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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**

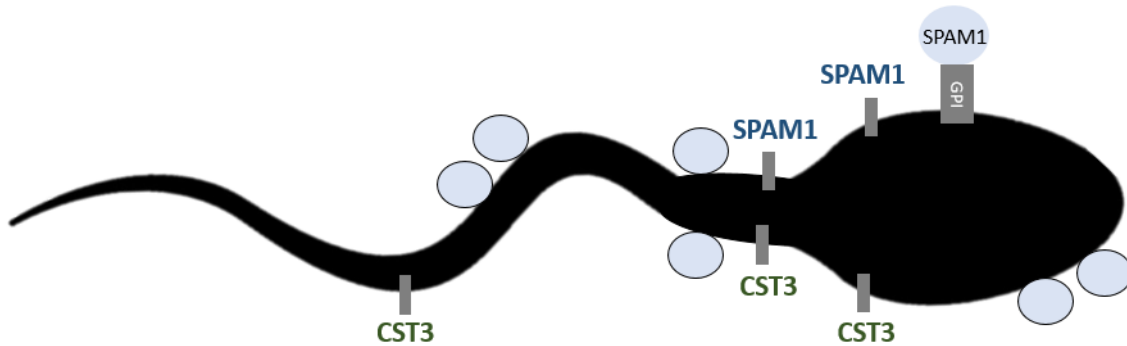
56 The migration of spermatozoa through the uterus is associated with sperm interactions with the  
57 uterine fluid (UF) and with uterine (or endometrial) epithelial cells (UECs), each mediated by  
58 specific components and triggering different effects on sperm.

### 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).

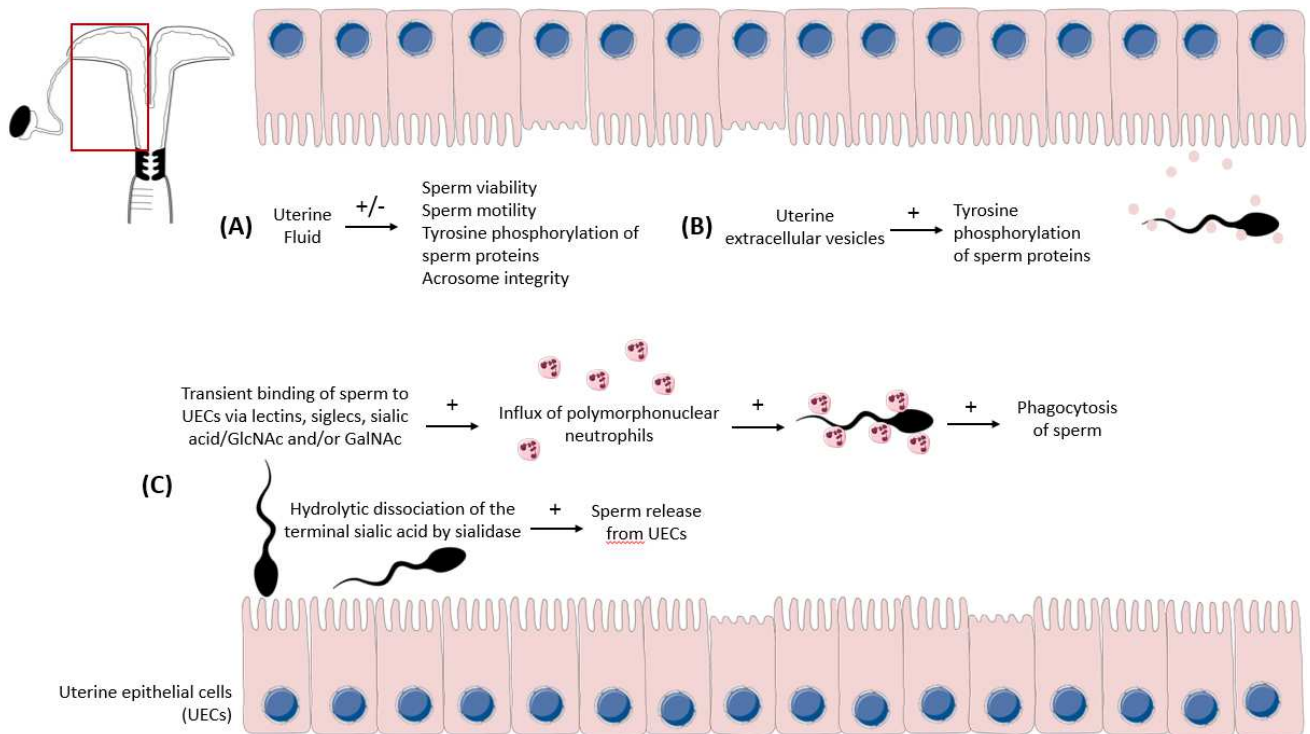
71 A comprehensive analysis of proteins present in the UF is now available in some mammals including  
72 cattle (Gegenfurtner et al., 2020), horses (Maloney et al., 2019) and humans (Kasvandik et al., 2020).  
73 However, specific proteins involved in sperm-UF interactions are poorly known (Figure 1). 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



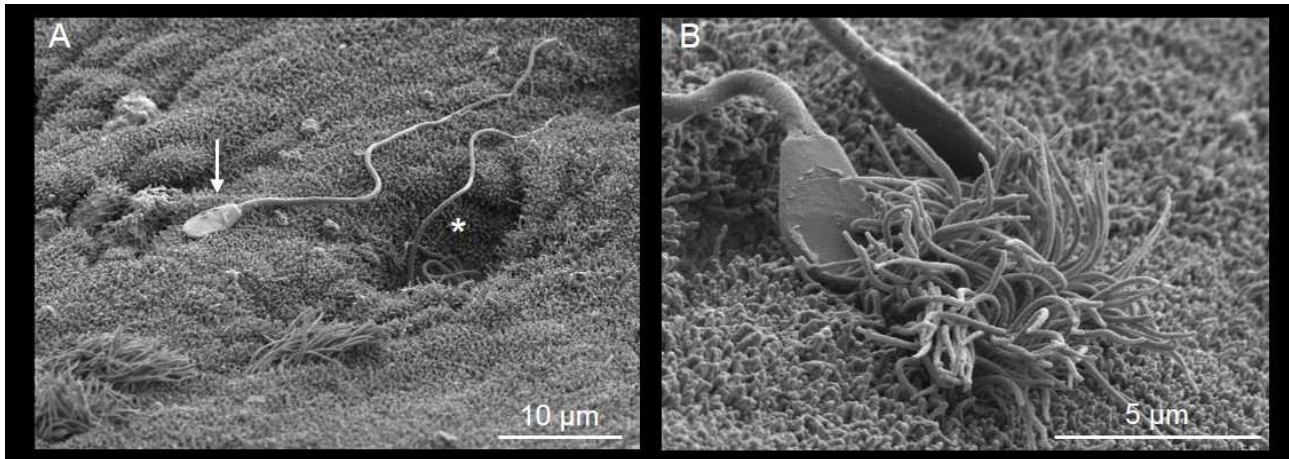
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124 **Figure 2. Summarized effects of interactions with the uterus on sperm physiology.** Sperm interact  
 125 with uterine fluid (A), uterine extracellular vesicles (B) and uterine epithelial cells (UEC, C). Sperm-UEC  
 126 interactions imply sialic 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 PGE<sub>2</sub>, 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<sup>x</sup> or  
206 Lewis<sup>y</sup> 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).

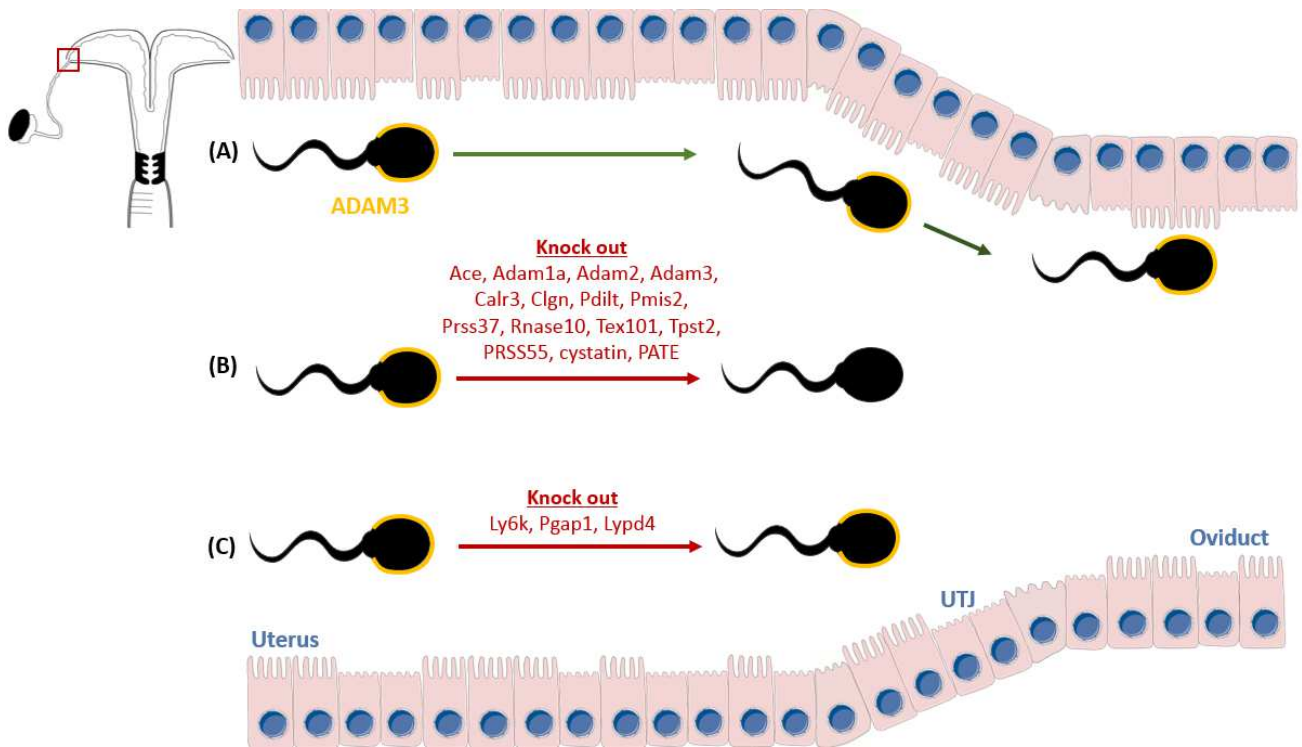
230 Beyond sperm mobility and morphology, the contractions of the uterus are also involved in the  
231 transit of the spermatozoa. In the sow after intrauterine insemination, spermatozoa can be found  
232 within minutes in the UTJ thanks to uterine contractions (Langendijk et al., 2005). The short 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 metalloproteinase 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 Wilmut, 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).

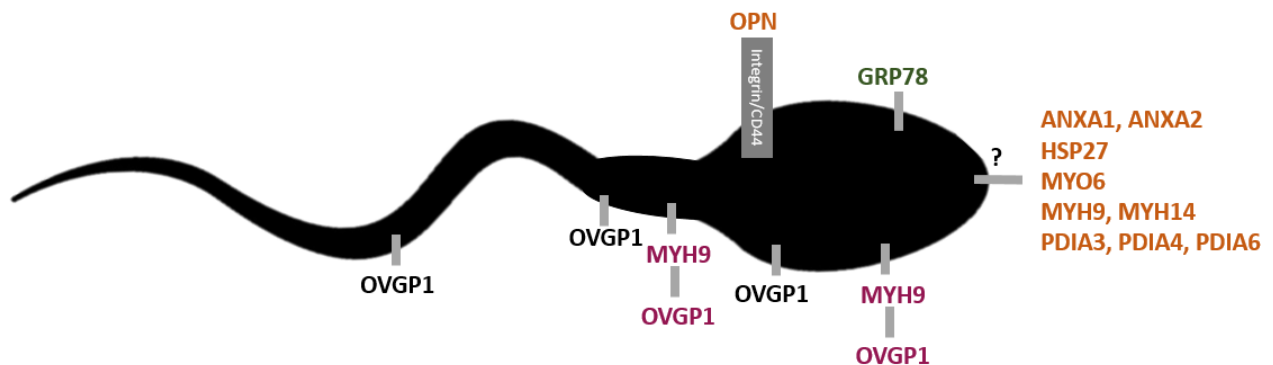
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340 The functional roles of OVGPI, a glycoprotein more abundant in the OF of various mammals during  
341 estrus than at other stages of cycle, has been given special attention (for review, see (Aviles et al.,  
342 2010)). The protein is not present 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).

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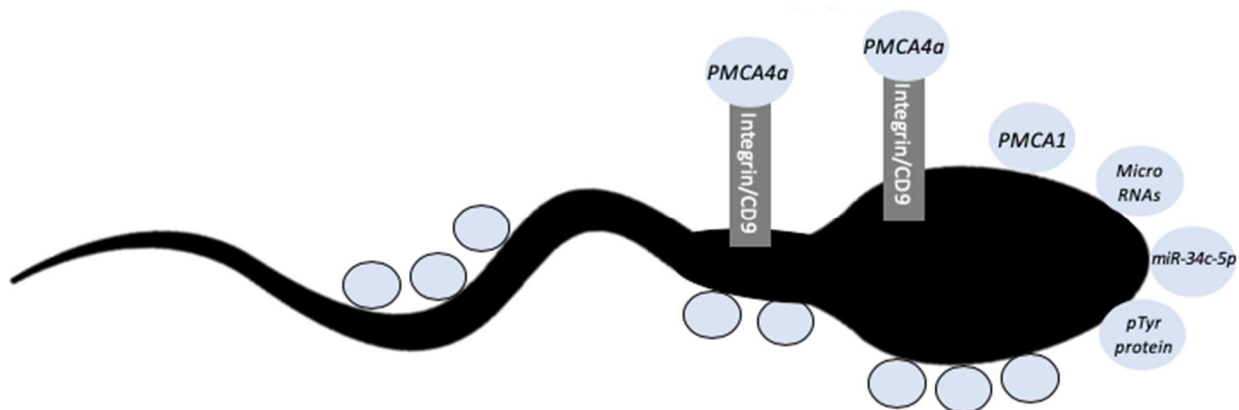
#### 396 **4.2. Effects of interactions with oviductal extracellular vesicles on sperm physiology**

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).

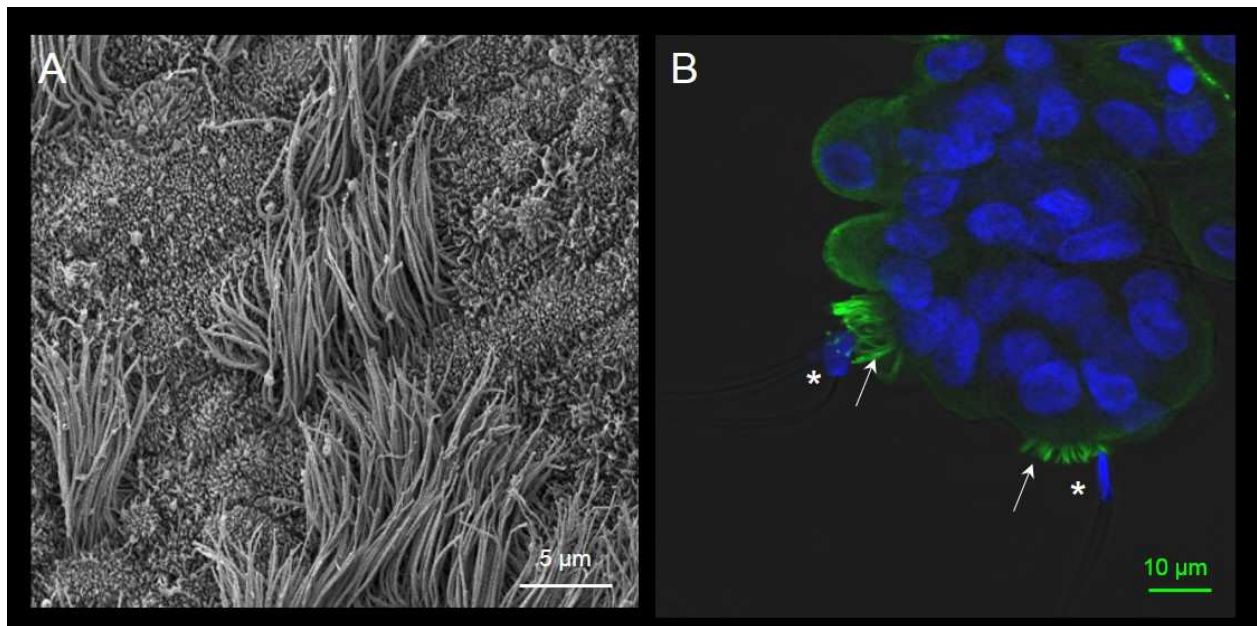
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### 453 **4.3. Binding to oviduct epithelial cells: formation of a functional sperm reservoir**

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  $\alpha$ -tubulin) in green. Asterisks indicate sperm heads; arrows indicate cilia. Source: K. Reynaud.

474

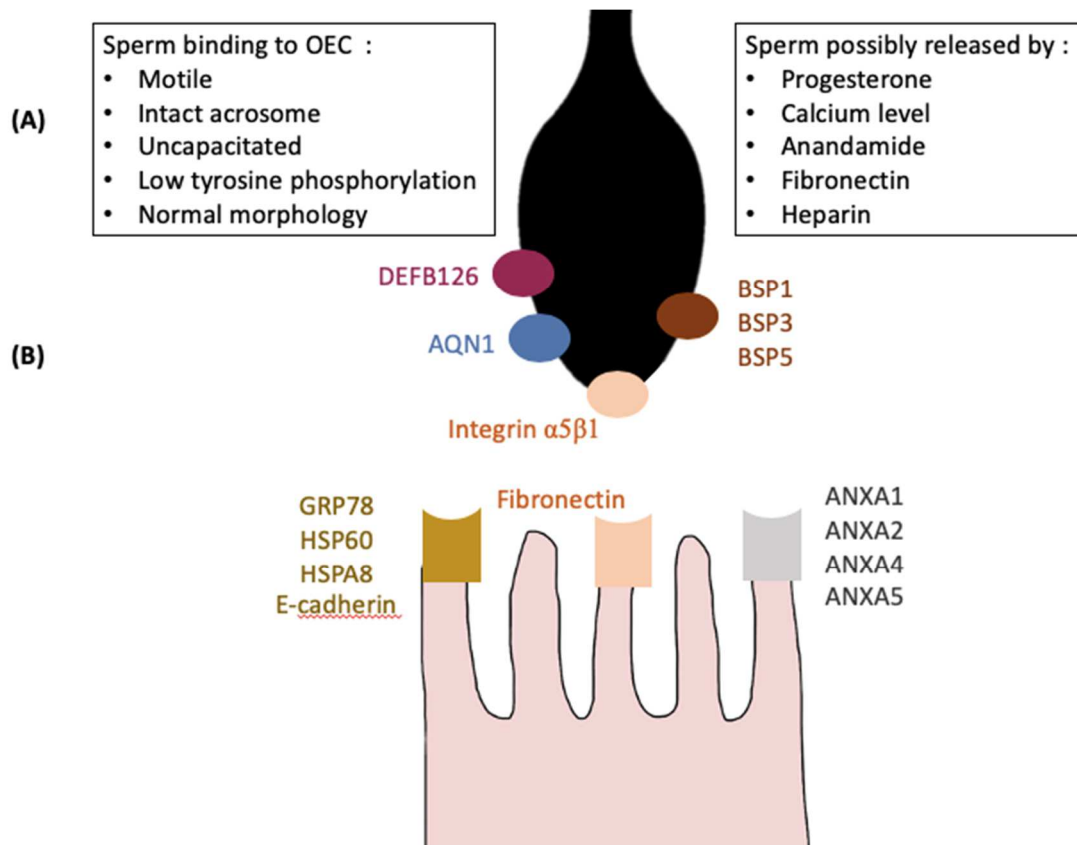
475

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<sup>X</sup>) 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***

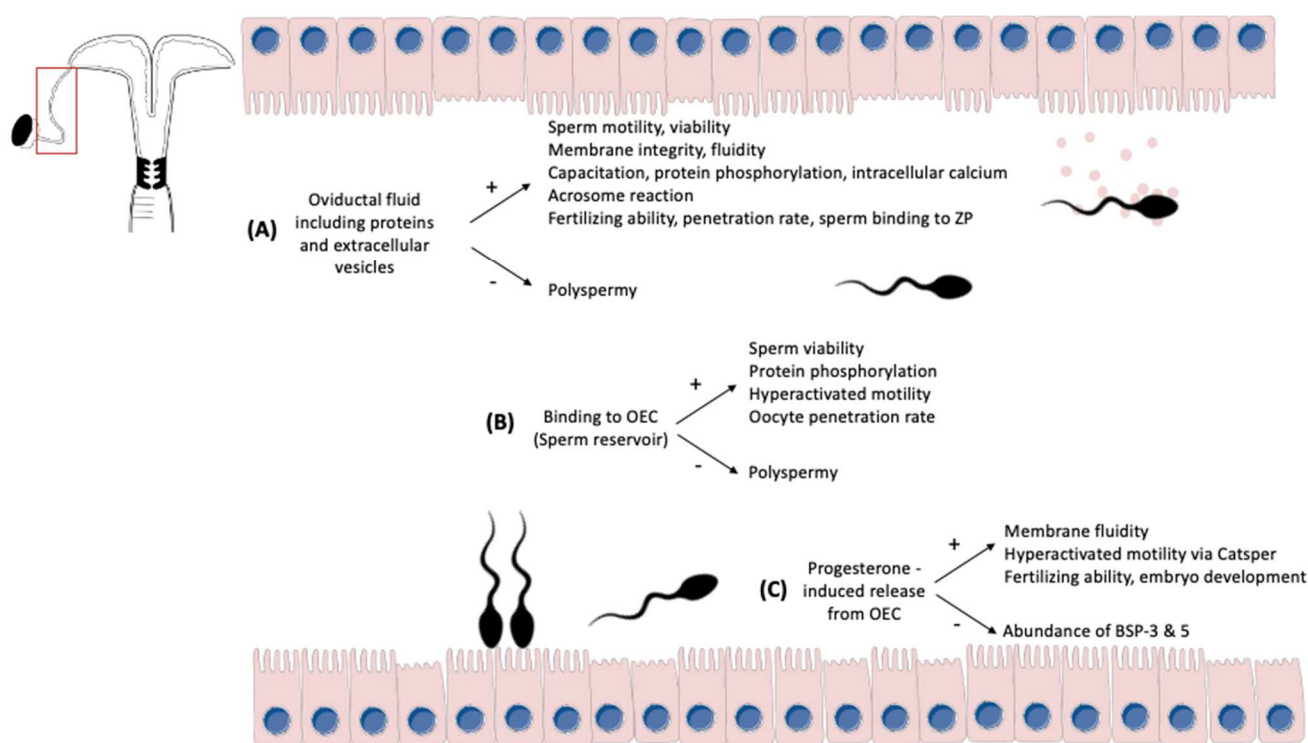
556 Binding to oviductal cells or OEC apical membrane preparations prolongs sperm lifespan, as shown  
557 *in vitro* in cattle (Boilard et al., 2002; Boilard et al., 2004), pigs (Fazeli et al., 2003; Yeste et al.,  
558 2009) and humans (Morales et al., 1996; Murray and Smith, 1997) (Figure 9). This 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  $\alpha$ estradiol had no effect on bull sperm  
 575 release from OECs *in vitro*, the releasing effect of progesterone was inhibited by  $\alpha$ estradiol in a dose-  
 576 dependent manner in cattle (Lamy et al., 2017), showing that both progesterone and  $\alpha$ 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

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