in the uterus has an impact on mechanisms of sperm selection and survival (for reviews, see
 172 Fair et al., 2019; Miller, 2018; Rickard et al., 2019). In species with a deposit of semen in the
 173 vagina, most spermatozoa reach the uterus after elimination of seminal plasma by the cervix,
 174 whereas in species with a natural deposit of semen in the uterus such as the horse and pig, or after
 175 intrauterine insemination, both spermatozoa and seminal plasma interact with the endometrium. In
 176 addition to sperm, the seminal plasma is involved in the immune and inflammatory response of the
 177 endometrium after insemination (Schjenken and Robertson, 2015). In cattle after mating, the bulk of
 178 seminal plasma is expected to be eliminated by the cervix but *in vitro* experiments indicate a
 179 potential inhibitory impact of the seminal plasma on the viability and transmigration of PMNs
 180 through the endometrium and on their production of reactive oxygen species (Aloe et al., 2012). The

181 seminal plasma of stallions was shown to increase the endometrial expression of IL-1 and IL-8
182 associated with inflammation in mares (Fedorka et al., 2016). In addition, the equine seminal plasma
183 was reported to reduce sperm binding to neutrophils and the formation of NETs, which may allow
184 more spermatozoa to reach the oviduct (Alghamdi and Foster, 2005). Contrary to horses, the bovine
185 seminal plasma was shown to increase sperm-neutrophil binding, suggesting species-specific
186 mechanisms (Alghamdi et al., 2009). In pigs, the regulation of endometrial immune and
187 inflammatory response by seminal plasma was shown to be mediated by seminal exosomes (Bai et
188 al., 2018a). When porcine UECs were treated with exosomes from seminal plasma, RNA transcripts
189 related to immune and inflammatory response, such as CCL20 and interleukin 1, were up-regulated.
190 Up-regulation of CCL20 was also demonstrated in the uterine endometrium from naturally mated
191 pigs. As CCL20 recruits lymphocytes towards the epithelial tissue (Baba et al., 1997), it was
192 suggested that seminal exosomes are involved in the recruitment and entry of lymphocytes in the
193 porcine uterus (Bai et al., 2018b). Altogether, the results from *in vitro* and *in vivo* studies in several
194 mammalian species suggest that the seminal plasma plays an important role in sperm survival in the
195 female genital tract by protecting spermatozoa against negative effects of UF and controlling
196 inflammatory and immune activation of the endometrium. Moreover, interactions between sperm
197 sialic acids and uterine Siglecs activate downstream signaling pathways in endometrial cells, which
198 may in turn modulate the immune response (Tecele et al., 2019). The innate immune response of the
199 uterus may also be important for subsequent embryo development as it clears the uterine cavity and
200 improves endometrial receptivity for implantation (Chastant and Saint-Dizier, 2019; Katila, 2012).
201 Although spermatozoa are foreign cells for the female, an adaptive (or acquired) immune response
202 toward spermatozoa has been reported only at low incidence in humans (2-3% of women with
203 antisperm antibodies) (Clark and Schust, 2013). The mechanisms that allow this immune privilege
204 for male gametes in the female reproductive tract are still poorly known. However, the unusual
205 glycosylation signals on both spermatozoa and seminal plasma glycoproteins, namely the Lewis^x or
206 Lewis^y sequences, may play important roles in the uterine tolerance toward spermatozoa (for review,
207 see Clark and Schust, 2013).

208 To summarize, the uterine environment has both a negative effect on sperm number and viability,
209 and a positive action on the regulation of sperm function, protecting them from premature
210 capacitation and improving their ability to bind cumulus cells. This dual activity may result in the
211 selection of the fittest sperm subpopulation and elimination of abnormal ones by immune cells
212 recruited by the immune response induced by sperm binding to UEC and seminal plasma action. EVs
213 might be interesting players in these complex interactions.

214

215 **3. Sperm interactions with the utero-tubal junction**

216 ***3.1. Factors involved in sperm migration up to the utero-tubal junction***

217 The migration of spermatozoa up to the oviduct is the result of a combination of several male and
218 female parameters. As spermatozoa swim in the uterine fluid to reach the UTJ, sperm mobility and
219 morphology are expected to be limiting factors of sperm migration. After intrauterine insemination in
220 sows, an increase in the proportion of morphologically abnormal sperm collected in the backflow
221 from uterus to vagina was observed while this proportion was lower among sperm recovered in the
222 UTJ (Garcia-Vazquez et al., 2015). Indeed, almost all spermatozoa that colonize the UTJ had a
223 normal morphology. However, even if it is expected that normal morphology is required to transit in
224 the female tract, it is not clear which mechanisms are actually involved in the selection of normal
225 spermatozoa and which sperm morphological parameters, such as head size or flagella length, are of
226 critical importance (Garcia-Vazquez et al., 2016). Furthermore, in some mammals including dogs in
227 which a long interval can occur between mating and fertilization (up to 9 days), sperm storage seems

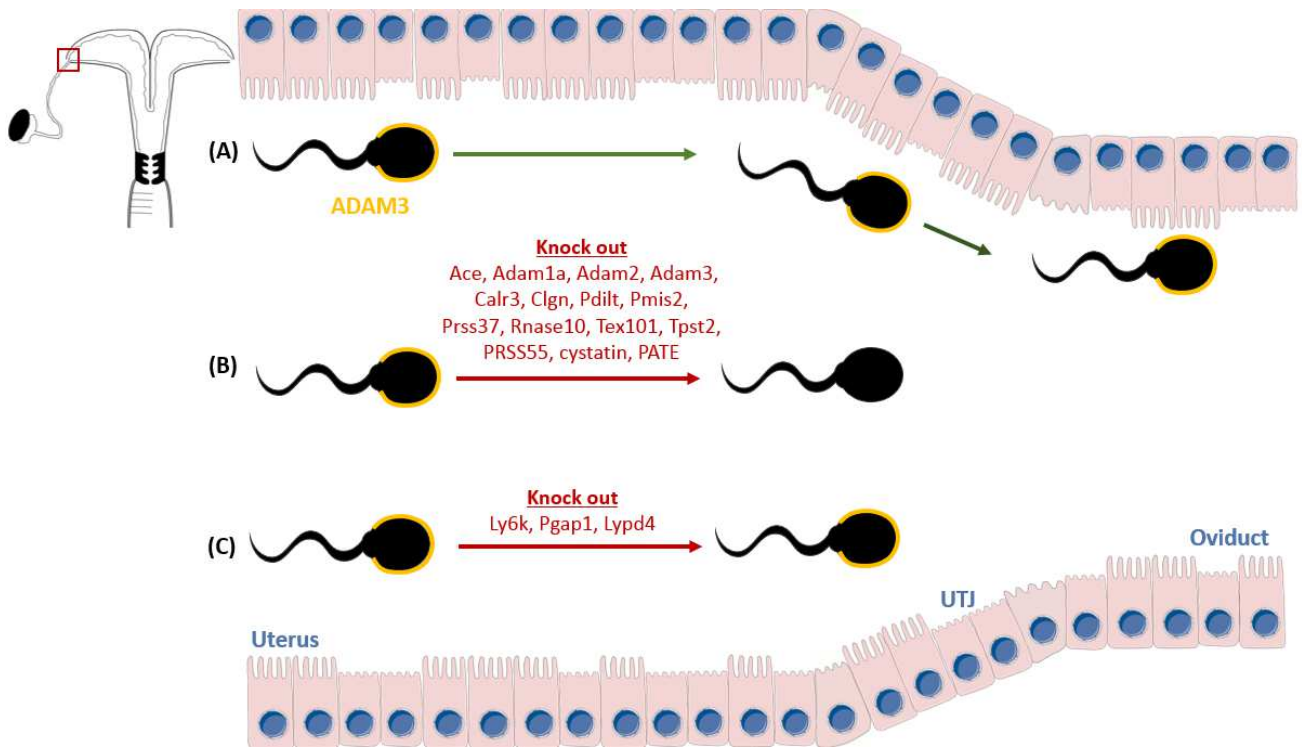
228 to occur mainly within the uterine glands and in the UTJ (England and Burgess, 2003; Rijsselaere et
229 al., 2004).

230 Beyond sperm mobility and morphology, the contractions of the uterus are also involved in the
231 transit of the spermatozoa. In the sow after intrauterine insemination, spermatozoa can be found
232 within minutes in the UTJ thanks to uterine contractions (Langendijk et al., 2005). The short duration
233 of sperm transit from the uterus to the oviduct cannot be explained by the sole mobility of
234 spermatozoa but rather by the existence of transporting waves induced by myometrial contractions
235 (Langendijk et al., 2002). The uterine contractions do transport spermatozoa from the uterus to the
236 UTJ but also remove lots of live and dead spermatozoa from the uterus by waves of contractions,
237 also called fundo-cervical peristalsis in humans (Kunz and Leyendecker, 2002), in the opposite
238 direction than those bringing sperm to the UTJ. In the mare within 4 h after intrauterine
239 insemination, some spermatozoa were observed in the oviduct while most of them were eliminated in
240 the vagina by uterine contractions (Katila et al., 2000).

241 ***3.2. Sperm molecules required to cross the utero-tubal junction***

242 When spermatozoa reach the tip of the uterine horn, they have to cross the UTJ, connecting the
243 uterus to the oviduct. The UTJ is a functional barrier between the uterus and the oviduct, selecting
244 sperm with normal mobility and specific surface molecular properties. Indeed, null mouse mutants
245 for more than 15 different genes are infertile because their sperm cannot pass through the UTJ
246 despite normal sperm mobility and morphology (for reviews, see (Fujihara et al., 2018; Xiong et al.,
247 2019); Figure 4). Except *Ly6k*, *Pgap1* and *Lypd4*, these mutants share a common feature, the absence
248 or the dislocation of sperm membrane protein A disintegrin and metallopeptidase domain 3
249 (ADAM3) in the detergent-rich membrane domain. Therefore, ADAM3 is suggested to be an
250 important factor for sperm migration to the oviduct in the mouse. The precise mechanism by which
251 ADAM3 facilitates the passage of sperm through the UTJ is unknown. Interestingly, all these
252 mutants are not only unable to migrate to the oviduct but also to bind to the zona pellucida,
253 suggesting that similar mechanisms might be involved in sperm transit and zona binding. The
254 distribution of ADAM3 was not affected in spermatozoa from *Ly6K*, *Pgap1* and *Lypd4* KO mice,
255 which suggests that mechanisms other than those involved in the correct distribution of ADAM3 on
256 sperm surface are involved in sperm migration through the UTJ in mouse. So far similar mechanisms
257 of sperm selection based on sperm surface proteins have not been evidenced in other species.

258



259

260 **Figure 4. Mechanisms of sperm transport through the utero-tubal junction (UTJ) identified in**
 261 **the mouse.** (A) Spermatozoa with correct distribution of ADAM3 pass through the UTJ; (B) Genes involved in the
 262 correct distribution of ADAM3 on sperm surface and in sperm passage through the UTJ; (C) Genes involved in sperm
 263 passage through the UTJ without targeting ADAM3, assuming other potential mechanisms. References for corresponding
 264 null mutants: *Ace* (Krege et al., 1995), *Adam1a* (Nishimura et al., 2004), *Adam2* (Cho et al., 1998), *Adam3* (Shamsadin et
 265 al., 1999), *Calr3* (Ikawa et al., 2011), *Clgn* (Ikawa et al., 1997), *Ly6k* (Fujihara et al., 2014), *Pdilt* (Tokuhiro et al., 2012),
 266 *Pgap* (Ueda et al., 2007), *Pmis2* (Yamaguchi et al., 2012), *Prss37* (Shen et al., 2013), *Prss55* (Shang et al., 2018),
 267 *Rnase10* (Krutskikh et al., 2012), *Tex101* (Fujihara et al., 2013), *Tpst2* (Marcello et al., 2011), *Cystatin* (CST), Prostate
 268 and testis expressed proteins (PATE), lymphocyte antigen 6 (Ly6)/Plaur domain (*lypd*) (Fujihara et al., 2019).

269

270 4. Sperm interactions with the oviduct

271 After mating or insemination, a very small proportion of spermatozoa reach the oviduct. Genital
 272 tracts collected after insemination in cows and gilts evidenced no more than a few dozens to
 273 hundreds of sperm within the oviduct (Hunter, 1981; Hunter et al., 1991; Hunter and Wilmot, 1984;
 274 Sostaric et al., 2008). As oviducts are small intra-abdominal organs not accessible on animals
 275 without surgery or slaughter, exact information on oviductal sperm behavior *in vivo* is scarce and
 276 most data were obtained from in-vitro models using oviductal fluids collected post-mortem or from
 277 cell culture.

278 4.1. Effects of interactions with oviductal fluid and secreted proteins on sperm physiology

279 The oviductal fluid (OF) is a complex mixture of molecules originated from selective blood
 280 transudation and secretions of oviduct epithelial cells (OECs), and with possible participation of
 281 follicular and peritoneal fluids (for review, see (Saint-Dizier et al., 2019)). The composition of OF
 282 differs from that of the UF in terms of ions (Hugentobler et al., 2007a), metabolites (Hugentobler et
 283 al., 2007b; Hugentobler et al., 2008) and macromolecules (Soleilhavoup et al., 2016) and as such, has
 284 specific effect on sperm physiology. Many *in vitro* studies reported beneficial effects of OEC
 285 secretions on sperm viability, motility and capacitation in various mammals including cattle (Abe et

286 al., 1995a; Bergqvist et al., 2006; Grippo et al., 1995; McNutt and Killian, 1991), pigs (Coy et al.,
287 2010; Kumaresan et al., 2012), sheep (El-Shahat et al., 2018) and dogs (Kawakami et al., 1998).
288 Fluctuating effects of OF on sperm capacitation were observed depending on the time at which
289 sperm parameters are measured and on the stage in the cycle. A 5-min exposure to pre-ovulatory OF
290 was sufficient to increase significantly the proportion of sperm with phosphorylated tyrosine in pigs
291 (Kumaresan et al., 2014). Bull sperm incubated with estrous OF displayed globally higher tyrosine
292 phosphorylation levels (Kumaresan et al., 2019) and higher ability to undergo acrosome reaction
293 (Grippo et al., 1995; Parrish et al., 1989) and to fertilize oocytes *in vitro* (Grippo et al., 1995)
294 compared with fluids collected at other stages of cycle. Also, differences in sperm fertilizing ability
295 were evidenced after incubation with isthmic and ampullary OF (Grippo et al., 1995), suggesting
296 region-specific effects on sperm physiology. Interestingly, variation in terms of response to OF were
297 observed between bulls with different fertility in the field (Kumaresan et al., 2016), which may
298 explain differences in pregnancy rates between males with comparable semen quality.

299
300 Relatively high levels of bicarbonate, albumin, high-density lipoproteins (HDL) and phospholipids
301 (leading to high phospholipid:cholesterol ratio) present in the peri-ovulatory OF have been proposed
302 as effectors of sperm cholesterol efflux leading to capacitation and acrosome reaction (Bergqvist and
303 Rodriguez-Martinez, 2006; Ehrenwald et al., 1990; Rodriguez-Martinez, 2007; Tienthai et al., 2004).
304 Furthermore, incubation with OF protein extracts reproduced most beneficial effects of OF on sperm
305 viability, motility and acrosome integrity in cattle (Boquest et al., 1999; Kumaresan et al., 2005;
306 Kumaresan et al., 2006) and humans (Zumoffen et al., 2010), suggesting probable central roles
307 played by OF proteins in the modulation of sperm functions. Antioxidant enzymes such as catalase
308 and superoxyde dismutase present in the OF (Kobayashi et al., 2014; Lapointe et al., 1998) may
309 protect spermatozoa from oxidative damages and promote their survival in the oviductal
310 environment. Moreover, it was hypothesized that OF proteins maintain sperm membrane integrity by
311 avoiding proteolytic damages, neutralizing toxic by-products of sperm metabolism and/or by
312 reducing metabolism (Boquest et al., 1999). However, the exact mechanisms by which oviductal
313 proteins affect sperm physiology are still unknown.

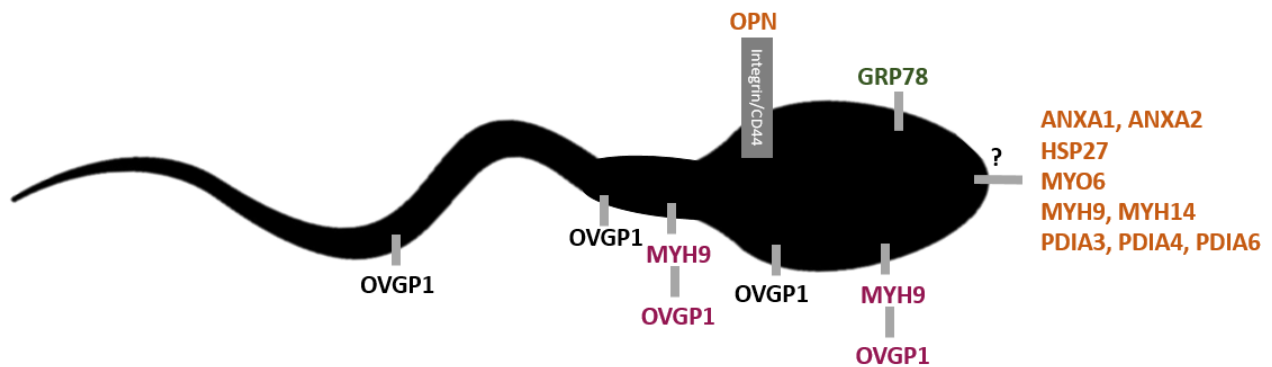
314
315 In order to obtain an exhaustive list of sperm-interacting proteins in the OF, our group compared the
316 proteomes (assessed by nanoLC-MS/MS) of bull sperm pre-incubated or not with cow OF collected
317 at pre-ovulatory, post-ovulatory and luteal phases of the estrous cycle. A total of 27 sperm-
318 interacting proteins ranging from 16 to 230 kDa were quantified on sperm, including the oviduct-
319 specific glycoprotein OVGPI as most abundant (Lamy et al., 2018). This was in accord with
320 previous candidate-based approaches in which OVGPI was immunolocalized on various mammalian
321 spermatozoa (Abe et al., 1995b; King and Killian, 1994; Lippes and Wagh, 1989; Yang et al., 2015).
322 In addition, new OF sperm-interacting proteins were identified including annexins (ANXA1,
323 ANXA2), heat shock proteins (HSP27, GRP78), three myosins (MYH9, MYH14, MYO6) and
324 proteins of the protein disulfide isomerase family (PDIA3, PDIA4, PDIA6) (Lamy et al., 2018)
325 (Figure 5). Annexins A1 and/or A2 were previously identified as sperm receptors on OEC apical side
326 in cattle (Ignotz et al., 2007) and pigs (Teijeiro et al., 2009). Furthermore, MYH9 was previously
327 identified as a binding partner of OVGPI on monkey sperm (Kadam et al., 2006). Therefore,
328 oviductal proteins may also interact with each other in the OF and form protein complexes
329 competing with available interacting sites on sperm. Of interest, the abundance of interacting
330 proteins on sperm differed according to the cycle stage and was not related to the initial abundance
331 of specific proteins measured in the OF (Lamy et al., 2016a; Lamy et al., 2018). This indicates that
332 highly selective sperm-protein interactions take place in the oviduct and suggests specific (unknown)
333 mechanisms of sperm binding depending on the protein environment. Furthermore, while OVGPI
334 was by far the most abundant protein on sperm before ovulation, a number of proteins including
335 MYH9, MYH14, HSP27, ANXA1 and ANXA2 interacted with sperm only after ovulation or at

336 higher abundance at post-ovulatory than at pre-ovulatory stage of cycle (Lamy et al., 2018),
337 suggesting important role at the time of ovulation, possibly on sperm release from the oviductal
338 sperm reservoir (see below).

339
340 The functional roles of OVGPI, a glycoprotein more abundant in the OF of various mammals during
341 estrus than at other stages of cycle, has been given special attention (for review, see (Aviles et al.,
342 2010)). The protein is not present in rats and megabats as *OVGPI* became a pseudogene in these two
343 species (Moros-Nicolas et al., 2018). Female mice with a null mutation for OVGPI displayed a slight
344 decrease in litter size after mating (−14% with no statistical difference with controls), showing that
345 OVGPI is not essential for fertilization, at least in mice (Araki et al., 2003). The comparison of the
346 amino acid sequences of various mammalian OVGPI revealed significant differences between
347 species, especially in the C-terminal region (Aviles et al., 2010), making it difficult to extrapolate the
348 potential roles of OVGPI on fertilization from one species to another. In cattle, spermatozoa
349 incubated with purified OVGPI displayed higher motility, viability (Abe et al., 1995b; Choudhary et
350 al., 2017), membrane integrity and capacitation status (Choudhary et al., 2017) than untreated
351 controls. Under capacitating conditions, OVGPI enhanced sperm protein tyrosine phosphorylation
352 and acrosome reaction in hamster (Saccary et al., 2013; Yang et al., 2015) and human (Zhao et al.,
353 2016) in a time-dependent manner, with first stimulating effects observed after only 5 min (Saccary
354 et al., 2013). Native OVGPI was more effective than recombinant non-glycosylated OVGPI on
355 various buffalo sperm functions, inferring important roles played by OVGPI glycosylation
356 (Choudhary et al., 2017). Furthermore, pretreatment of either sperm or oocyte with recombinant
357 hamster OVGPI prior to co-incubation was shown to increase the number of sperm bound to the
358 zona pellucida (Yang et al., 2015), indicating modulating roles on gamete interaction.

359
360 There is limited information on the role played by other oviductal proteins on sperm functions.
361 Osteopontin (OPN), like OVGPI, is a glycoprotein present in the OF at highest abundance around
362 ovulation time (Liu et al., 2015; Soleilhavoup et al., 2016). OPN was shown to bind on the post-
363 equatorial region of bull ejaculated sperm, possibly via integrin and CD44 receptors (Souza et al.,
364 2008), and promoted induced-acrosome reaction *in vitro* (Monaco et al., 2009) (Figure 5). Since
365 OPN is already present on ejaculated sperm, it was suggested that contact with OF changes OPN
366 pattern on sperm heads and therefore facilitates sperm interactions with oocyte (Souza et al., 2008).
367 In mice, anti-OPN antibody added *in vitro* reduced the rates of fertilization, cleavage and blastocyst
368 formation (Liu et al., 2015), suggesting a beneficial role of OPN in these steps. In pigs, in which high
369 incidence of polyspermy typically occurs during IVF, OPN reduced polyspermy and increased
370 fertilization efficiency during IVF (Hao et al., 2006).

371



372

373 **Figure 5. Identification and localization of sperm-interacting proteins in the oviductal fluid.**

374 The heat shock protein GRP78 interacts with acrosomal cap of human sperm (Marin-Briggiler et al., 2010).
375 OVGPI was shown to associate with the sperm head region and midpiece in human (Lippes and Wagh, 1989;
376 Zhao et al., 2016) and hamster (Yang et al., 2015) but with the whole surface of bull sperm (Abe et al., 1995b;

377 King and Killian, 1994). MYH9 was proposed to be OVGP1 receptor on monkey sperm head and midpiece
378 (Kadam et al. 2006). Osteopontin (OPN) interacts with bull sperm post-equatorial region probably via
379 integrins and CD44 (Souza et al. 2008). Additional sperm-interacting proteins were identified in the bovine
380 OF although their localization on sperm is still unknown (Lamy et al., 2018).

381

382

383 Heat shock proteins such as HSPA8 and GRP78 are present on the surface of OECs (Elliott et al.,
384 2009; Marin-Briggiler et al., 2010) and as soluble proteins in the OF (Lamy et al., 2016a). The use of
385 recombinant HSPA8 allowed to reproduce the beneficial effects of oviductal plasma membranes on
386 long-term survival in cattle, pigs and sheep (Elliott et al., 2009; Lloyd et al., 2009; Moein-Vaziri et
387 al., 2014) and improved post-freezing sperm survival in cattle (Holt et al, 2015). In addition,
388 recombinant HSPA8 also enhanced boar sperm membrane fluidity after a 15-min exposure and
389 improved monospermic fertilization compared to non-exposed controls *in vitro* (Moein-Vaziri et al.,
390 2014). Furthermore, human spermatozoa incubated with recombinant HSP60 or GRP78 under
391 capacitating conditions showed increased sperm intracellular calcium levels compared with controls
392 (Lachance et al., 2007). Recombinant GRP78 was shown to bind to the acrosomal cap of human
393 sperm and modulate zona pellucida interaction in a calcium-dependent manner (Marin-Briggiler et
394 al., 2010).

395

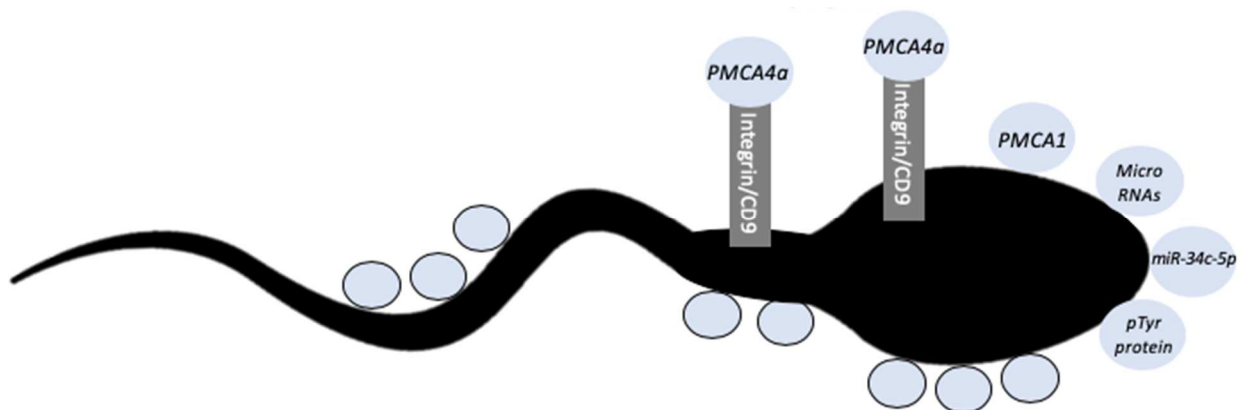
396 **4.2. Effects of interactions with oviductal extracellular vesicles on sperm physiology**

397 Oviductal extracellular vesicles (oEVs), also called oviductosomes, have recently gained attention
398 for their interactions with gametes/early embryos and potential effects on fertility (for review, see
399 (Alminana and Bauersachs, 2019)). Observation of oEVs merging with the head, midpiece and tail of
400 sperm was evidenced in mice (Al-Dossary et al., 2015), pigs (Alcantara-Neto et al., 2020a) and cats
401 (Ferraz et al., 2019). A flow cytometry analysis of bull sperm co-incubated with fluorochrome-
402 labelled oEVs showed a progressive sperm uptake starting after a single min of incubation (Franchi
403 et al., 2020). As for sperm-OEC interactions, not all sperm appear able to interact with oEVs: a
404 plateau was reached with 62% of sperm displaying oEV interactions after 2 h of co-incubation in
405 cattle (Franchi et al., 2020), and 68% of sperm after 3 h of co-incubation in mice (Bathala et al.,
406 2018).

407 Recent data in mammals evidenced important roles played by oEVs on sperm physiology. In pigs,
408 our group showed that oEVs increased sperm motility and viability and reduced polyspermy without
409 affecting the global fertilization rate, reproducing the beneficial effect of OF on *in vitro* fertilization
410 (Alcantara-Neto et al., 2020b). Incubation of cat sperm with oEVs sustained a greater percentage of
411 motile sperm for 24 h and increased sperm fertilizing capacity *in vitro* (Ferraz et al. 2019). The effect
412 of oEVs on sperm acrosome reaction appears species-specific. In cats, oEVs prevented premature
413 acrosomal exocytosis (Ferraz et al., 2019). On the opposite, oEVs from bovine OF provoked a rise in
414 bull sperm intracellular calcium, stimulated protein tyrosine phosphorylation and induced an
415 acrosome reaction (Franchi et al., 2020). Interestingly, oEVs from the ampulla and isthmus showed
416 similar but not identical effects on bull sperm calcium entry, suggesting that sperm physiology may
417 be modulated differentially close to the fertilization site in the ampulla (Franchi et al., 2020).

418 The molecular content of oEVs includes a large number of proteins, small RNAs and metabolites
419 that fluctuate throughout the reproductive cycle and especially around the time of ovulation,
420 probably under hormonal influence (Alminana et al., 2017; Fereshteh et al., 2018; Gatien et al.,
421 2019; Laezer et al., 2020). Among sperm proteins, plasma membrane calcium/calmodulin-dependent
422 calcium ATPases (PMCA), in particular PMCA4, are important fertility-modulating proteins since
423 they act as calcium efflux pump required for sperm hyperactivated motility and fertilizing ability

424 (Schuh et al., 2004). PMCA1 and 4a were shown to be major forms of PMCA in mice oEVs and
 425 detected at much higher abundance around the time of ovulation (at pro-estrus/estrus) than at other
 426 stages of the cycle (Al-Dossary et al., 2013; Bathala et al., 2018). Co-incubation assays indicated that
 427 mouse sperm are able to integrate PMCA4a from oEVs over the sperm head and midpiece (Al-
 428 Dossary et al., 2015; Al-Dossary et al., 2013). A fusion mechanism involving integrins ($\alpha 5\beta 1$ and
 429 $\alpha v\beta 3$) and CD9 tetraspanin expressed on sperm and oEVs was proposed (Al-Dossary et al., 2015).
 430 Further studies evidenced that oEVs can deliver enzymatically active PMCA1 and tyrosine-
 431 phosphorylated proteins to murine sperm and that this delivery was higher in capacitated than in
 432 uncapacitated sperm (Bathala et al., 2018). As PMCA were also detected in human oEVs, it was
 433 proposed that the delivery of fertility-modulating proteins to sperm by oEVs was preserved in
 434 humans (Bathala et al., 2018). Moreover, oEVs seem able to deliver microRNAs in intracellular
 435 sperm subcompartments in mice (Fereshteh et al., 2018). Transferred microRNAs were mainly
 436 localized in sperm head while the microRNA *miR-34c-5p*, which is only sperm-derived in the
 437 embryo and crucial for the first embryo cleavage, was specifically concentrated near the centrosome
 438 (Fereshteh et al., 2018) (Figure 6). These data identify oEVs as key components for sperm
 439 acquisition of fertilizing ability and for the quality of the early embryo. Further studies are needed to
 440 understand by which mechanisms oEV-derived molecules localize in specific sperm sub-
 441 compartments to perform their function.



442

443

444 **Figure 6. Identification and localization of oviductal extracellular vesicles and intravesicular**
 445 **molecules interacting with spermatozoa.** Oviductal EVs (in blue) were shown to merge with sperm head
 446 and midpiece in mice (Al-Dossary et al. 2015), and cats (Ferraz et al., 2019) but also with sperm tail in pigs
 447 (Alcantara-Neto et al., 2020a). Plasma membrane calcium ATPases (PMCA) 4a and tyrosine-phosphorylated
 448 proteins (pTyr protein) can be delivered to mouse sperm via oEVs through integrin and CD9 tetraspanin (Al-
 449 Dossary et al., 2013, 2015). PMCA1 and tyrosine phosphorylated proteins can also be delivered to sperm head
 450 via oEVs (Bathala et al., 2018). Intravesicular microRNAs can also be transferred to sperm head in mice
 451 (Fereshteh et al., 2018).

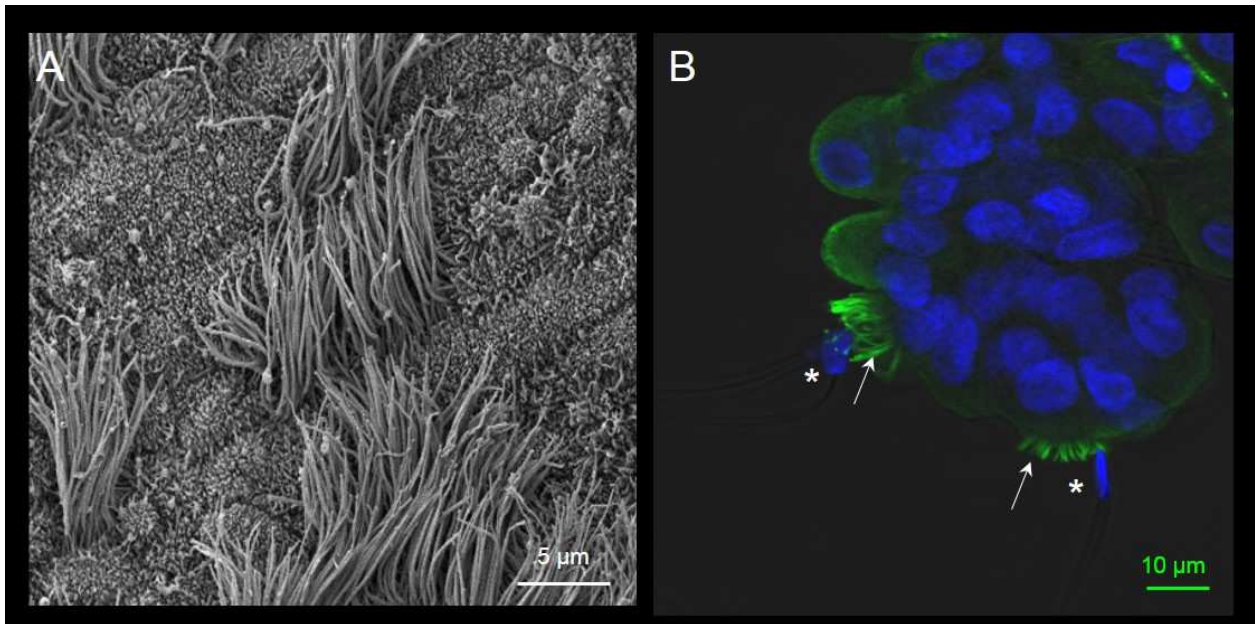
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453 **4.3. Binding to oviduct epithelial cells: formation of a functional sperm reservoir**

454 Mating or insemination in mammals occurs usually hours and up to a couple of days before
 455 ovulation, making sperm storage advantageous for successful fertilization. After passing the barrier
 456 of the UTJ, a subpopulation of spermatozoa adhere to the luminal epithelium of the caudal part of the
 457 oviduct, namely the isthmus, where they can be stored for hours to days (in most mammals), and
 458 even months (in bats), before their release around the time of ovulation to migrate toward the site of
 459 fertilization (Brussow et al., 2008; Holt and Fazeli, 2016; Hunter and Wilmut, 1984).

460 This 'functional sperm reservoir' forms approximately 8-12 h after insemination in cows (Wilmot
461 and Hunter, 1984). Oviductal sperm reservoirs have been identified in a number of mammals
462 including cattle (Hunter and Wilmot, 1984), sheep (Hunter and Nichol, 1983), pigs (Hunter, 1981),
463 rabbits (Overstreet and Cooper, 1978), rodents (Smith and Yanagimachi, 1991; Suarez, 1987) and
464 humans (Baillie et al., 1997). The oviduct epithelium contains both non-ciliated and ciliated cells.
465 Microscopic observation of bovine oviducts after insemination evidenced that sperm bound by their
466 head to OECs with a preference for ciliated cells (Ardon et al., 2016; Lefebvre et al., 1995; Sostaric
467 et al., 2008) (Figure 7).

468



469

470 **Figure 7. Sperm interactions with oviduct epithelial cells (OECs) in cattle.** (A) SEM picture of the
471 luminal surface of oviduct epithelium composed of ciliated and non-ciliated cells. (B) Confocal microscopy
472 picture of bull sperm interacting with bovine oviduct epithelial cells *in vitro*. Nuclei appeared in blue, cilia
473 (acetylated α -tubulin) in green. Asterisks indicate sperm heads; arrows indicate cilia. Source: K. Reynaud.

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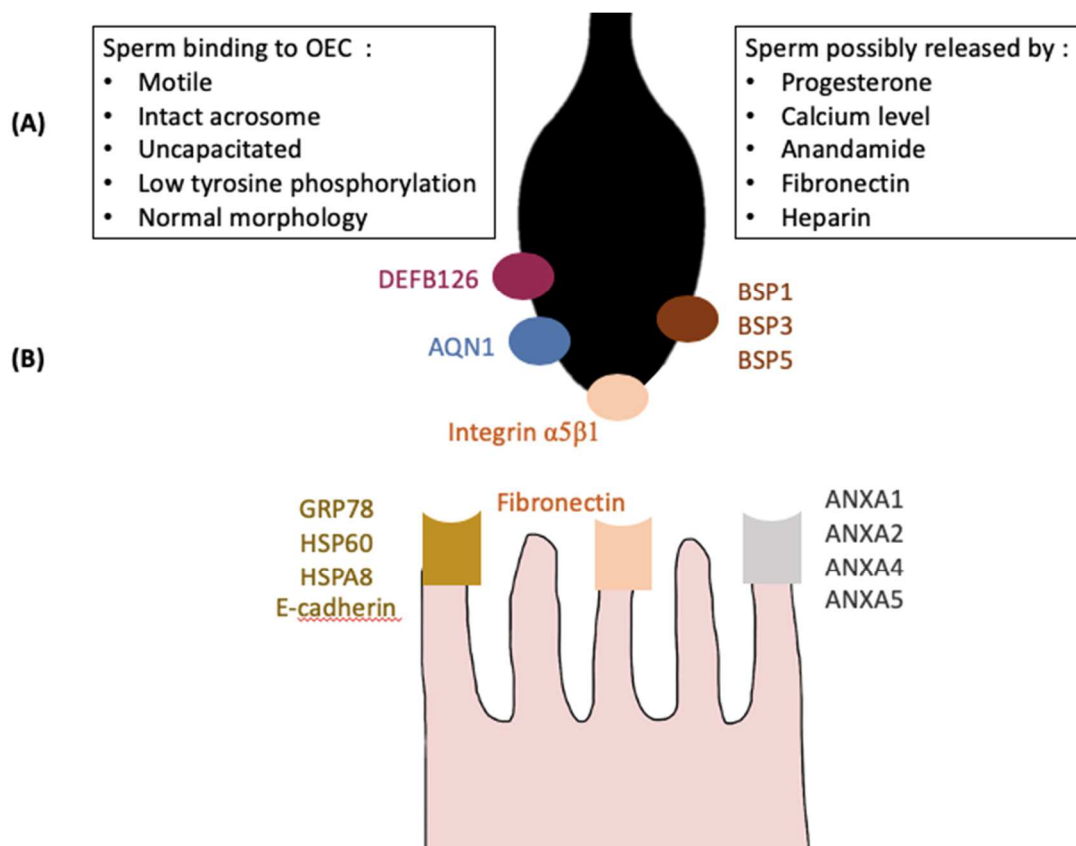
475

476 *In vitro*, sperm bind in equivalent numbers to isthmic and ampullary explants in cattle and pigs
477 (Fazeli et al., 2004; Lefebvre et al., 1995; Petrunkina et al., 2001; Sostaric et al., 2008) as well as *in*
478 *vivo*, after surgical sperm infusion into the oviduct of pre-ovulatory cows (Lefebvre et al., 1995). It is
479 thus likely that sperm form a reservoir in the isthmus because it is the first region encountered
480 beyond the UTJ. However, sperm binding is not restricted to the caudal isthmus: in mice, in which
481 very thin oviductal wall allowed direct observation of spermatozoa (from transgenic males)
482 expressing green fluorescent protein (GFP) in their acrosome by live cell imaging, frequent
483 detachment and reattachment were observed as sperm ascended toward the oocyte and most sperm
484 located in the ampulla were found attached to the epithelium (Chang and Suarez, 2012).

485

486 There is evidence that not all sperm have the ability to bind to the oviduct epithelium (Figure 8).
487 Studies conducted in human and cattle showed that approximately 20% to 50% of frozen-thawed and
488 Percoll-washed spermatozoa were able to bind to OEC monolayers or oviduct explants *in vitro*
(Ellington et al., 1999; Gualtieri and Talevi, 2003). It was shown that only motile, uncapacitated and

489 acrosome-intact sperm with a normal phenotype selectively bound to OECs *in vitro* (Ellington et al.,
 490 1999; Fazeli et al., 1999; Gualtieri and Talevi, 2000; Leemans et al., 2014; Lefebvre and Suarez,
 491 1996; Petrunkina et al., 2004; Thomas et al., 1994). In pigs, the ability to bind to OECs *in vitro*
 492 correlated with the ability of spermatozoa to swell in response to hypo-osmotic stress and to recover
 493 their initial volume after induced stress (Khalil et al., 2006). When bound and unbound boar sperm
 494 were compared during incubation with porcine OECs during 24 h, the percentage of viable and
 495 morphologically normal sperm was higher and increased over time in the bound population (Yeste et
 496 al., 2014). After sperm sex sorting in pigs, both X-and Y-bearing sperm bound at equivalent numbers
 497 to porcine oviduct aggregates (Winters et al., 2018). Furthermore, a high incidence of morphological
 498 abnormalities and cytoplasmic droplets, as well as abnormal or unstable chromatin, was shown to
 499 significantly reduce the ability of sperm to bind to OECs in human and pigs (Ardon et al., 2008;
 500 Ellington et al., 1999; Petrunkina et al., 2001; Waberski et al., 2006). This supports the general idea
 501 that after crossing of the UTJ, a functional sperm reservoir is formed with a highly selected
 502 population of top quality spermatozoa that are not (or not fully) capacitated.



503

504 **Figure 8. Sperm interactions with oviduct epithelial cell and underlying mechanisms.** (A) Sperm
 505 parameters for binding to OECs and candidates for the induction of sperm release around the time of ovulation
 506 are indicated in left and right squares, respectively. (B) Sperm surface proteins potentially involved in sperm
 507 binding to OECs include the spermadhesin AQN1, Binders of Sperm Proteins (BSPs) 1, 3 and 5, integrin
 508 $\alpha 5\beta 1$ and beta defensin 126 (DEFB26). Sperm receptors identified at the luminal surface of OECs include the
 509 chaperones GRP78, HSP60 and HSPA8, E-cadherin, fibronectin (as specific partner of integrin $\alpha 5\beta 1$) and
 510 various members of the annexin (ANX) family. Refer to the text for related species and references.

511 Sperm binding to the oviduct epithelium is carbohydrate-dependent, as shown by extensive
 512 inhibition of sperm binding by competition assays in the presence of glycans (Cortes et al., 2004;
 513 Green et al., 2001; Lefebvre et al., 1997; Sostaric et al., 2008; Sostaric et al., 2005). The use of

514 glycan arrays allowed to identify 6-sialylated biantennary N-acetyllactosamine and Lewis X
515 trisaccharide (Le^X) as the motifs that bind porcine sperm whereas bull sperm specifically bind the
516 closely related isomere Lewis A motif (for review, see (Miller, 2018)). Various proteins that
517 potentially contain the above carbohydrates have been identified as sperm receptors on the luminal
518 surface of the oviduct epithelium (Figure 8). The chaperones GRP78, HSP60 and HSPA8, a highly
519 conserved member of the HSP70 family, are expressed at the luminal surface of the oviduct
520 epithelium and were shown to bind spermatozoa in human (Lachance et al., 2007; Marin-Briggiler et
521 al., 2010), cattle (Boilard et al., 2004; Elliott et al., 2009; Holt et al., 2015) and pigs (Elliott et al.,
522 2009). Furthermore, affinity purification of proteins extracted from oviductal apical membranes
523 identified annexins A1, A2, A4 and A5 as other sperm-interacting proteins in cattle (Ignotz et al.,
524 2007) whereas annexin A2 (ANXA2) was also proposed as the main sperm binding isoform in pigs
525 (Teijeiro et al., 2009). On the other hand, epithelial cadherin (E-cadherin), a protein involved in
526 calcium-dependent somatic cell adhesion, was identified as a sperm receptor in the bovine oviduct
527 (Caballero et al., 2014). Finally, fibronectin, a high molecular weight glycoprotein present at the
528 apical surface of the oviduct epithelium in human and cattle (Inan et al., 2004; Osycka-Salut et al.,
529 2017) was shown to interact with bovine sperm through $\alpha 5 \beta 1$, an integrin expressed in the sperm of
530 several species (Osycka-Salut et al., 2017). It was proposed that an increase in fibronectin levels in
531 the oviductal fluid during the pre-ovulatory period promotes sperm release in cattle (Osycka-Salut et
532 al., 2017).

533 Epididymal sperm of various species were found to be able to bind to OECs, yet with a much lower
534 binding capacity than ejaculated sperm (Gwathmey et al., 2006; Gwathmey et al., 2003; Henry et al.,
535 2015; Petrunkina et al., 2001; Silva et al., 2014). Beta-defensin 126 (DEFB126), a protein from the
536 corpus epididymis and integral part of the sperm glycocalyx, was shown to be critical for sperm
537 attachment to the macaque oviduct epithelium (Tollner et al., 2008). Removal or alteration of
538 DEFB126 in primate sperm reduced the capacity of spermatozoa to bind to oviduct explants and
539 treatment of explants with soluble DEFB126 demonstrated that DEFB126 associated predominantly
540 with secretory non-ciliated cells (Tollner et al., 2008).

541 Spermatozoa from various species are able to bind to heterologous OECs (Ellington et al., 1998;
542 Petrunkina et al., 2004), which is in favor of common mechanisms of oviduct-sperm interactions
543 among species. Several families of seminal plasma proteins like the BSPs (Binder of Sperm Proteins)
544 are adsorbed at the sperm surface at ejaculation and are involved in the establishment of sperm
545 reservoir in cattle (Talevi and Gualtieri, 2010). BSPs consist of an N-terminal domain followed by
546 two fibronectin type II domains possessing phospholipid and heparin binding sites (for review, see
547 (Plante et al., 2016)). BSP1 (formerly called PDC-109), the most abundant protein in the bovine
548 seminal plasma, as well as BSP3 and BSP5, were shown to promote binding of epididymal bull
549 sperm to bovine oviductal explants (Gwathmey et al., 2006; Gwathmey et al., 2003). In the pig, the
550 most abundant proteins in the seminal plasma are members of the spermadhesin family (Topfer-
551 Petersen et al., 1998). The spermadhesin AQN1 was shown to recognize a wide range of glycans and
552 to inhibit boar sperm binding to OECs when added in the culture medium (Ekhlas-Hundrieser et al.,
553 2005), suggesting a role in the formation of the oviductal sperm reservoir in pigs.

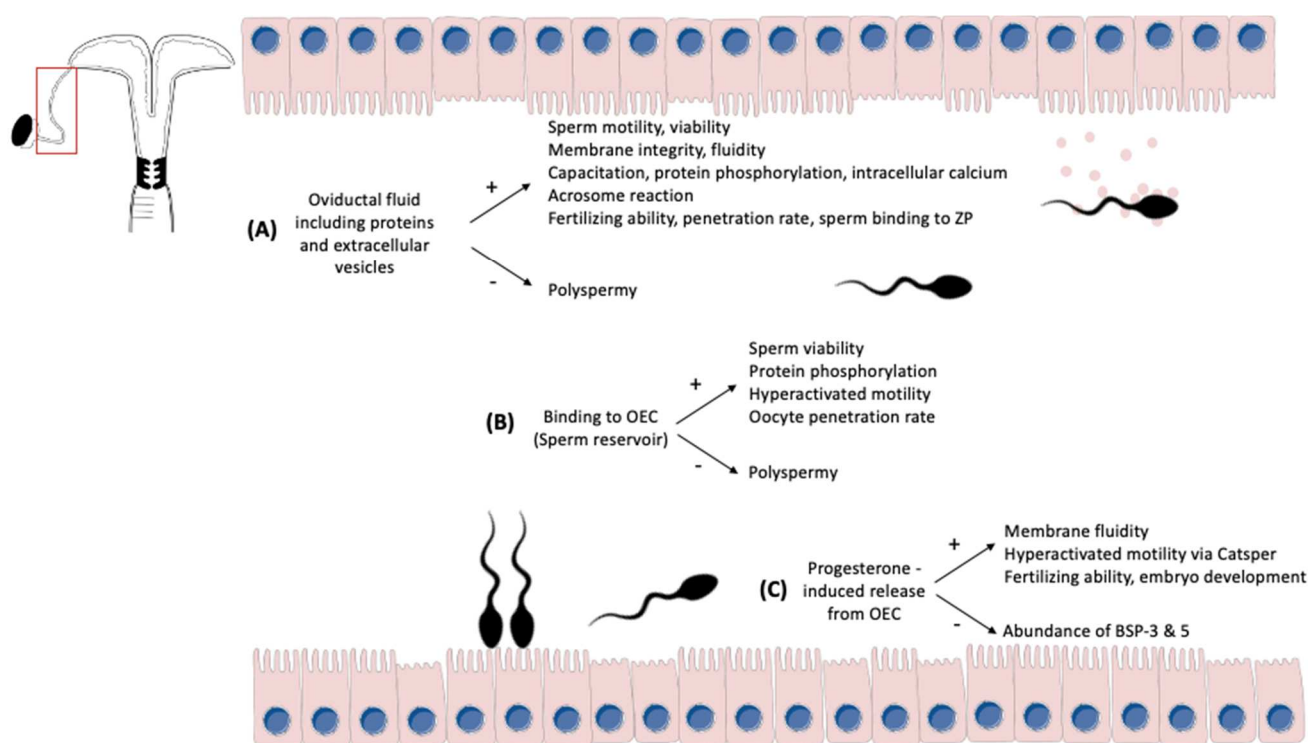
554 ***4.4. Effects of interaction with oviduct epithelial cells on sperm physiology***

556 Binding to oviductal cells or OEC apical membrane preparations prolongs sperm lifespan, as shown
557 *in vitro* in cattle (Boilard et al., 2002; Boilard et al., 2004), pigs (Fazeli et al., 2003; Yeste et al.,
558 2009) and humans (Morales et al., 1996; Murray and Smith, 1997) (Figure 9). This beneficial effect
559 on sperm viability was more pronounced with oviductal cells than with epithelial cells from

560 mammary glands or kidney, showing oviduct-specific effects (Boilard et al., 2002; Moein-Vaziri et
 561 al., 2014; Yeste et al., 2009). Moreover, direct cell contact seems optimal for sperm survival as co-
 562 incubation with OEC-conditioned medium had much lower efficiency for maintaining boar sperm
 563 viability over time (Yeste et al., 2009).

564 Various factors fluctuating in the oviduct fluid around the time of ovulation have been proposed as
 565 sperm releasing factors, including calcium level (Bosch et al., 2001; Gervasi et al., 2016),
 566 anandamide (Gervasi et al., 2016; Gervasi et al., 2009; Kumar et al., 2017; Osycka-Salut et al.,
 567 2012), fibronectin (Osycka-Salut et al., 2017), sulfated glycosaminoglycans such as heparin (Ardon
 568 et al., 2016; Talevi and Gualtieri, 2001; Tienthai, 2015) and ovarian steroid hormones (Hunter, 2008;
 569 Lamy et al., 2016b). Using bovine OEC culture system, we showed that bull sperm bound to OECs
 570 can be released by physiological nanomolar concentrations of progesterone (Lamy et al., 2017).

571 Similarly, progesterone was recently shown to induce sperm release from OEC aggregates in pigs
 572 (Machado et al., 2019). Bull sperm detached from OECs by the action of progesterone displayed
 573 decreased levels of BSP-3 and BSP-5 (Ramal-Sanchez et al., 2020), supporting a role of BSPs in
 574 progesterone-induced sperm release. Furthermore, although α estradiol had no effect on bull sperm
 575 release from OECs *in vitro*, the releasing effect of progesterone was inhibited by α estradiol in a dose-
 576 dependent manner in cattle (Lamy et al., 2017), showing that both progesterone and α estradiol are
 577 likely to be involved in sperm release. It is worth noting that only 50 to 75% of bound sperm can be
 578 released through the action of progesterone (Lamy et al., 2017; Machado et al., 2019; Romero-
 579 Aguirregomez-corta et al., 2019), indicating that the ability of sperm to respond to the releasing
 580 signal, in addition to its ability to bind to OECs, are highly selective steps toward the oocyte.



581

582 **Figure 9. Summarized effects of interactions with the oviduct on sperm physiology.** (A) Effects of
 583 sperm interaction with the oviductal fluid including soluble proteins and oviductal extracellular vesicles
 584 (oEVs) on sperm physiology; (B) Effects of interactions with oviductal epithelial cells (OECs, formation of an
 585 oviductal sperm reservoir) on sperm physiology; (C) Effect of sequential binding to OECs then release by the
 586 action of progesterone on sperm physiology. See the text for corresponding references.

587 Recent data in pigs and cattle indicate that sperm bound to OECs requires hyperactive motility to
588 detach themselves from OECs, an action likely mediated by progesterone-triggered calcium influx
589 through the cation channel of spermatozoa (CatSper) (Machado et al., 2019; Romero-
590 Aguirregomezcorta et al., 2019). Hyperactivated motility is a particular asymmetrical flagellar
591 movement that enhances the ability of sperm to penetrate the cumulus oophorus and the zona
592 pellucida (Suarez, 2008). In mice, sperm hyperactive motility is typically observed each time sperm
593 detach from the oviduct epithelium (Chang and Suarez, 2012; DeMott and Suarez, 1992). In
594 accordance with data in cattle and pigs, murine sperm lacking CatSper are unable to display
595 hyperactive motility and detach from the oviduct epithelium (Ho et al., 2009). Progesterone was
596 shown to be able to induce or increase sperm hyperactive motility in the hamster (Noguchi et al.,
597 2008), mouse (Perez-Cerezales et al., 2016) and macaque (Sumigama et al., 2015). However, the role
598 of progesterone in sperm detachment from the sperm reservoir remains to be investigated in these
599 species. It is however likely that sperm hyperactivated motility is initiated in the caudal isthmus, i.e.
600 relatively far from the fertilization site, in order to detach from the sperm reservoir. In addition,
601 although the cumulus cells and zona pellucida are known to induce the acrosome reaction, recent
602 data in mice indicate that most spermatozoa begin to react in the isthmus, thus before reaching the
603 site of fertilization in the ampulla (Hino et al., 2016; La Spina et al., 2016).

604 Sperm binding to the oviductal isthmus is not absolutely mandatory for sperm to acquire their
605 fertilizing ability: when rabbits, sheep and pigs were surgically inseminated directly into the ampulla
606 (*via* the infundibulum) or into the abdominal cavity, fertilization did take place (Hunter, 2011).
607 Nonetheless, a large amount of data show that binding to OECs and subsequent release has beneficial
608 effects not only on sperm viability and motility but also on sperm capacitation and fertilizing
609 capacity (Figure 9). Tyrosine phosphorylation of tail-associated protein was shown to increase over
610 time in dog and stallion sperm bound to oviduct explants compared with unbound sperm (Leemans et
611 al., 2014; Petrunkina et al., 2004). Specific patterns of protein phosphorylation located in the
612 equatorial segment and tail were also observed in subpopulations of bound sperm in pigs (Lopez-
613 Ubeda et al., 2017). Furthermore, bull sperm released from OECs by the action of progesterone
614 showed increased membrane fluidity and displayed major lipidomic and proteomic changes, some of
615 which related to sperm capacitation (Ramal-Sanchez et al., 2020). In addition, bull sperm submitted
616 to the sequential binding and progesterone-induced or heparin-induced release from OECs showed
617 higher *in vitro* fertilizing capacity compared to controls without OECs (Gualtieri and Talevi, 2003;
618 Lamy et al., 2017). In pigs, pre-incubation of sperm with OECs reduced polyspermy and increased
619 oocyte penetration rate compared with controls (Bureau et al., 2000). In another study, number of
620 porcine zygotes and sperm nuclear decondensation were improved after sperm-OEC binding and
621 release compared to unbound sperm (Lopez-Ubeda et al., 2017).

622 Finally, a positive relationship was evidenced between the capacity of sperm to bind to homologous
623 oviduct explants and male fertility in pigs (Khalil et al., 2006; Waberski et al., 2005) and cattle (De
624 pauw et al., 2002; Saraf et al., 2019). Further studies are now needed to determine if sperm-oviduct-
625 binding *in vitro* tests may be used for accurate prediction of male fertility in the field.

626 **5. Conclusions**

627 The interactions taking place between sperm and the female reproductive tract operate a drastic
628 selection among male gametes, leading to a small subpopulation of top quality spermatozoa at the
629 site of fertilization. Sperm selection involves uterine contractions to remove dead and abnormal
630 spermatozoa from the uterus but also various mechanisms including sperm phagocytosis mediated by

631 uterine inflammatory response, key molecules on sperm surface to cross the UTJ, binding to the
632 oviductal sperm reservoir and then ability to respond to the releasing signal at the time of ovulation.
633 Altogether, results show that the seminal plasma plays important roles in modulating the female
634 immune response against sperm cells and protein interactions in female secretions. Effects of specific
635 interactions between seminal proteins coating the sperm surface and female fluid components would
636 bring new knowledge on the exact role of male secretions in sperm transit and survival in the route
637 toward the oocyte. Although molecules involved in sperm transit to the oviduct have gained recent
638 insights in mice, the mechanisms allowing sperm to cross the UTJ in other mammalian species
639 remain unexplored. Furthermore, the mechanisms and functions of sperm interactions with genital
640 tract secretions, especially in the uterine cavity, have been rather poorly investigated and deserve
641 further studies. From *in vitro* studies, sperm interactions with oviductal cells appear to promote
642 sperm survival and prevent precocious capacitation, but in some specific conditions to contribute to
643 sperm capacitation and acquisition of fertilizing competence. Recent data highlight the dynamic
644 hormone-regulated changes in the composition of uterine and oviductal fluids that may explain the
645 lack of consistency recorded in *in vitro* studies. Finally, recent research suggest that EVs in the UF
646 and OF act as natural cargos bringing key molecules from the female genital tract compartment onto
647 male gametes for the success of fertilization. New knowledge in the cross-talk between spermatozoa
648 and the female genital tract may provide new tools for a more accurate evaluation of fertility and to
649 improve fertility in natural pregnancies as well as assisted reproductive technologies.

650

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658

659 **References**

- 660 Abe, H., Sendai, Y., Satoh, T. and Hoshi, H., 1995a. Secretory products of bovine oviductal epithelial cells
661 support the viability and motility of bovine spermatozoa in culture *in vitro*, *J Exp Zool.* 272, 54-61.
662 Abe, H., Sendai, Y., Satoh, T. and Hoshi, H., 1995b. Bovine oviduct-specific glycoprotein: a potent factor for
663 maintenance of viability and motility of bovine spermatozoa *in vitro*, *Mol Reprod Dev.* 42, 226-32.
664 Akthar, I., Suarez, S., Morillo, V.A., Sasaki, M., Ezz, M.A., Takahashi, K.I., Shimada, M., Marey, M.A. and
665 Miyamoto, A., 2019. Sperm enter glands of preovulatory bovine endometrial explants and initiate
666 inflammation, *Reproduction.* 1, 19-0414.
667 Al-Dossary, A.A., Strehler, E.E. and Martin-DeLeon, P.A., 2013. Expression and secretion of plasma
668 membrane Ca²⁺-ATPase 4a (PMCA4a) during murine estrus: association with oviductal exosomes
669 and uptake in sperm, *PLoS One.* 8, e80181.
670 Al-Dossary, A.A., Bathala, P., Caplan, J.L. and Martin-DeLeon, P.A., 2015. Oviductosome-Sperm Membrane
671 Interaction in Cargo Delivery: DETECTION OF FUSION AND UNDERLYING MOLECULAR
672 PLAYERS USING THREE-DIMENSIONAL SUPER-RESOLUTION STRUCTURED
673 ILLUMINATION MICROSCOPY (SR-SIM), *J Biol Chem.* 290, 17710-23.
674 Alcantara-Neto, A., Schmaltz, L., Caldas, E., Blache, M.C., Mermillod, P. and Alminana, C., 2020a. Porcine
675 oviductal extracellular vesicles interact with gametes and regulate sperm motility and survival,
676 *Theriogenology.* in press.

677 Alcântara-Neto, A., Fernandez-Rufete, M., Corbin, E., Tsikis, G., Uzbekov, R., Garanina, A.S., Coy, P.,
678 Alminana, C. and Mermillod, P., 2019. Oviduct fluid extracellular vesicles regulate polyspermy
679 during porcine in vitro fertilization, *Reprod Fertil Dev.* RD19058 Accepted 18 July 2019

680 Alcântara-Neto, A.S., Fernandez-Rufete, M., Corbin, E., Tsikis, G., Uzbekov, R., Garanina, A.S., Coy, P.,
681 Alminana, C. and Mermillod, P., 2020b. Oviduct fluid extracellular vesicles regulate polyspermy
682 during porcine in vitro fertilisation, *Reprod Fertil Dev.* 32, 409-418.

683 Alghamdi, A.S. and Foster, D.N., 2005. Seminal DNase frees spermatozoa entangled in neutrophil
684 extracellular traps, *Biol Reprod.* 73, 1174-81.

685 Alghamdi, A.S., Lovaas, B.J., Bird, S.L., Lamb, G.C., Rendahl, A.K., Taube, P.C. and Foster, D.N., 2009.
686 Species-specific interaction of seminal plasma on sperm-neutrophil binding, *Anim Reprod Sci.* 114,
687 331-44.

688 Alminana, C. and Bauersachs, S., 2019. Extracellular Vesicles in the Oviduct: Progress, Challenges and
689 Implications for the Reproductive Success, *Bioengineering (Basel)*. 6.

690 Alminana, C., Corbin, E., Tsikis, G., Alcântara-Neto, A.S., Labas, V., Reynaud, K., Galio, L., Uzbekov, R.,
691 Garanina, A.S., Druart, X. and Mermillod, P., 2017. Oviduct extracellular vesicles protein content and
692 their role during oviduct-embryo cross-talk, *Reproduction.* 154, 153-168.

693 Aloe, S., Weber, F., Behr, B., Sauter-Louis, C. and Zerbe, H., 2012. Modulatory effects of bovine seminal
694 plasma on uterine inflammatory processes, *Reproduction in domestic animals = Zuchthygiene.* 47, 12-
695 9.

696 Araki, Y., Nohara, M., Yoshida-Komiya, H., Kuramochi, T., Ito, M., Hoshi, H., Shinkai, Y. and Sendai, Y.,
697 2003. Effect of a null mutation of the oviduct-specific glycoprotein gene on mouse fertilization,
698 *Biochem J.* 374, 551-7.

699 Ardon, F., Helms, D., Sahin, E., Bollwein, H., Topfer-Petersen, E. and Waberski, D., 2008. Chromatin-
700 unstable boar spermatozoa have little chance of reaching oocytes in vivo, *Reproduction.* 135, 461-70.

701 Ardon, F., Markello, R.D., Hu, L., Deutsch, Z.I., Tung, C.K., Wu, M. and Suarez, S.S., 2016. Dynamics of
702 Bovine Sperm Interaction with Epithelium Differ Between Oviductal Isthmus and Ampulla, *Biol*
703 *Reprod.* 95, 90.

704 Aviles, M., Gutierrez-Adan, A. and Coy, P., 2010. Oviductal secretions: will they be key factors for the future
705 ARTs?, *Mol Hum Reprod.* 16, 896-906.

706 Baba, D., Kashiwabara, S., Honda, A., Yamagata, K., Wu, Q., Ikawa, M., Okabe, M. and Baba, T., 2002.
707 Mouse sperm lacking cell surface hyaluronidase PH-20 can pass through the layer of cumulus cells
708 and fertilize the egg, *J Biol Chem.* 277, 30310-4.

709 Baba, M., Imai, T., Nishimura, M., Kakizaki, M., Takagi, S., Hieshima, K., Nomiyama, H. and Yoshie, O.,
710 1997. Identification of CCR6, the specific receptor for a novel lymphocyte-directed CC chemokine
711 LARC, *J Biol Chem.* 272, 14893-8.

712 Bai, R., Latifi, Z., Kusama, K., Nakamura, K., Shimada, M. and Imakawa, K., 2018a. Induction of immune-
713 related gene expression by seminal exosomes in the porcine endometrium, *Biochemical and*
714 *biophysical research communications.* 495, 1094-1101.

715 Bai, R., Latifi, Z., Kusama, K., Nakamura, K., Shimada, M. and Imakawa, K., 2018b. Induction of immune-
716 related gene expression by seminal exosomes in the porcine endometrium, *Biochem Biophys Res*
717 *Commun.* 495, 1094-1101.

718 Baillie, H.S., Pacey, A.A., Warren, M.A., Scudamore, I.W. and Barratt, C.I.R., 1997. Greater numbers of
719 human spermatozoa associate with endosalpingeal cells derived from the isthmus compared with
720 those from the ampulla, *Hum Reprod.* 12, 1985-1992.

721 Baker, M.A., 2016. Proteomics of post-translational modifications of mammalian spermatozoa, *Cell Tissue*
722 *Res.* 363, 279-287.

723 Bathala, P., Fereshteh, Z., Li, K., Al-Dossary, A.A., Galileo, D.S. and Martin-DeLeon, P.A., 2018. Oviductal
724 extracellular vesicles (oviductosomes, OVS) are conserved in humans: murine OVS play a pivotal
725 role in sperm capacitation and fertility, *Mol Hum Reprod.* 24, 143-157.

726 Bergmann, A., Taylor, U. and Rath, D., 2012. Flow-cytometric evaluation of lectin binding moieties on
727 porcine uterine epithelial cells, *Reprod Domest Anim.* 47, 77.

728 Bergmann, A., Taylor, U. and Rath, D., 2013. Sperm binding to porcine uterine epithelial cells might be lectin
729 mediated, *Reprod Fertil Dev.* 25, 152.

730 Bergqvist, A.S. and Rodriguez-Martinez, H., 2006. Sulphated glycosaminoglycans (S-GAGs) and syndecans
731 in the bovine oviduct, *Anim Reprod Sci.* 93, 46-60.

732 Bergqvist, A.S., Ballester, J., Johannisson, A., Hernandez, M., Lundeheim, N. and Rodriguez-Martinez, H.,
733 2006. In vitro capacitation of bull spermatozoa by oviductal fluid and its components, *Zygote*. 14,
734 259-73.

735 Boilard, M., Bailey, J., Collin, S., Dufour, M. and Sirard, M.A., 2002. Effect of bovine oviduct epithelial cell
736 apical plasma membranes on sperm function assessed by a novel flow cytometric approach, *Biol*
737 *Reprod.* 67, 1125-32.

738 Boilard, M., Reyes-Moreno, C., Lachance, C., Massicotte, L., Bailey, J.L., Sirard, M.A. and Leclerc, P., 2004.
739 Localization of the chaperone proteins GRP78 and HSP60 on the luminal surface of bovine oviduct
740 epithelial cells and their association with spermatozoa, *Biol Reprod.* 71, 1879-89.

741 Boquest, A.C., Smith, J.F., Briggs, R.M., Duganzich, D.M. and Summers, P.M., 1999. Effects of bovine
742 oviductal proteins on bull spermatozoal function, *Theriogenology*. 51, 583-95.

743 Bosch, P., de Avila, J.M., Ellington, J.E. and Wright, R.W., Jr., 2001. Heparin and Ca²⁺-free medium can
744 enhance release of bull sperm attached to oviductal epithelial cell monolayers, *Theriogenology*. 56,
745 247-60.

746 Brinkmann, V., Reichard, U., Goosmann, C., Fauler, B., Uhlemann, Y., Weiss, D.S., Weinrauch, Y. and
747 Zychlinsky, A., 2004. Neutrophil extracellular traps kill bacteria, *Science*. 303, 1532-5.

748 Brohi, R.D. and Huo, L.J., 2017. Posttranslational Modifications in Spermatozoa and Effects on Male Fertility
749 and Sperm Viability, *OMICS*. 21, 245-256.

750 Brussow, K.P., Ratky, J. and Rodriguez-Martinez, H., 2008. Fertilization and early embryonic development in
751 the porcine fallopian tube, *Reprod Domest Anim.* 43 Suppl 2, 245-51.

752 Bureau, M., Bailey, J.L. and Sirard, M.A., 2000. Influence of oviductal cells and conditioned medium on
753 porcine gametes, *Zygote*. 8, 139-44.

754 Burns, G., Brooks, K., Wildung, M., Navakanitworakul, R., Christenson, L.K. and Spencer, T.E., 2014.
755 Extracellular vesicles in luminal fluid of the ovine uterus, *PLoS One*. 9, e90913.

756 Caballero, J.N., Gervasi, M.G., Veiga, M.F., Dalvit, G.C., Perez-Martinez, S., Cetica, P.D. and Vazquez-
757 Levin, M.H., 2014. Epithelial cadherin is present in bovine oviduct epithelial cells and gametes, and is
758 involved in fertilization-related events, *Theriogenology*. 81, 1189-206.

759 Chang, H. and Suarez, S.S., 2012. Unexpected flagellar movement patterns and epithelial binding behavior of
760 mouse sperm in the oviduct, *Biol Reprod.* 86, 140, 1-8.

761 Chastant, S. and Saint-Dizier, M., 2019. Inflammation: friend or foe of bovine reproduction?, *Anim Reprod.*
762 16, 539-547.

763 Chirinos, M., Durand, M., Gonzalez-Gonzalez, M.E., Hernandez-Silva, G., Maldonado-Rosas, I., Lopez, P.
764 and Larrea, F., 2017. Uterine flushings from women treated with levonorgestrel affect sperm
765 functionality in vitro, *Reproduction*. 154, 607-614.

766 Cho, C., O'Dell Bunch, D., Faure, J.-E., Goulding, E.H., Eddy, E.M., Primakoff, P. and Myles, D.G., 1998.
767 Fertilization Defects in Sperm from Mice Lacking Fertilin β , *Science*. 281, 1857-1859.

768 Choudhary, S., Kumaresan, A., Kumar, M., Chhillar, S., Malik, H., Kumar, S., Kaushik, J.K., Datta, T.K. and
769 Mohanty, A.K., 2017. Effect of recombinant and native buffalo OVGP1 on sperm functions and in
770 vitro embryo development: a comparative study, *J Anim Sci Biotechnol.* 8, 69.

771 Clark, G.F. and Schust, D.J., 2013. Manifestations of immune tolerance in the human female reproductive
772 tract, *Front Immunol.* 4, 26.

773 Cortes, P.P., Orihuela, P.A., Zuniga, L.M., Velasquez, L.A. and Croxatto, H.B., 2004. Sperm binding to
774 oviductal epithelial cells in the rat: role of sialic acid residues on the epithelial surface and sialic acid-
775 binding sites on the sperm surface, *Biol Reprod.* 71, 1262-9.

776 Coy, P. and Aviles, M., 2010. What controls polyspermy in mammals, the oviduct or the oocyte?, *Biol Rev*
777 *Camb Philos Soc.* 85, 593-605.

778 Coy, P., Lloyd, R., Romar, R., Satake, N., Matas, C., Gadea, J. and Holt, W.V., 2010. Effects of porcine pre-
779 ovulatory oviductal fluid on boar sperm function, *Theriogenology*. 74, 632-42.

780 De pauw, I., Van Soom, A., Laevens, H., Verberckmoes, S. and de Kruif, A., 2002. Sperm binding to
781 epithelial oviduct explants in bulls with different nonreturn rates investigated with a new in vitro
782 model, *Biol Reprod.* 67, 1073-1079.

783 DeMott, R.P. and Suarez, S.S., 1992. Hyperactivated sperm progress in the mouse oviduct, *Biol Reprod.* 46,
784 779-85.

785 Ehrenwald, E., Foote, R.H. and Parks, J.E., 1990. Bovine oviductal fluid components and their potential role
786 in sperm cholesterol efflux, *Mol Reprod Dev.* 25, 195-204.

787 Ekhlasi-Hundrieser, M., Gohr, K., Wagner, A., Tsoleva, M., Petrunkina, A. and Topfer-Petersen, E., 2005.
788 Spermadhesin AQN1 is a candidate receptor molecule involved in the formation of the oviductal
789 sperm reservoir in the pig, *Biol Reprod.* 73, 536-45.

790 El-Shahat, K.H., Taysser, M.I., Badr, M.R. and Zaki, K.A., 2018. Effect of oviduct and follicular fluids on
791 ram sperm capacitation and acrosome reaction in vitro, *Int J Vet Sci Med.* 6, S57-S62.

792 Ellington, J.E., Jones, A.E., Davitt, C.M., Schneider, C.S., Brisbois, R.S., Hiss, G.A. and Wright, R.W., Jr.,
793 1998. Human sperm function in co-culture with human, macaque or bovine oviduct epithelial cell
794 monolayers, *Hum Reprod.* 13, 2797-804.

795 Ellington, J.E., Evenson, D.P., Wright, R.W., Jr., Jones, A.E., Schneider, C.S., Hiss, G.A. and Brisbois, R.S.,
796 1999. Higher-quality human sperm in a sample selectively attach to oviduct (fallopian tube) epithelial
797 cells in vitro, *Fertil Steril.* 71, 924-9.

798 Elliott, R.M., Lloyd, R.E., Fazeli, A., Sostaric, E., Georgiou, A.S., Satake, N., Watson, P.F. and Holt, W.V.,
799 2009. Effects of HSPA8, an evolutionarily conserved oviductal protein, on boar and bull spermatozoa,
800 *Reproduction.* 137, 191-203.

801 Elweza, A.E., Ezz, M.A., Acosta, T.J., Talukder, A.K., Shimizu, T., Hayakawa, H., Shimada, M., Imakawa,
802 K., Zaghoul, A.H. and Miyamoto, A., 2018. A proinflammatory response of bovine endometrial
803 epithelial cells to active sperm in vitro, *Mol Reprod Dev.* 85, 215-226.

804 England, G.C. and Burgess, C.M., 2003. Survival of dog spermatozoa within the reproductive tract of the
805 bitch, *Reprod. Domest. Anim.* 38, 325-326.

806 Ezz, M.A., Marey, M.A., Elweza, A.E., Kawai, T., Heppelmann, M., Pfarrer, C., Balboula, A.Z., Montaser,
807 A., Imakawa, K., Zaabel, S.M., Shimada, M. and Miyamoto, A., 2019. TLR2/4 signaling pathway
808 mediates sperm-induced inflammation in bovine endometrial epithelial cells in vitro, *PLoS ONE.* 14.

809 Fair, S., Meade, K., Reynaud, K., Druart, X. and de Graaf, S.P., 2019. The biological mechanisms regulating
810 sperm selection by the ovine cervix, *Reproduction.* 1, 18-0595.

811 Fazeli, A., Duncan, A.E., Watson, P.F. and Holt, W.V., 1999. Sperm-oviduct interaction: induction of
812 capacitation and preferential binding of uncapacitated spermatozoa to oviductal epithelial cells in
813 porcine species, *Biol Reprod.* 60, 879-86.

814 Fazeli, A., Affara, N.A., Hubank, M. and Holt, W.V., 2004. Sperm-induced modification of the oviductal gene
815 expression profile after natural insemination in mice, *Biol Reprod.* 71, 60-5.

816 Fazeli, A., Elliott, R.M., Duncan, A.E., Moore, A., Watson, P.F. and Holt, W.V., 2003. In vitro maintenance
817 of boar sperm viability by a soluble fraction obtained from oviductal apical plasma membrane
818 preparations, *Reproduction.* 125, 509-17.

819 Fedorka, C.E., Scoggin, K.E., Woodward, E.M., Squires, E.L., Ball, B.A. and Troedsson, M., 2016. The effect
820 of select seminal plasma proteins on endometrial mRNA cytokine expression in mares susceptible to
821 persistent mating-induced endometritis, *Reproduction in domestic animals = Zuchthygiene.* 30,
822 12813.

823 Fereshteh, Z., Schmidt, S.A., Al-Dossary, A.A., Accerbi, M., Arighi, C., Cowart, J., Song, J.L., Green, P.J.,
824 Choi, K., Yoo, S. and Martin-DeLeon, P.A., 2018. Murine Oviductosomes (OVS) microRNA
825 profiling during the estrous cycle: Delivery of OVS-borne microRNAs to sperm where miR-34c-5p
826 localizes at the centrosome, *Sci Rep.* 8, 16094.

827 Ferraz, M., Carothers, A., Dahal, R., Noonan, M.J. and Songsasen, N., 2019. Oviductal extracellular vesicles
828 interact with the spermatozoon's head and mid-piece and improves its motility and fertilizing ability in
829 the domestic cat, *Sci Rep.* 9, 9484.

830 Fichtner, T., Kotarski, F., Gartner, U., Conejeros, I., Hermosilla, C., Wrenzycki, C. and Taubert, A., 2020.
831 Bovine sperm samples induce different NET phenotypes in a NADPH oxidase-, PAD4-, and Ca⁺⁺-
832 dependent process, *Biol Reprod.* 102, 902-914.

833 Franchi, A., Cubilla, M., Guidobaldi, H.A., Bravo, A.A. and Giojalas, L.C., 2016. Uterosome-like vesicles
834 prompt human sperm fertilizing capability, *Mol Hum Reprod.* 22, 833-841.

835 Franchi, A., Moreno-Irusta, A., Dominguez, E.M., Adre, A.J. and Giojalas, L.C., 2020. Extracellular vesicles
836 from oviductal isthmus and ampulla stimulate the induced acrosome reaction and signaling events
837 associated with capacitation in bovine spermatozoa, *J Cell Biochem.* 121, 2877-2888.

838 Fujihara, Y., Okabe, M. and Ikawa, M., 2014. GPI-anchored protein complex, LY6K/TEX101, is required for
839 sperm migration into the oviduct and male fertility in mice, *Biology of reproduction.* 90.

840 Fujihara, Y., Miyata, H. and Ikawa, M., 2018. Factors controlling sperm migration through the oviduct
841 revealed by gene-modified mouse models, *Exp Anim.* 67, 91-104.

842 Fujihara, Y., Tokuhira, K., Muro, Y., Kondoh, G., Araki, Y., Ikawa, M. and Okabe, M., 2013. Expression of
843 TEX101, regulated by ACE, is essential for the production of fertile mouse spermatozoa, *Proc Natl*
844 *Acad Sci U S A.* 110, 8111-6.

845 Fujihara, Y., Noda, T., Kobayashi, K., Oji, A., Kobayashi, S., Matsumura, T., Larasati, T., Oura, S., Kojima-
846 Kita, K., Yu, Z., Matzuk, M.M. and Ikawa, M., 2019. Identification of multiple male reproductive
847 tract-specific proteins that regulate sperm migration through the oviduct in mice, *Proc Natl Acad Sci*
848 *U S A.* 116, 18498-18506.

849 Gadella, B.M., 2017. Reproductive tract modifications of the boar sperm surface, *Mol Reprod Dev.* 84, 822-
850 831.

851 Garcia-Vazquez, F.A., Gadea, J., Matas, C. and Holt, W.V., 2016. Importance of sperm morphology during
852 sperm transport and fertilization in mammals, *Asian journal of andrology.* 18, 844-850.

853 Garcia-Vazquez, F.A., Hernandez-Caravaca, I., Matas, C., Soriano-Ubeda, C., Abril-Sanchez, S. and
854 Izquierdo-Rico, M.J., 2015. Morphological study of boar sperm during their passage through the
855 female genital tract, *J Reprod Dev.* 61, 407-13.

856 Gatién, J., Mermillod, P., Tsikis, G., Bernardi, O., Janati Idrissi, S., Uzbekov, R., Le Bourhis, D., Salvetti, P.,
857 Alminana, C. and Saint-Dizier, M., 2019. Metabolomic Profile of Oviductal Extracellular Vesicles
858 across the Estrous Cycle in Cattle, *Int J Mol Sci.* 20.

859 Gegenfurtner, K., Frohlich, T., Flenkenthaler, F., Kusters, M., Fritz, S., Desnoes, O., Le Bourhis, D., Salvetti,
860 P., Sandra, O., Charpigny, G., Mermillod, P., Lonergan, P., Wolf, E. and Arnold, G.J., 2020. Genetic
861 merit for fertility alters the bovine uterine luminal fluid proteome, *Biol Reprod.* 102, 730-739.

862 Gervasi, M.G., Rapanelli, M., Ribeiro, M.L., Farina, M., Billi, S., Franchi, A.M. and Perez Martinez, S., 2009.
863 The endocannabinoid system in bull sperm and bovine oviductal epithelium: role of anandamide in
864 sperm-oviduct interaction, *Reproduction.* 137, 403-14.

865 Gervasi, M.G., Osycka-Salut, C., Sanchez, T., Alonso, C.A., Lladós, C., Castellano, L., Franchi, A.M.,
866 Villalon, M. and Perez-Martinez, S., 2016. Sperm Release From the Oviductal Epithelium Depends
867 on Ca(2+) Influx Upon Activation of CB1 and TRPV1 by Anandamide, *J Cell Biochem.* 117, 320-33.

868 Green, C.E., Bredl, J., Holt, W.V., Watson, P.F. and Fazeli, A., 2001. Carbohydrate mediation of boar sperm
869 binding to oviductal epithelial cells in vitro, *Reproduction.* 122, 305-15.

870 Griffiths, G.S., Miller, K.A., Galileo, D.S. and Martin-DeLeon, P.A., 2008a. Murine SPAM1 is secreted by
871 the estrous uterus and oviduct in a form that can bind to sperm during capacitation: acquisition
872 enhances hyaluronic acid-binding ability and cumulus dispersal efficiency, *Reproduction.* 135, 293-
873 301.

874 Griffiths, G.S., Galileo, D.S., Reese, K. and Martin-DeLeon, P.A., 2008b. Investigating the role of murine
875 epididymosomes and uterosomes in GPI-linked protein transfer to sperm using SPAM1 as a model,
876 *Mol Reprod Dev.* 75, 1627-36.

877 Grippo, A.A., Way, A.L. and Killian, G.J., 1995. Effect of bovine ampullary and isthmic oviductal fluid on
878 motility, acrosome reaction and fertility of bull spermatozoa, *J Reprod Fertil.* 105, 57-64.

879 Gualtieri, R. and Talevi, R., 2000. In vitro cultured bovine oviductal cells bind acrosome-intact sperm and
880 retain this ability upon sperm release, *Biol Reprod.* 62, 1754-1762.

881 Gualtieri, R. and Talevi, R., 2003. Selection of highly fertilization-competent bovine spermatozoa through
882 adhesion to the Fallopian tube epithelium in vitro, *Reproduction.* 125, 251-8.

883 Gwathmey, T.M., Ignatz, G.G. and Suarez, S.S., 2003. PDC-109 (BSP-A1/A2) promotes bull sperm binding
884 to oviductal epithelium in vitro and may be involved in forming the oviductal sperm reservoir, *Biol*
885 *Reprod.* 69, 809-15.

886 Gwathmey, T.M., Ignatz, G.G., Mueller, J.L., Manjunath, P. and Suarez, S.S., 2006. Bovine seminal plasma
887 proteins PDC-109, BSP-A3, and BSP-30-kDa share functional roles in storing sperm in the oviduct,
888 *Biol Reprod.* 75, 501-7.

889 Hao, Y., Mathialagan, N., Walters, E., Mao, J., Lai, L., Becker, D., Li, W., Critser, J. and Prather, R.S., 2006.
890 Osteopontin reduces polyspermy during in vitro fertilization of porcine oocytes, *Biol Reprod.* 75, 726-
891 33.

892 Henry, F., Eder, S., Reynaud, K., Schon, J., Wibbelt, G., Fontbonne, A. and Muller, K., 2015. Seminal fluid
893 promotes in vitro sperm-oviduct binding in the domestic cat (*Felis catus*), *Theriogenology.* 83, 1373-
894 80.

- 895 Hino, T., Muro, Y., Tamura-Nakano, M., Okabe, M., Tateno, H. and Yanagimachi, R., 2016. The Behavior
896 and Acrosomal Status of Mouse Spermatozoa In Vitro, and Within the Oviduct During Fertilization
897 after Natural Mating, *Biol Reprod.* 95, 50.
- 898 Ho, K., Wolff, C.A. and Suarez, S.S., 2009. CatSper-null mutant spermatozoa are unable to ascend beyond the
899 oviductal reservoir, *Reprod Fertil Dev.* 21, 345-50.
- 900 Holt, W.V. and Fazeli, A., 2016. Sperm selection in the female mammalian reproductive tract. Focus on the
901 oviduct: Hypotheses, mechanisms, and new opportunities, *Theriogenology.* 85, 105-12.
- 902 Holt, W.V., Del Valle, I. and Fazeli, A., 2015. Heat shock protein A8 stabilizes the bull sperm plasma
903 membrane during cryopreservation: Effects of breed, protein concentration, and mode of use,
904 *Theriogenology.* 84, 693-701.
- 905 Hugentobler, S.A., Morris, D.G., Sreenan, J.M. and Diskin, M.G., 2007a. Ion concentrations in oviduct and
906 uterine fluid and blood serum during the estrous cycle in the bovine, *Theriogenology.* 68, 538-48.
- 907 Hugentobler, S.A., Humpherson, P.G., Leese, H.J., Sreenan, J.M. and Morris, D.G., 2008. Energy substrates
908 in bovine oviduct and uterine fluid and blood plasma during the oestrous cycle, *Mol Reprod Dev.* 75,
909 496-503.
- 910 Hugentobler, S.A., Diskin, M.G., Leese, H.J., Humpherson, P.G., Watson, T., Sreenan, J.M. and Morris, D.G.,
911 2007b. Amino acids in oviduct and uterine fluid and blood plasma during the estrous cycle in the
912 bovine, *Mol Reprod Dev.* 74, 445-54.
- 913 Hunter, R.H., 1981. Sperm transport and reservoirs in the pig oviduct in relation to the time of ovulation, *J*
914 *Reprod Fertil.* 63, 109-17.
- 915 Hunter, R.H., 2008. Sperm release from oviduct epithelial binding is controlled hormonally by peri-ovulatory
916 graafian follicles, *Mol Reprod Dev.* 75, 167-74.
- 917 Hunter, R.H., 2011. Sperm head binding to epithelium of the oviduct isthmus is not an essential preliminary to
918 mammalian fertilization - review, *Zygote.* 19, 265-9.
- 919 Hunter, R.H. and Nichol, R., 1983. Transport of spermatozoa in the sheep oviduct: preovulatory sequestering
920 of cells in the caudal isthmus, *J Exp Zool.* 228, 121-8.
- 921 Hunter, R.H. and Wilmut, I., 1984. Sperm transport in the cow: peri-ovulatory redistribution of viable cells
922 within the oviduct, *Reprod Nutr Dev.* 24, 597-608.
- 923 Hunter, R.H., Flechon, B. and Flechon, J.E., 1991. Distribution, morphology and epithelial interactions of
924 bovine spermatozoa in the oviduct before and after ovulation: a scanning electron microscope study,
925 *Tissue Cell.* 23, 641-56.
- 926 Ignatz, G.G., Cho, M.Y. and Suarez, S.S., 2007. Annexins are candidate oviductal receptors for bovine sperm
927 surface proteins and thus may serve to hold bovine sperm in the oviductal reservoir, *Biol Reprod.* 77,
928 906-13.
- 929 Ikawa, M., Wada, I., Kominami, K., Watanabe, D., Toshimori, K., Nishimune, Y. and Okabe, M., 1997. The
930 putative chaperone calmeglin is required for sperm fertility, *Nature.* 387, 607-11.
- 931 Ikawa, M., Tokuhira, K., Yamaguchi, R., Benham, A.M., Tamura, T., Wada, I., Satouh, Y., Inoue, N. and
932 Okabe, M., 2011. Calsperin Is a Testis-specific Chaperone Required for Sperm Fertility, *Journal of*
933 *Biological Chemistry.* 286, 5639-5646.
- 934 Inan, S., Giray, G., Vatansever, H.S., Ozbilgin, K., Kuscü, N.K. and Sayhan, S., 2004. Immunolocalization of
935 integrins and fibronectin in tubal pregnancy, *Acta Histochem.* 106, 235-43.
- 936 Kadam, K.M., D'Souza, S.J., Bandivdekar, A.H. and Natraj, U., 2006. Identification and characterization of
937 oviductal glycoprotein-binding protein partner on gametes: epitopic similarity to non-muscle myosin
938 IIA, MYH 9, *Mol Hum Reprod.* 12, 275-82.
- 939 Kasvandik, S., Saarma, M., Kaart, T., Rooda, I., Velthut-Meikas, A., Ehrenberg, A., Gemzell, K., Lalitkumar,
940 P.G., Salumets, A. and Peters, M., 2020. Uterine Fluid Proteins for Minimally Invasive Assessment of
941 Endometrial Receptivity, *J Clin Endocrinol Metab.* 105.
- 942 Katila, T., 2012. Post-mating inflammatory responses of the uterus, *Reprod Domest Anim.* 47 Suppl 5, 31-41.
- 943 Katila, T., Sankari, S. and Makela, O., 2000. Transport of spermatozoa in the reproductive tracts of mares,
944 *Journal of reproduction and fertility. Supplement.* 56, 571-8.
- 945 Kawakami, E., Hori, T. and Tsutsui, T., 1998. Induction of dog sperm capacitation by oviductal fluid, *J Vet*
946 *Med Sci.* 60, 197-202.
- 947 Khalil, A.A., Petrunkina, A.M., Sahin, E., Waberski, D. and Topfer-Petersen, E., 2006. Enhanced binding of
948 sperm with superior volume regulation to oviductal epithelium, *J Androl.* 27, 754-65.

- 949 King, R.S. and Killian, G.J., 1994. Purification of bovine estrus-associated protein and localization of binding
950 on sperm, *Biol Reprod.* 51, 34-42.
- 951 Kobayashi, M., Wada, M., Hori, T. and Kawakami, E., 2014. Superoxide dismutase activity in the oviductal
952 and uterine fluid of the bitch and the effects of the enzyme on viability, motility and hyperactivation
953 of canine sperm in vitro, *J Vet Med Sci.* 76, 741-3.
- 954 Krege, J.H., John, S.W., Langenbach, L.L., Hodgins, J.B., Hagaman, J.R., Bachman, E.S., Jennette, J.C.,
955 O'Brien, D.A. and Smithies, O., 1995. Male-female differences in fertility and blood pressure in ACE-
956 deficient mice, *Nature.* 375, 146-8.
- 957 Krutskikh, A., Poliandri, A., Cabrera-Sharp, V., Dacheux, J.L., Poutanen, M. and Huhtaniemi, I., 2012.
958 Epididymal protein Rnase10 is required for post-testicular sperm maturation and male fertility, *Faseb*
959 *J.* 26, 4198-209.
- 960 Kumar, V., Kumaresan, A., Kumar, D.S.P., Lathika, S., Nayak, S., Kishor Saraf, K., Nag, B.S.P., Chhillar, S.,
961 Kumar Datta, T. and Kumar Mohanty, T., 2017. Anandamide exerts a suppressive effect on sperm
962 binding to oviduct explants through CB1 receptors in the water buffalo (*Bubalus bubalis*), *Anim*
963 *Reprod Sci.* 185, 188-194.
- 964 Kumaresan, A., Ansari, M.R. and Garg, A., 2005. Modulation of post-thaw sperm functions with oviductal
965 proteins in buffaloes, *Anim Reprod Sci.* 90, 73-84.
- 966 Kumaresan, A., Johannisson, A. and Bergqvist, A.S., 2016. Sperm function during incubation with oestrus
967 oviductal fluid differs in bulls with different fertility, *Reprod Fertil Dev.*
- 968 Kumaresan, A., Ansari, M.R., Garg, A. and Kataria, M., 2006. Effect of oviductal proteins on sperm functions
969 and lipid peroxidation levels during cryopreservation in buffaloes, *Anim Reprod Sci.* 93, 246-57.
- 970 Kumaresan, A., Johannisson, A., Saravia, F. and Bergqvist, A.S., 2012. The effect of oviductal fluid on
971 protein tyrosine phosphorylation in cryopreserved boar spermatozoa differs with the freezing method,
972 *Theriogenology.* 77, 588-99.
- 973 Kumaresan, A., Gonzalez, R., Johannisson, A. and Bergqvist, A.S., 2014. Dynamic quantification of
974 intracellular calcium and protein tyrosine phosphorylation in cryopreserved boar spermatozoa during
975 short-time incubation with oviductal fluid, *Theriogenology.* 82, 1145-53.
- 976 Kumaresan, A., Johannisson, A., Humblot, P. and Bergqvist, A.S., 2019. Effect of bovine oviductal fluid on
977 motility, tyrosine phosphorylation, and acrosome reaction in cryopreserved bull spermatozoa,
978 *Theriogenology.* 124, 48-56.
- 979 Kunz, G. and Leyendecker, G., 2002. Uterine peristaltic activity during the menstrual cycle: characterization,
980 regulation, function and dysfunction, *Reprod Biomed Online.* 4 Suppl 3, 5-9.
- 981 La Spina, F.A., Puga Molina, L.C., Romarowski, A., Vitale, A.M., Falzone, T.L., Krapf, D., Hirohashi, N. and
982 Buffone, M.G., 2016. Mouse sperm begin to undergo acrosomal exocytosis in the upper isthmus of
983 the oviduct, *Dev Biol.* 411, 172-182.
- 984 Lachance, C., Bailey, J.L. and Leclerc, P., 2007. Expression of Hsp60 and Grp78 in the human endometrium
985 and oviduct, and their effect on sperm functions, *Hum Reprod.* 22, 2606-14.
- 986 Laezer, I., Palma-Vera, S.E., Liu, F., Frank, M., Trakooljul, N., Vernunft, A., Schoen, J. and Chen, S., 2020.
987 Dynamic profile of EVs in porcine oviductal fluid during the periovulatory period, *Reproduction.* 159,
988 371-382.
- 989 Lamy, J., Labas, V., Harichaux, G., Tsikis, G., Mermillod, P. and Saint-Dizier, M., 2016a. Regulation of the
990 bovine oviductal fluid proteome, *Reproduction.* 152, 629-644.
- 991 Lamy, J., Liere, P., Pianos, A., Aprahamian, F., Mermillod, P. and Saint-Dizier, M., 2016b. Steroid hormones
992 in bovine oviductal fluid during the estrous cycle, *Theriogenology.* 86, 1409-20.
- 993 Lamy, J., Corbin, E., Blache, M.C., Garanina, A.S., Uzbekov, R., Mermillod, P. and Saint-Dizier, M., 2017.
994 Steroid hormones regulate sperm-oviduct interactions in the bovine, *Reproduction.* 154, 497-508.
- 995 Lamy, J., Nogues, P., Combes-Soia, L., Tsikis, G., Labas, V., Mermillod, P., Druart, X. and Saint-Dizier, M.,
996 2018. Identification by proteomics of oviductal sperm-interacting proteins, *Reproduction.*
- 997 Langendijk, P., Soede, N.M. and Kemp, B., 2005. Uterine activity, sperm transport, and the role of boar
998 stimuli around insemination in sows, *Theriogenology.* 63, 500-13.
- 999 Langendijk, P., Bouwman, E., Kidson, A., Kirkwood, R., Soede, N. and Kemp, B., 2002. Role of myometrial
1000 activity in sperm transport through the genital tract and in fertilization in sows, *Reproduction.* 123,
1001 683-690.
- 1002 Lapointe, S., Sullivan, R. and Sirard, M.A., 1998. Binding of a bovine oviductal fluid catalase to mammalian
1003 spermatozoa, *Biol Reprod.* 58, 747-53.

- 1004 Lee, R.K., Tseng, H.C., Hwu, Y.M., Fan, C.C., Lin, M.H., Yu, J.J., Yeh, L.Y. and Li, S.H., 2018. Expression
1005 of cystatin C in the female reproductive tract and its effect on human sperm capacitation, *Reprod Biol*
1006 *Endocrinol.* 16, 8.
- 1007 Leemans, B., Gadella, B.M., Sostaric, E., Nelis, H., Stout, T.A., Hoogewijs, M. and Van Soom, A., 2014.
1008 Oviduct binding and elevated environmental pH induce protein tyrosine phosphorylation in stallion
1009 spermatozoa, *Biol Reprod.* 91, 13.
- 1010 Lefebvre, R. and Suarez, S.S., 1996. Effect of capacitation on bull sperm binding to homologous oviductal
1011 epithelium, *Biol Reprod.* 54, 575-82.
- 1012 Lefebvre, R., Lo, M.C. and Suarez, S.S., 1997. Bovine sperm binding to oviductal epithelium involves fucose
1013 recognition, *Biol Reprod.* 56, 1198-204.
- 1014 Lefebvre, R., Chenoweth, P.J., Drost, M., Leclear, C.T., MacCubbin, M., Dutton, J.T. and Suarez, S.S., 1995.
1015 Characterization of oviductal sperm reservoir in cattle, *Biol Reprod.* 53, 1066-1074.
- 1016 Lippes, J. and Wagh, P.V., 1989. Human oviductal fluid (hOF) proteins. IV. Evidence for hOF proteins
1017 binding to human sperm, *Fertil Steril.* 51, 89-94.
- 1018 Liu, Q., Xie, Q.Z., Zhou, Y. and Yang, J., 2015. Osteopontin is expressed in the oviduct and promotes
1019 fertilization and preimplantation embryo development of mouse, *Zygote.* 23, 622-30.
- 1020 Lloyd, R.E., Elliott, R.M., Fazeli, A., Watson, P.F. and Holt, W.V., 2009. Effects of oviductal proteins,
1021 including heat shock 70 kDa protein 8, on survival of ram spermatozoa over 48 h in vitro, *Reprod*
1022 *Fertil Dev.* 21, 408-18.
- 1023 Lopez-Ubeda, R., Garcia-Vazquez, F.A., Gadea, J. and Matas, C., 2017. Oviductal epithelial cells selected
1024 boar sperm according to their functional characteristics, *Asian J Androl.* 19, 396-403.
- 1025 Luongo, C., Abril-Sanchez, S., Hernandez, J.G. and Garcia-Vazquez, F.A., 2019. Seminal plasma mitigates
1026 the adverse effect of uterine fluid on boar spermatozoa, *Theriogenology.* 136, 28-35.
- 1027 Machado, S.A., Sharif, M., Wang, H., Bovin, N. and Miller, D.J., 2019. Release of Porcine Sperm from
1028 Oviduct Cells is Stimulated by Progesterone and Requires CatSper, *Sci Rep.* 9, 19546.
- 1029 Maloney, S.E., Khan, F.A., Chenier, T.S., Diel de Amorim, M., Anthony Hayes, M. and Scholtz, E.L., 2019.
1030 A comparison of the uterine proteome of mares in oestrus and dioestrus, *Reprod Domest Anim.* 54,
1031 473-479.
- 1032 Marcello, M.R., Jia, W., Leary, J.A., Moore, K.L. and Evans, J.P., 2011. Lack of tyrosylprotein
1033 sulfotransferase-2 activity results in altered sperm-egg interactions and loss of ADAM3 and ADAM6
1034 in epididymal sperm, *J Biol Chem.* 286, 13060-70.
- 1035 Marey, M.A., Matsukawa, H., Sasaki, M., Ezz, M.A., Yousef, M.S., Takahashi, K.I. and Miyamoto, A., 2019.
1036 Bovine oviduct epithelial cells suppress the phagocytic activity of neutrophils towards sperm but not
1037 for bacteria in vitro: Immunofluorescence and electron microscopic observations, *Histol Histopathol.*
1038 18172.
- 1039 Marey, M.A., Liu, J., Kowsar, R., Haneda, S., Matsui, M., Sasaki, M., Takashi, S., Hayakawa, H.,
1040 Wijayagunawardane, M.P., Hussein, F.M. and Miyamoto, A., 2014. Bovine oviduct epithelial cells
1041 downregulate phagocytosis of sperm by neutrophils: prostaglandin E2 as a major physiological
1042 regulator, *Reproduction.* 147, 211-9.
- 1043 Marin-Briggiler, C.I., Gonzalez-Echeverria, M.F., Munuce, M.J., Ghersevich, S., Caille, A.M., Hellman, U.,
1044 Corrigan, V.M. and Vazquez-Levin, M.H., 2010. Glucose-regulated protein 78 (Grp78/BiP) is
1045 secreted by human oviduct epithelial cells and the recombinant protein modulates sperm-zona
1046 pellucida binding, *Fertil Steril.* 93, 1574-84.
- 1047 Martin-DeLeon, P.A., 2006. Epididymal SPAM1 and its impact on sperm function, *Mol Cell Endocrinol.* 250,
1048 114-21.
- 1049 McNutt, T.L. and Killian, G.J., 1991. Influence of bovine follicular and oviduct fluids on sperm capacitation
1050 in vitro, *J Androl.* 12, 244-52.
- 1051 Miller, D.J., 2018. Review: The epic journey of sperm through the female reproductive tract, *Animal.* 12,
1052 s110-s120.
- 1053 Moein-Vaziri, N., Phillips, I., Smith, S., Alminana, C., Maside, C., Gil, M.A., Roca, J., Martinez, E.A., Holt,
1054 W.V., Pockley, A.G. and Fazeli, A., 2014. Heat-shock protein A8 restores sperm membrane integrity
1055 by increasing plasma membrane fluidity, *Reproduction.* 147, 719-32.
- 1056 Monaco, E., Gasparini, B., Boccia, L., De Rosa, A., Attanasio, L., Zicarelli, L. and Killian, G., 2009. Effect
1057 of osteopontin (OPN) on in vitro embryo development in cattle, *Theriogenology.* 71, 450-7.

- 1058 Morales, P., Palma, V., Salgado, A.M. and Villalon, M., 1996. Sperm interaction with human oviductal cells
1059 in vitro, *Hum Reprod.* 11, 1504-9.
- 1060 Moros-Nicolas, C., Fouchecourt, S., Goudet, G. and Monget, P., 2018. Genes Encoding Mammalian
1061 Oviductal Proteins Involved in Fertilization are Subjected to Gene Death and Positive Selection, *J*
1062 *Mol Evol.* 86, 655-667.
- 1063 Murray, S.C. and Smith, T.T., 1997. Sperm interaction with fallopian tube apical membrane enhances sperm
1064 motility and delays capacitation, *Fertil Steril.* 68, 351-7.
- 1065 Nishimura, H., Kim, E., Nakanishi, T. and Baba, T., 2004. Possible function of the ADAM1a/ADAM2
1066 Fertilin complex in the appearance of ADAM3 on the sperm surface, *J Biol Chem.* 279, 34957-62.
- 1067 Noguchi, T., Fujinoki, M., Kitazawa, M. and Inaba, N., 2008. Regulation of hyperactivation of hamster
1068 spermatozoa by progesterone, *Reprod Med Biol.* 7, 63-74.
- 1069 Osycka-Salut, C., Gervasi, M.G., Pereyra, E., Cella, M., Ribeiro, M.L., Franchi, A.M. and Perez-Martinez, S.,
1070 2012. Anandamide induces sperm release from oviductal epithelia through nitric oxide pathway in
1071 bovines, *PLoS One.* 7, e30671.
- 1072 Osycka-Salut, C.E., Castellano, L., Fornes, D., Beltrame, J.S., Alonso, C., Jawerbaum, A., Franchi, A., Diaz,
1073 E.S. and Perez Martinez, S., 2017. "Fibronectin from oviductal cells fluctuates during the estrous
1074 cycle and contributes to sperm-oviduct interaction in cattle", *J Cell Biochem.*
- 1075 Overstreet, J.W. and Cooper, G.W., 1978. Sperm transport in the reproductive tract of the female rabbit: II.
1076 The sustained phase of transport, *Biol Reprod.* 19, 115-32.
- 1077 Parrish, J.J., Susko-Parrish, J.L., Handrow, R.R., Sims, M.M. and First, N.L., 1989. Capacitation of bovine
1078 spermatozoa by oviduct fluid, *Biol Reprod.* 40, 1020-5.
- 1079 Perez-Cerezales, S., Lopez-Cardona, A.P. and Gutierrez-Adan, A., 2016. Progesterone effects on mouse
1080 sperm kinetics in conditions of viscosity, *Reproduction.* 151, 501-7.
- 1081 Petrunkina, A.M., Simon, K., Gunzel-Apel, A.R. and Topfer-Petersen, E., 2004. Kinetics of protein tyrosine
1082 phosphorylation in sperm selected by binding to homologous and heterologous oviductal explants:
1083 how specific is the regulation by the oviduct?, *Theriogenology.* 61, 1617-34.
- 1084 Petrunkina, A.M., Gehlhaar, R., Drommer, W., Waberski, D. and Topfer-Petersen, E., 2001. Selective sperm
1085 binding to pig oviductal epithelium in vitro, *Reproduction.* 121, 889-96.
- 1086 Plante, G., Prud'homme, B., Fan, J., Lafleur, M. and Manjunath, P., 2016. Evolution and function of
1087 mammalian binder of sperm proteins, *Cell Tissue Res.* 363, 105-27.
- 1088 Qiao, F., Ge, H., Ma, X., Zhang, Y., Zuo, Z., Wang, M. and Wang, Y., 2018. Bovine uterus-derived exosomes
1089 improve developmental competence of somatic cell nuclear transfer embryos, *Theriogenology.* 114,
1090 199-205.
- 1091 Ramal-Sanchez, M., Bernabo, N., Tsikis, G., Blache, M.C., Labas, V., Druart, X., Mermillod, P. and Saint-
1092 Dizier, M., 2020. Progesterone induces sperm release from oviductal epithelial cells by modifying
1093 sperm proteomics, lipidomics and membrane fluidity, *Mol Cell Endocrinol.* 504, 110723.
- 1094 Rath, D., Knorr, C. and Taylor, U., 2016. Communication requested: Boar semen transport through the uterus
1095 and possible consequences for insemination, *Theriogenology.* 85, 94-104.
- 1096 Rath, D., Schuberth, H.J., Coy, P. and Taylor, U., 2008. Sperm interactions from insemination to fertilization,
1097 *Reproduction in domestic animals = Zuchthygiene.* 5, 2-11.
- 1098 Rickard, J.P., Pool, K.R., Druart, X. and de Graaf, S.P., 2019. The fate of spermatozoa in the female
1099 reproductive tract: A comparative review, *Theriogenology.* 137, 104-112.
- 1100 Rijsselaere, T., Van Soom, A., Van Cruchten, S., Coryn, M., Gortz, K., Maes, D. and de Kruif, A., 2004.
1101 Sperm distribution in the genital tract of the bitch following artificial insemination in relation to the
1102 time of ovulation, *Reproduction.* 128, 801-11.
- 1103 Rodriguez-Martinez, H., 2007. Role of the oviduct in sperm capacitation, *Theriogenology.* 68, S138-S146.
- 1104 Rodriguez-Martinez, H., Nicander, L., Viring, S., Einarsson, S. and Larsson, K., 1990. Ultrastructure of the
1105 uterotubal junction in preovulatory pigs, *Anat Histol Embryol.* 19, 16-36.
- 1106 Romero-Aguirregomez-corta, J., Cronin, S., Donnellan, E. and Fair, S., 2019. Progesterone induces the release
1107 of bull spermatozoa from oviductal epithelial cells, *Reprod Fertil Dev.*
- 1108 Saccary, L., She, Y.M., Oko, R. and Kan, F.W., 2013. Hamster oviductin regulates tyrosine phosphorylation
1109 of sperm proteins during in vitro capacitation, *Biol Reprod.* 89, 38.
- 1110 Saint-Dizier, M., Schoen, J., Chen, S., Banliat, C. and Mermillod, P., 2019. Composing the Early Embryonic
1111 Microenvironment: Physiology and Regulation of Oviductal Secretions, *Int J Mol Sci.* 21.

- 1112 Saraf, K.K., Singh, R.K., Kumaresan, A., Nayak, S., Chhillar, S., Lathika, S., Datta, T.K. and Mohanty, T.K.,
 1113 2019. Sperm functional attributes and oviduct explant binding capacity differs between bulls with
 1114 different fertility ratings in the water buffalo (*Bubalus bubalis*), *Reprod Fertil Dev.* 31, 395-403.
- 1115 Schjenken, J.E. and Robertson, S.A., 2014. Seminal fluid and immune adaptation for pregnancy--comparative
 1116 biology in mammalian species, *Reproduction in domestic animals = Zuchthygiene.* 3, 27-36.
- 1117 Schjenken, J.E. and Robertson, S.A., 2015. Seminal Fluid Signalling in the Female Reproductive Tract:
 1118 Implications for Reproductive Success and Offspring Health, *Adv Exp Med Biol.* 868, 127-58.
- 1119 Schuh, K., Cartwright, E.J., Jankevics, E., Bundschu, K., Liebermann, J., Williams, J.C., Armesilla, A.L.,
 1120 Emerson, M., Oceandy, D., Knobloch, K.P. and Neyses, L., 2004. Plasma membrane Ca²⁺ ATPase
 1121 4 is required for sperm motility and male fertility, *J Biol Chem.* 279, 28220-6.
- 1122 Shamsadin, R., Adham, I.M., Nayernia, K., Heinlein, U.A., Oberwinkler, H. and Engel, W., 1999. Male mice
 1123 deficient for germ-cell cyritestin are infertile, *Biology of reproduction.* 61, 1445-51.
- 1124 Shang, X., Shen, C., Liu, J., Tang, L., Zhang, H., Wang, Y., Wu, W., Chi, J., Zhuang, H., Fei, J. and Wang,
 1125 Z., 2018. Serine protease PRSS55 is crucial for male mouse fertility via affecting sperm migration and
 1126 sperm-egg binding, *Cell Mol Life Sci.* 75, 4371-4384.
- 1127 Shen, C., Kuang, Y., Liu, J., Feng, J., Chen, X., Wu, W., Chi, J., Tang, L., Wang, Y., Fei, J. and Wang, Z.,
 1128 2013. Prss37 Is Required for Male Fertility in the Mouse, *Biology of reproduction.*
- 1129 Silva, E., Kadirvel, G., Jiang, R., Bovin, N. and Miller, D., 2014. Multiple proteins from ejaculated and
 1130 epididymal porcine spermatozoa bind glycan motifs found in the oviduct, *Andrology.* 2, 763-71.
- 1131 Smith, T.T. and Yanagimachi, R., 1991. Attachment and release of spermatozoa from the caudal isthmus of
 1132 the hamster oviduct, *J Reprod Fertil.* 91, 567-73.
- 1133 Soleilhavoup, C., Riou, C., Tsikis, G., Labas, V., Harichaux, G., Kohnke, P., Reynaud, K., de Graaf, S.P.,
 1134 Gerard, N. and Druart, X., 2016. Proteomes of the female genital tract during the oestrous cycle, *Mol*
 1135 *Cell Proteomics.* 15, 93-108.
- 1136 Sostaric, E., van de Lest, C.H., Colenbrander, B. and Gadella, B.M., 2005. Dynamics of carbohydrate
 1137 affinities at the cell surface of capacitating bovine sperm cells, *Biol Reprod.* 72, 346-57.
- 1138 Sostaric, E., Dieleman, S.J., van de Lest, C.H., Colenbrander, B., Vos, P.L., Garcia-Gil, N. and Gadella, B.M.,
 1139 2008. Sperm binding properties and secretory activity of the bovine oviduct immediately before and
 1140 after ovulation, *Mol Reprod Dev.* 75, 60-74.
- 1141 Souza, C.E., Moura, A.A., Monaco, E. and Killian, G.J., 2008. Binding patterns of bovine seminal plasma
 1142 proteins A1/A2, 30 kDa and osteopontin on ejaculated sperm before and after incubation with isthmic
 1143 and ampullary oviductal fluid, *Anim Reprod Sci.* 105, 72-89.
- 1144 Suarez, S.S., 1987. Sperm transport and motility in the mouse oviduct: observations in situ, *Biol Reprod.* 36,
 1145 203-10.
- 1146 Suarez, S.S., 2008. Control of hyperactivation in sperm, *Hum Reprod Update.* 14, 647-57.
- 1147 Sullivan, R., 2016. Epididymosomes: Role of extracellular microvesicles in sperm maturation, *Front Biosci*
 1148 *(Schol Ed).* 8, 106-14.
- 1149 Sumigama, S., Mansell, S., Miller, M., Lishko, P.V., Cherr, G.N., Meyers, S.A. and Tollner, T., 2015.
 1150 Progesterone Accelerates the Completion of Sperm Capacitation and Activates CatSper Channel in
 1151 Spermatozoa from the Rhesus Macaque, *Biol Reprod.* 93, 130.
- 1152 Talevi, R. and Gualtieri, R., 2001. Sulfated glycoconjugates are powerful modulators of bovine sperm
 1153 adhesion and release from the oviductal epithelium in vitro, *Biol Reprod.* 64, 491-498.
- 1154 Talevi, R. and Gualtieri, R., 2010. Molecules involved in sperm-oviduct adhesion and release,
 1155 *Theriogenology.* 73, 796-801.
- 1156 Taylor, U., Rath, D., Zerbe, H. and Schuberth, H.J., 2008. Interaction of intact porcine spermatozoa with
 1157 epithelial cells and neutrophilic granulocytes during uterine passage, *Reproduction in domestic*
 1158 *animals = Zuchthygiene.* 43, 166-75.
- 1159 Teclé, E., Reynoso, H.S., Wang, R. and Gagneux, P., 2019. The female reproductive tract contains multiple
 1160 innate sialic acid-binding immunoglobulin-like lectins (Siglecs) that facilitate sperm survival, *J Biol*
 1161 *Chem.* 294, 11910-11919.
- 1162 Teijeiro, J.M., Ignatz, G.G. and Marini, P.E., 2009. Annexin A2 is involved in pig (*Sus scrofa*) sperm-oviduct
 1163 interaction, *Mol Reprod Dev.* 76, 334-41.
- 1164 Thomas, P.G.A., Ball, B.A. and Brinsko, S.P., 1994. Interaction of equine spermatozoa with oviduct epithelial
 1165 cell explants is affected by estrous cycle and anatomic origin of explant, *Biol Reprod.* 51.

- 1166 Tienthai, P., 2015. The porcine sperm reservoir in relation to the function of hyaluronan, *J Reprod Dev.* 61,
1167 245-50.
- 1168 Tienthai, P., Johannisson, A. and Rodriguez-Martinez, H., 2004. Sperm capacitation in the porcine oviduct,
1169 *Anim Reprod Sci.* 80, 131-46.
- 1170 Tokuhiro, K., Ikawa, M., Benham, A.M. and Okabe, M., 2012. Protein disulfide isomerase homolog PDILT is
1171 required for quality control of sperm membrane protein ADAM3 and male infertility, *Proceedings of*
1172 *the National Academy of Sciences.*
- 1173 Tollner, T.L., Yudin, A.I., Tarantal, A.F., Treece, C.A., Overstreet, J.W. and Cherr, G.N., 2008. Beta-defensin
1174 126 on the surface of macaque sperm mediates attachment of sperm to oviductal epithelia, *Biol*
1175 *Reprod.* 78, 400-12.
- 1176 Topfer-Petersen, E., Romero, A., Varela, P.F., Ekhlesi-Hundrieser, M., Dostalova, Z., Sanz, L. and Calvete,
1177 J.J., 1998. Spermadhesins: a new protein family. Facts, hypotheses and perspectives, *Andrologia.* 30,
1178 217-24.
- 1179 Troedsson, M.H., Liu, I.K. and Crabo, B.G., 1998. Sperm transport and survival in the mare: a review,
1180 *Theriogenology.* 50, 807-18.
- 1181 Ueda, Y., Yamaguchi, R., Ikawa, M., Okabe, M., Morii, E., Maeda, Y. and Kinoshita, T., 2007. PGAP1
1182 Knock-out Mice Show Otocephaly and Male Infertility, *Journal of Biological Chemistry.* 282, 30373-
1183 30380.
- 1184 Viuff, D., Greve, T., Avery, B., Hyttel, P., Brockhoff, P.B. and Thomsen, P.D., 2000. Chromosome
1185 aberrations in in vitro-produced bovine embryos at days 2-5 post-insemination, *Biol Reprod.* 63,
1186 1143-8.
- 1187 Viuff, D., Hendriksen, P.J., Vos, P.L., Dieleman, S.J., Bibby, B.M., Greve, T., Hyttel, P. and Thomsen, P.D.,
1188 2001. Chromosomal abnormalities and developmental kinetics in in vivo-developed cattle embryos at
1189 days 2 to 5 after ovulation, *Biol Reprod.* 65, 204-8.
- 1190 Waberski, D., Magnus, F., Mendonca Ferreira, F., Petrunkina, A.M., Weitze, K.F. and Topfer-Petersen, E.,
1191 2005. Importance of sperm-binding assays for fertility prognosis of porcine spermatozoa,
1192 *Theriogenology.* 63, 470-84.
- 1193 Waberski, D., Magnus, F., Ardon, F., Petrunkina, A.M., Weitze, K.F. and Topfer-Petersen, E., 2006. Binding
1194 of boar spermatozoa to oviductal epithelium in vitro in relation to sperm morphology and storage
1195 time, *Reproduction.* 131, 311-8.
- 1196 Wilmut, I. and Hunter, R.H.F., 1984. Sperm Transport into the Oviducts of Heifers Mated Early in Estrus,
1197 *Reproduction Nutrition Development.* 24, 461-468.
- 1198 Winters, R.A., Nettenstrom, L.M., Lopez, D.G., Willenburg, K.L., Vishwanath, R., Bovin, N.V. and Miller,
1199 D.J., 2018. Effect of sorting boar spermatozoa by sex chromosomes on oviduct cell binding,
1200 *Theriogenology.* 108, 22-28.
- 1201 Xiong, W., Wang, Z. and Shen, C., 2019. An update of the regulatory factors of sperm migration from the
1202 uterus into the oviduct by genetically manipulated mice, *Mol Reprod Dev.* 86, 935-955.
- 1203 Yamaguchi, R., Fujihara, Y., Ikawa, M. and Okabe, M., 2012. Mice expressing aberrant sperm-specific
1204 protein PMIS2 produce normal-looking but fertilization-incompetent spermatozoa, *Mol Biol Cell.* 23,
1205 2671-9.
- 1206 Yanez-Mo, M., Siljander, P.R., Andreu, Z., Zavec, A.B., Borrás, F.E., Buzas, E.I., Buzas, K., Casal, E.,
1207 Cappello, F., Carvalho, J., Colas, E., Cordeiro-da Silva, A., Fais, S., Falcon-Perez, J.M., Ghobrial,
1208 I.M., Giebel, B., Gimona, M., Graner, M., Gursel, I., Gursel, M., Heegaard, N.H., Hendrix, A.,
1209 Kierulf, P., Kokubun, K., Kosanovic, M., Kralj-Iglic, V., Kramer-Albers, E.M., Laitinen, S., Lasser,
1210 C., Lener, T., Ligeti, E., Line, A., Lipps, G., Llorente, A., Lotvall, J., Mancek-Keber, M., Marcilla,
1211 A., Mittelbrunn, M., Nazarenko, I., Nolte-t Hoen, E.N., Nyman, T.A., O'Driscoll, L., Olivan, M.,
1212 Oliveira, C., Pallinger, E., Del Portillo, H.A., Reventos, J., Rigau, M., Rohde, E., Sammar, M.,
1213 Sanchez-Madrid, F., Santarem, N., Schallmoser, K., Ostenfeld, M.S., Stoorvogel, W., Stukelj, R., Van
1214 der Grein, S.G., Vasconcelos, M.H., Wauben, M.H. and De Wever, O., 2015. Biological properties of
1215 extracellular vesicles and their physiological functions, *J Extracell Vesicles.* 4, 27066.
- 1216 Yang, X., Zhao, Y. and Kan, F.W., 2015. Recombinant hamster oviductin is biologically active and exerts
1217 positive effects on sperm functions and sperm-ocyte binding, *PLoS One.* 10, e0123003.
- 1218 Yeste, M., Holt, W.V., Bonet, S., Rodriguez-Gil, J.E. and Lloyd, R.E., 2014. Viable and morphologically
1219 normal boar spermatozoa alter the expression of heat-shock protein genes in oviductal epithelial cells
1220 during co-culture in vitro, *Mol Reprod Dev.* 81, 805-19.

1221 Yeste, M., Lloyd, R.E., Badia, E., Briz, M., Bonet, S. and Holt, W.V., 2009. Direct contact between boar
1222 spermatozoa and porcine oviductal epithelial cell (OEC) cultures is needed for optimal sperm survival
1223 in vitro, *Anim Reprod Sci.* 113, 263-78.

1224 Yousef, M.S., Abd-Elhafeez, H.H., Talukder, A.K. and Miyamoto, A., 2019. Ovulatory follicular fluid
1225 induces sperm phagocytosis by neutrophils, but oviductal fluid around oestrus suppresses its
1226 inflammatory effect in the buffalo oviduct in vitro, *Mol Reprod Dev.* 86, 835-846.

1227 Zambrano, F., Carrau, T., Gartner, U., Seipp, A., Taubert, A., Felmer, R., Sanchez, R. and Hermosilla, C.,
1228 2016. Leukocytes coincubated with human sperm trigger classic neutrophil extracellular traps
1229 formation, reducing sperm motility, *Fertil Steril.* 106, 1053-1060 e1.

1230 Zhao, Y., Yang, X., Jia, Z., Reid, R.L., Leclerc, P. and Kan, F.W., 2016. Recombinant human oviductin
1231 regulates protein tyrosine phosphorylation and acrosome reaction, *Reproduction.* 152, 561-573.

1232 Zumoffen, C.M., Caille, A.M., Munuce, M.J., Cabada, M.O. and Ghersevich, S.A., 2010. Proteins from
1233 human oviductal tissue-conditioned medium modulate sperm capacitation, *Hum Reprod.* 25, 1504-12.

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1235