Sperm interactions with the female reproductive tract: A key for successful fertilization in mammals

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Abstract

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

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

1. Introduction

Ejaculated mammalian spermatozoa are not able to fertilize the oocyte; this ability is acquired following a series of molecular and physiological changes, collectively known as capacitation, which are accomplished during the transit of spermatozoa through the female genital tract. In addition to sperm acquisition of fertilizing competence, the maternal environment operates a dramatic sperm selection, resulting in a very low sperm:egg ratio in the site of fertilization (Hino et al., 2016). The maternal environment allows also long-term survival of a subpopulation of spermatozoa up to the time of ovulation. These crucial steps preceding fertilization imply sperm interactions with the complex and dynamic fluids present in the female reproductive tract and with epithelial cells lining its lumen, in addition to flows induced by muscular contractions of the female genital tract. Fertilization can occur in vitro, thus in the absence of these interactions, but the female tract may increase the efficiency and quality of fertilization. To illustrate, the rate of polyspermy and the incidence of chromosomal abnormalities in early embryos are generally much lower in vivo than under in vitro conditions (Coy and Aviles, 2010; Viuff et al., 2000; Viuff et al., 2001). Therefore, the mechanisms involved in sperm interactions with somatic cells and region-specific secretions in vivo are of particular importance for the understanding of factors determining male and female fertility, but also for the improvement of assisted reproductive technologies (ART) and for better evaluation/prediction of male fertility in human and farm animals.

The objective of this review is to provide an update on the effects of interactions in the uterus, utero-tubal junction (UTJ) and the oviduct (known as the fallopian tube in human) on sperm physiology, with emphasis on the oviduct where fertilization takes place. Physical and biochemical interactions of spermatozoa in the cervix have been recently reviewed (Fair et al., 2019; Rickard et al., 2019) and

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

2. Sperm interactions with the uterus

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

2.1. Sperm interactions with uterine fluid and extracellular vesicles

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

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

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

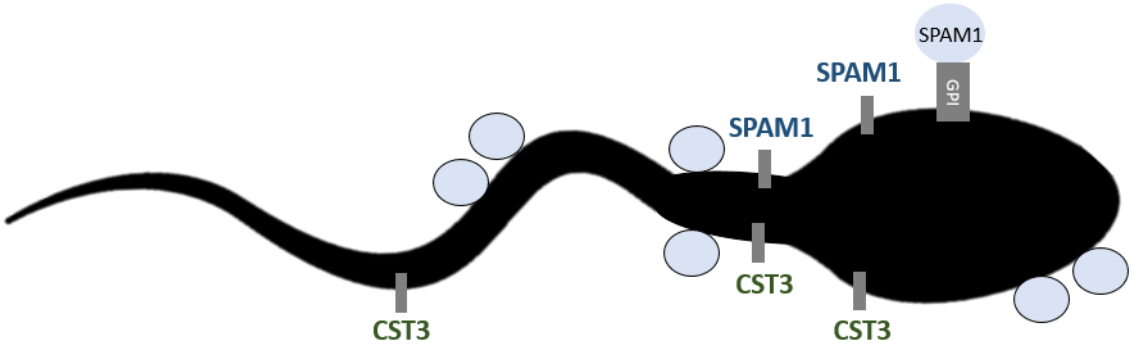

Figure 1. Identification and localization of uterine proteins and extracellular vesicles interacting with spermatozoa. Sperm Adhesion Molecule 1 (SPAM1) interacts with mouse sperm acrosome and midpiece (Griffiths et al., 2008a). Cystatin-C (CST3) interacts with sperm post-acrosomal region, midpiece and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

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

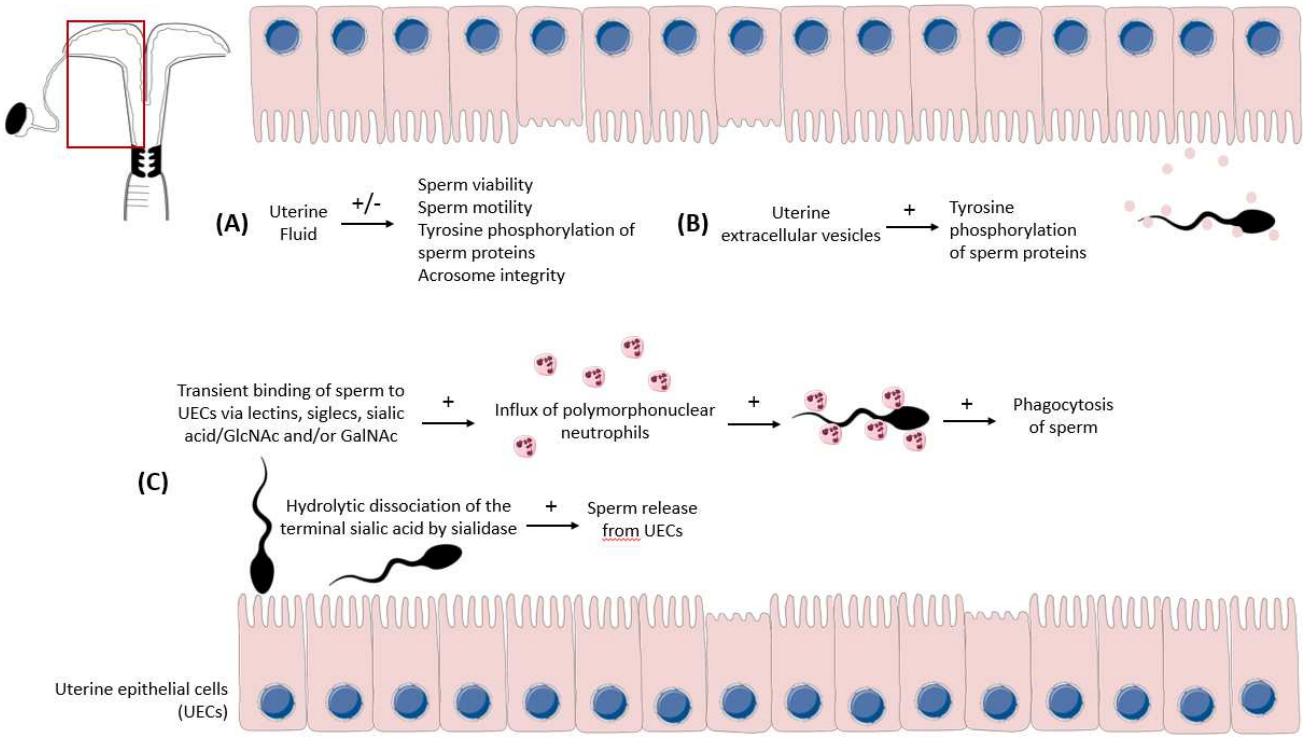

Figure 2. **Summarized effects of interactions with the uterus on sperm physiology**. Sperm interact with uterine fluid (A), uterine extracellular vesicles (B) and uterine epithelial cells (UEC, C). Sperm-UEC interactions imply sialic acid-binding immunoglobulin-like lectins (Siglecs) as well as sialic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

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

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

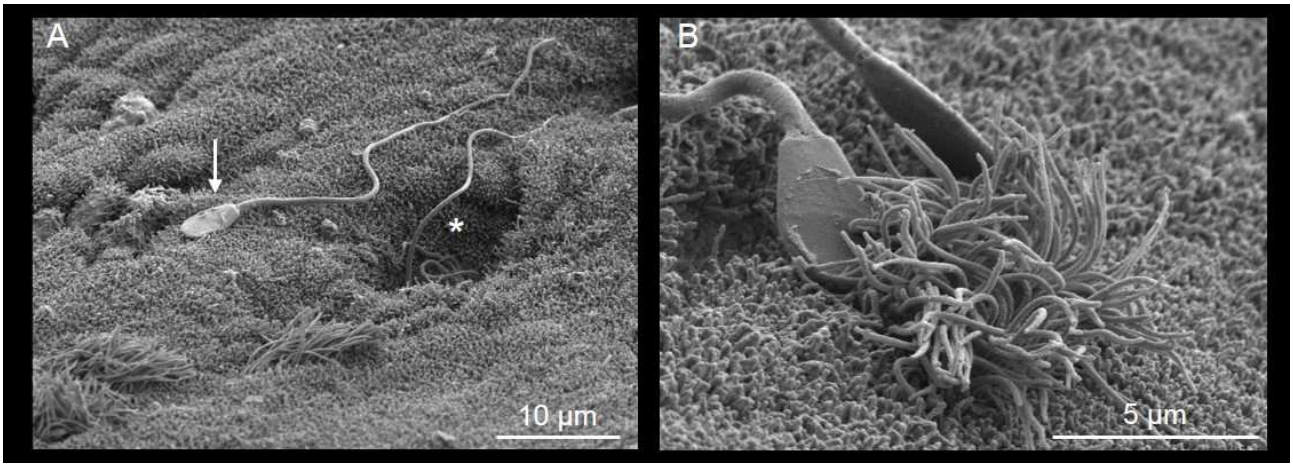

Figure 3. Scanning electron microscopy (SEM) images of dog sperm interacting with uterine epithelial cells *in vivo*. Uterine epithelial cells at the luminal surface (A, white arrow) and in uterine gland (A, asterisk). B: higher magnification showing sperm heads with intact plasma membrane interacting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

Sperm binding to UECs induces transient endometrial inflammation followed by the entry of polymorphonuclear neutrophils (PMNs) in the lumen and their binding to spermatozoa (Schjenken and Robertson, 2014). One possible role of PMN binding to spermatozoa is to eliminate by phagocytosis the spermatozoa not previously removed by uterine contractions. Scanning electron microscopy of bovine endometrial explants incubated with spermatozoa revealed the presence of spermatozoa in the uterine glands along with PMNs (Akthar et al., 2019). Spermatozoa induce an acute inflammatory response and upregulation of mRNA expression of IL8 and TLR2 in endometrial explants (Akthar et al., 2019). *In vitro* models of sperm interaction with bovine UECs showed that sperm binding triggers innate immunity with induction of a pro-inflammatory response (Elweza et al., 2018) through the Toll-like receptor 2/4 (TLR2/4) signaling pathway (Ezz et al., 2019). In the horse, the influx of PMNs into the uterine lumen was previously shown to be triggered via complement activation (Troedsson et al., 1998). Another mechanism of sperm elimination in the uterus is the formation of neutrophils extracellular traps (NETs), previously described for bacteria elimination (Brinkmann et al., 2004), which ensnare spermatozoa and hinder their motility. Sperm entrapment by NETs has been reported in horses (Alghamdi and Foster, 2005), cattle (Alghamdi et al., 2009; Fichtner et al., 2020) and humans (Zambrano et al., 2016). Spermatozoa might also be eliminated in the oviduct as PMNs were detected in the oviductal fluid of cyclic cows (Marey et al., 2014) and buffaloes (Yousef et al., 2019). However, in vitro data indicate that bovine oviduct epithelial cells around estrus secrete factors, including PGE_2, that suppress the phagocytic behavior of PMNs toward sperm but not toward bacteria (Marey et al., 2014; Marey et al., 2019; Yousef et al., 2019).

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

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

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

3. Sperm interactions with the utero-tubal junction

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

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

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

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

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

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

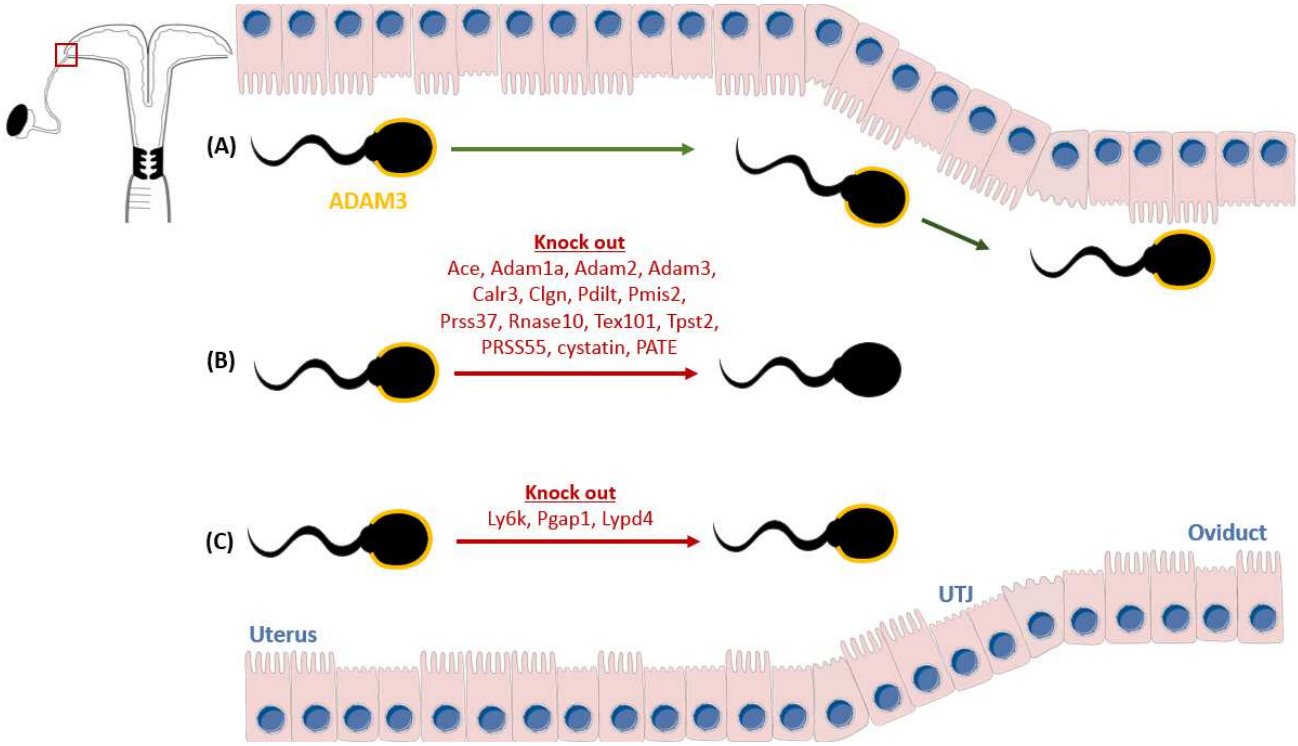

Figure 4. Mechanisms of sperm transport through the utero-tubal junction (UTJ) identified in the mouse. (A) Spermatozoa with correct distribution of ADAM3 pass through the UTJ; (B) Genes involved in the correct distribution of ADAM3 on sperm surface and in sperm passage through the UTJ; (C) Genes involved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

4. Sperm interactions with the oviduct

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

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

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

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

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

In order to obtain an exhaustive list of sperm-interacting proteins in the OF, our group compared the proteomes (assessed by nanoLC-MS/MS) of bull sperm pre-incubated or not with cow OF collected at pre-ovulatory, post-ovulatory and luteal phases of the estrous cycle. A total of 27 sperm-interacting proteins ranging from 16 to 230 kDa were quantified on sperm, including the oviduct-specific glycoprotein OVGP1 as most abundant (Lamy et al., 2018). This was in accord with previous candidate-based approaches in which OVGP1 was immunolocalized on various mammalian spermatozoa (Abe et al., 1995b; King and Killian, 1994; Lippes and Wagh, 1989; Yang et al., 2015). In addition, new OF sperm-interacting proteins were identified including annexins (ANXA1, ANXA2), heat shock proteins (HSP27, GRP78), three myosins (MYH9, MYH14, MYO6) and proteins of the protein disulfide isomerase family (PDIA3, PDIA4, PDIA6) (Lamy et al., 2018) (Figure 5). Annexins A1 and/or A2 were previously identified as sperm receptors on OEC apical side in cattle (Ignotz et al., 2007) and pigs (Teijeiro et al., 2009). Furthermore, MYH9 was previously identified as a binding partner of OVGP1 on monkey sperm (Kadam et al., 2006). Therefore, oviductal proteins may also interact with each other in the OF and form protein complexes competing with available interacting sites on sperm. Of interest, the abundance of interacting proteins on sperm differed according to the cycle stage and was not related to the initial abundance of specific proteins measured in the OF (Lamy et al., 2016a; Lamy et al., 2018). This indicates that highly selective sperm-protein interactions take place in the oviduct and suggests specific (unknown) mechanisms of sperm binding depending on the protein environment. Furthermore, while OVGP1 was by far the most abundant protein on sperm before ovulation, a number of proteins including MYH9, MYH14, HSP27, ANXA1 and ANXA2 interacted with sperm only after ovulation or at

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

The functional roles of OVGP1, a glycoprotein more abundant in the OF of various mammals during estrus than at other stages of cycle, has been given special attention (for review, see (Aviles et al., 2010)). The protein is not present in rats and megabats as *OVGP1* became a pseudogene in these two species (Moros-Nicolas et al., 2018). Female mice with a null mutation for OVGP1 displayed a slight decrease in litter size after mating (−14% with no statistical difference with controls), showing that OVGP1 is not essential for fertilization, at least in mice (Araki et al., 2003). The comparison of the amino acid sequences of various mammalian OVGP1 revealed significant differences between species, especially in the C-terminal region (Aviles et al., 2010), making it difficult to extrapolate the potential roles of OVGP1 on fertilization from one species to another. In cattle, spermatozoa incubated with purified OVGP1 displayed higher motility, viability (Abe et al., 1995b; Choudhary et al., 2017), membrane integrity and capacitation status (Choudhary et al., 2017) than untreated controls. Under capacitating conditions, OVGP1 enhanced sperm protein tyrosine phosphorylation and acrosome reaction in hamster (Saccary et al., 2013; Yang et al., 2015) and human (Zhao et al., 2016) in a time-dependent manner, with first stimulating effects observed after only 5 min (Saccary et al., 2013). Native OVGP1 was more effective than recombinant non-glycosylated OVGP1 on various buffalo sperm functions, inferring important roles played by OVGP1 glycosylation (Choudhary et al., 2017). Furthermore, pretreatment of either sperm or oocyte with recombinant hamster OVGP1 prior to co-incubation was shown to increase the number of sperm bound to the zona pellucida (Yang et al., 2015), indicating modulating roles on gamete interaction.

There is limited information on the role played by other oviductal proteins on sperm functions. Osteopontin (OPN), like OVGP1, is a glycoprotein present in the OF at highest abundance around ovulation time (Liu et al., 2015; Soleilhavoup et al., 2016). OPN was shown to bind on the post-equatorial region of bull ejaculated sperm, possibly via integrin and CD44 receptors (Souza et al., 2008), and promoted induced-acrosome reaction *in vitro* (Monaco et al., 2009) (Figure 5). Since OPN is already present on ejaculated sperm, it was suggested that contact with OF changes OPN pattern on sperm heads and therefore facilitates sperm interactions with oocyte (Souza et al., 2008). In mice, anti-OPN antibody added *in vitro* reduced the rates of fertilization, cleavage and blastocyst formation (Liu et al., 2015), suggesting a beneficial role of OPN in these steps. In pigs, in which high incidence of polyspermy typically occurs during IVF, OPN reduced polyspermy and increased fertilization efficiency during IVF (Hao et al., 2006).

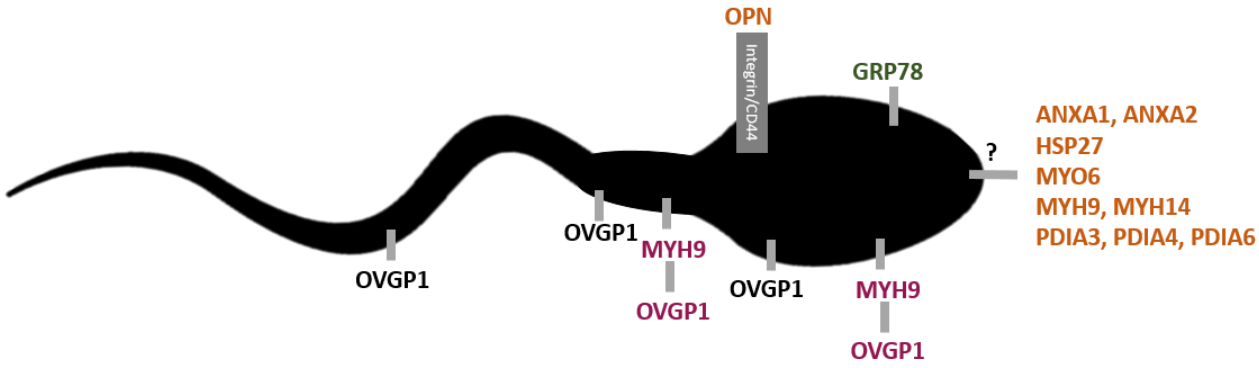

Figure 5. Identification and localization of sperm-interacting proteins in the oviductal fluid. The heat shock protein GRP78 interacts with acrosomal cap of human sperm (Marin-Briggiler et al., 2010). OVGP1 was shown to associate with the sperm head region and midpiece in human (Lippes and Wagh, 1989; Zhao et al., 2016) and hamster (Yang et al., 2015) but with the whole surface of bull sperm (Abe et al., 1995b;

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

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

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

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

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

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

(Schuh et al., 2004). PMCA1 and 4a were shown to be major forms of PMCAs in mice oEVs and detected at much higher abundance around the time of ovulation (at pro-estrus/estrus) than at other stages of the cycle (Al-Dossary et al., 2013; Bathala et al., 2018). Co-incubation assays indicated that mouse sperm are able to integrate PMCA4a from oEVs over the sperm head and midpiece (Al-Dossary et al., 2015; Al-Dossary et al., 2013). A fusion mechanism involving integrins ($\alpha5\beta1$ and $\alpha v\beta3$) and CD9 tetraspanin expressed on sperm and oEVs was proposed (Al-Dossary et al, 2015). Further studies evidenced that oEVs can deliver enzymatically active PMCA1 and tyrosine-phosphorylated proteins to murine sperm and that this delivery was higher in capacitated than in uncapacitated sperm (Bathala et al., 2018). As PMCAs were also detected in human oEVs, it was proposed that the delivery of fertility-modulating proteins to sperm by oEVs was preserved in humans (Bathala et al., 2018). Moreover, oEVs seem able to deliver microRNAs in intracellular sperm subcompartments in mice (Fereshteh et al., 2018). Transferred microRNAs were mainly localized in sperm head while the microRNA *miR-34c-5p*, which is only sperm-derived in the embryo and crucial for the first embryo cleavage, was specifically concentrated near the centrosome (Fereshteh et al., 2018) (Figure 6). These data identify oEVs as key components for sperm acquisition of fertilizing ability and for the quality of the early embryo. Further studies are needed to understand by which mechanisms oEV-derived molecules localize in specific sperm sub-compartments to perform their function.

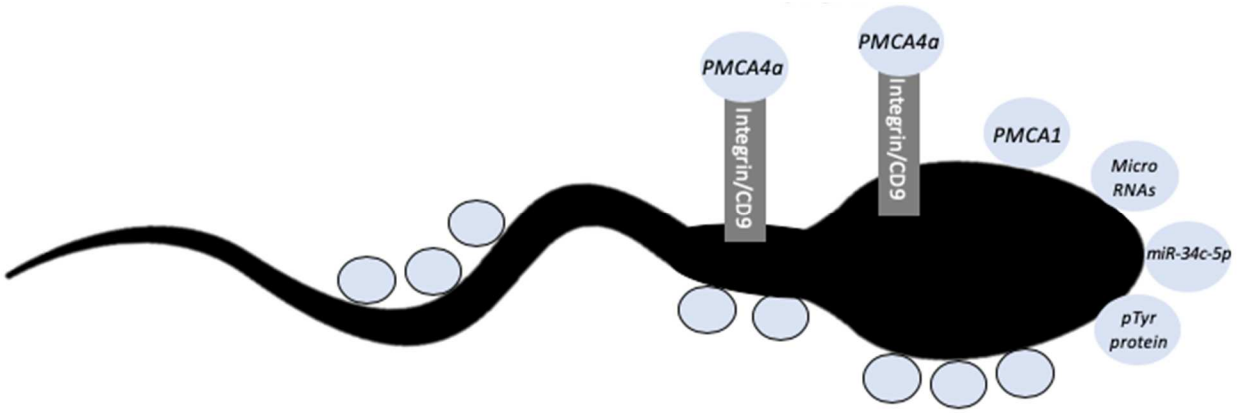

Figure 6. Identification and localization of oviductal extracellular vesicles and intravesicular molecules interacting with spermatozoa. Oviductal EVs (in blue) were shown to merge with sperm head and midpiece in mice (Al-Dossary et al. 2015), and cats (Ferraz et al., 2019) but also with sperm tail in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

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

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

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

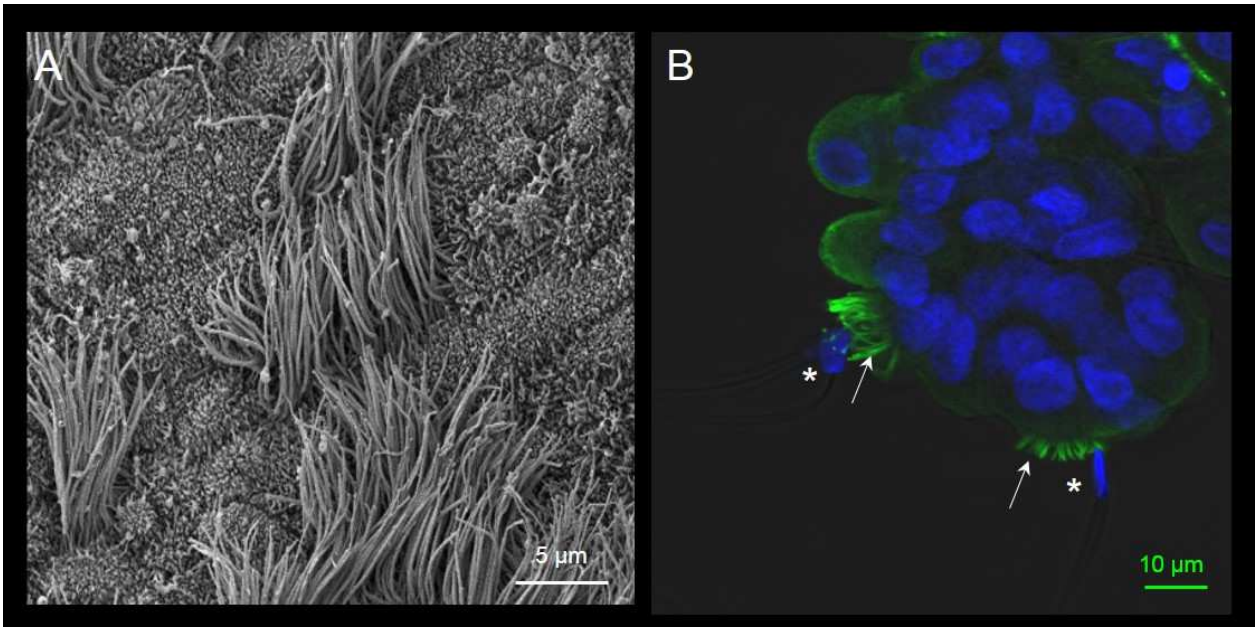

Figure 7. Sperm interactions with oviduct epithelial cells (OECs) in cattle. (A) SEM picture of the luminal surface of oviduct epithelium composed of ciliated and non-ciliated cells. (B) Confocal microscopy picture of bull sperm interacting with bovine oviduct epithelial cells *in vitro*. Nuclei appeared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

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

There is evidence that not all sperm have the ability to bind to the oviduct epithelium (Figure 8). Studies conducted in human and cattle showed that approximately 20% to 50% of frozen-thawed and 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

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

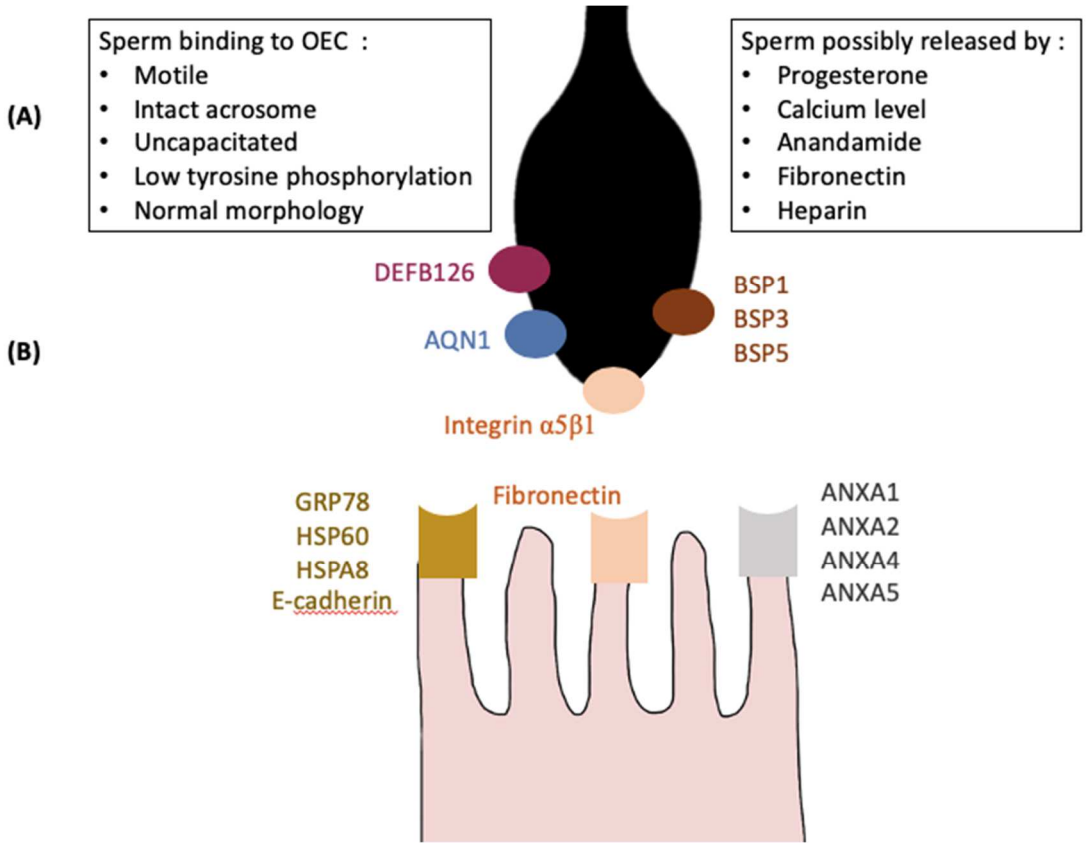

Figure 8. Sperm interactions with oviduct epithelial cell and underlying mechanisms. (A) Sperm parameters for binding to OECs and candidates for the induction of sperm release around the time of ovulation are indicated in left and right squares, respectively. (B) Sperm surface proteins potentially involved in sperm binding to OECs include the spermadhesin AQN1, Binders of Sperm Proteins (BSPs) 1, 3 and 5, integrin α5β1 and beta defensin 126 (DEFB26). Sperm receptors identified at the luminal surface of OECs include the chaperones GRP78, HSP60 and HSPA8, E-cadherin, fibronectin (as specific partner of integrin α5β1) and various members of the annexin (ANX) family. Refer to the text for related species and references.

Sperm binding to the oviduct epithelium is carbohydrate-dependent, as shown by extensive inhibition of sperm binding by competition assays in the presence of glycans (Cortes et al., 2004; 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 $\alpha5\beta1$, 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 AQN1was shown to recognize a wide range of glycans and
552 to inhibit boar sperm binding to OECs when added in the culture medium (Ekhlasi-Hundrieser et al.,
553 2005), suggesting a role in the formation of the oviductal sperm reservoir in pigs.
554
555 ***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

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

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

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

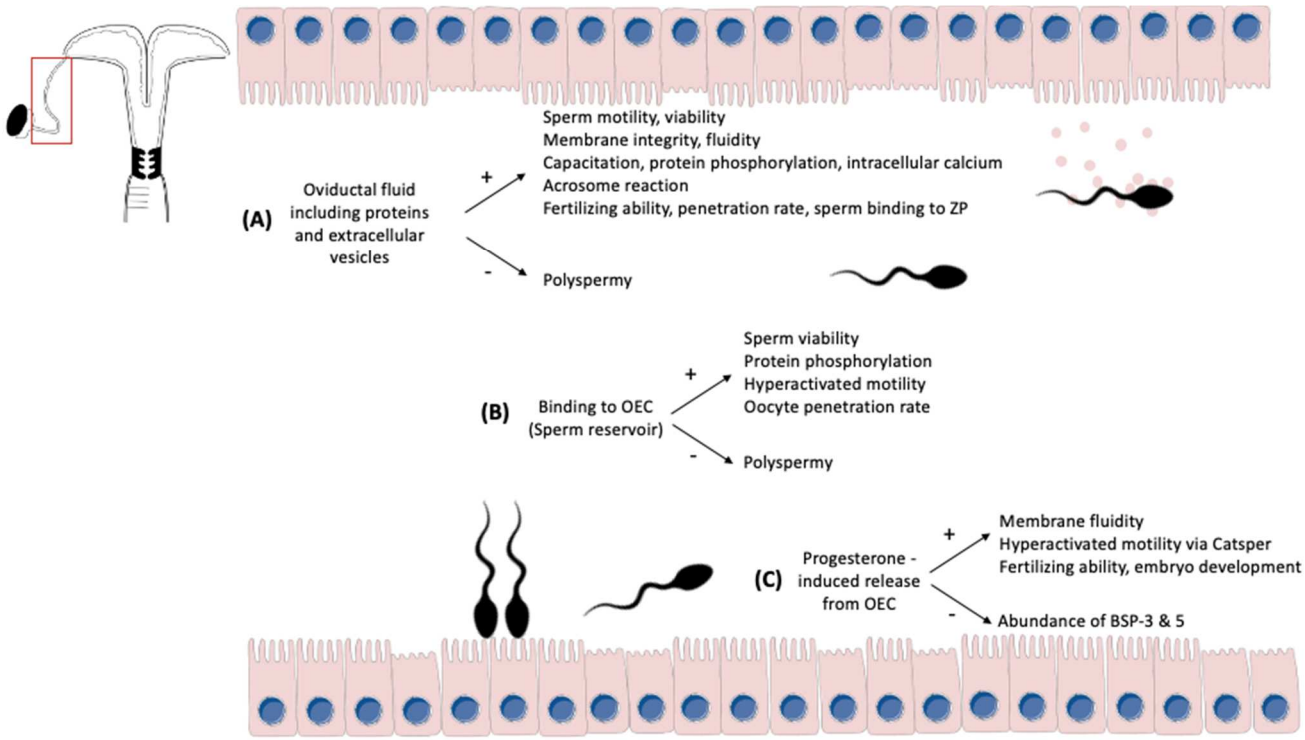

Figure 9. Summarized effects of interactions with the oviduct on sperm physiology. (A) Effects of sperm interaction with the oviductal fluid including soluble proteins and oviductal extracellular vesicles (oEVs) on sperm physiology; (B) Effects of interactions with oviductal epithelial cells (OECs, formation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

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

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

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

5. Conclusions

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

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

Acknowledgments

We thank Marc Chodkievicz for careful reading and edition of this manuscript. We thank Thierry Meylheuc, from the imaging facility at the microscopy and imaging platform MIMA2 (INRAe, Jouy-en-Josas, France), Maryse Meurisse and Marie-Claire Blache, from the microscopy and imaging platform PIC (INRAe, Nouzilly, France), for their help with scanning electronic and confocal microscopy images. MSD thanks the CNRS for full-time delegation in the UMR Unit during this year.

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