REPRODUCTION
REVIEW

Oviductal secretion and gamete interaction

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Abstract

Experimental evidence from the last 30 years supports the fact that the oviduct is involved in the modulation of the reproductive process in eutherian mammals. Oviductal secretion contains molecules that contribute to regulation of gamete function, gamete interaction, and the early stages of embryo development. The oviductal environment would act as a sperm reservoir, maintaining sperm viability, and modulating the subpopulation of spermatozoa that initiates the capacitation process. It could also contribute to prevent the premature acrosome reaction and to reduce polyspermy. Many studies have reported the beneficial effects of the oviductal environment on fertilization and on the first stages of embryo development. Some oviductal factors have been identified in different mammalian species. The effects of oviductal secretion on the reproductive process could be thought to result from the dynamic combined action (inhibitory or stimulatory) of multiple factors present in the oviductal lumen at different stages of the ovulatory cycle and in the presence of gametes or embryos. It could be hypothesized that the absence of a given molecule would not affect fertility as its action could be compensated by another factor with similar functions. However, any alteration in this balance could affect certain events of the reproductive process and could perhaps impair fertility. Thus, the complexity of the reproductive process warrants a continuous research effort to unveil the mechanisms and factors behind its regulation in the oviductal microenvironment.

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The oviduct

The oviduct of eutherian mammals is the organ where the fertilization process takes place. It is a seromuscular tubular organ, whose distal part surrounds the ovary and whose proximal portion is attached to the uterus. Based on morphological and anatomical differences, the oviduct can be divided into four segments (composed of similar cell types, but in different proportions): the infundibulum (with the fimbriae surrounding the ovary), the ampulla, the isthmus, and the uterotubal junction (Fig. 1; Hess *et al*. 2006, Suarez 2006).

The ampulla is the site of oocyte fertilization. The mucosa of the ampulla shows a very complex pattern of folds, which are projected toward the oviductal lumen (Hess *et al*. 2006, Suarez 2006). The isthmic mucosa contains fewer folds than the ampulla.

The oviductal epithelium is mainly formed by columnar ciliated cells and secretory cells (showing surface microvilli); lymphoid cells can be observed close to the basement membrane. The secretory nonciliated columnar cells present a typical structure of cells that actively synthesize proteins (Suarez 2006). Marked differences in the morphological characteristics of the secretory granules from oviductal cells were reported in different species analyzed. In cattle, during the follicular phase of the estrous cycle, nonciliated cells of the ampulla and fimbriae contain large amount of secretory granules, while in the isthmus the number of cytoplasm granules was smaller and show different structural characteristics (Killian 2011).

Primate oviductal epithelial cells possess estrogen and progesterone receptors and undergo cyclical changes related to the menstrual cycle (Brenner *et al*. 1990, Hess *et al*. 2006). In the presence of progesterone, after estradiol levels decrease, loss of *ciliated* epithelium occurs and the secretory cells tend to lose their biosynthetic structures. Estrogens stimulate the secretion of the oviductal epithelium and this secretion is highest in the proliferative phase (Lippes *et al*. 1981, Suarez 2006, Killian 2011). The oviductal fluid contains amino acids, proteins, simple, and complex carbohydrates, ions, lipids, and phospholipids. Some of these components are metabolic substrates, such as lactate, pyruvic acid, amino acids, and glucose, whose levels differ from those present in the uterine fluid and the serum (Leese 1988, Leese *et al*. 2008, Hugentobler *et al*. 2010). Experimental evidence indicated that ion concentrations in oviductal fluid also differ from those of serum, suggesting that the oviductal epithelium modulates ion levels (Leese 1988, Leese *et al*. 2008, Hugentobler *et al*. 2010).

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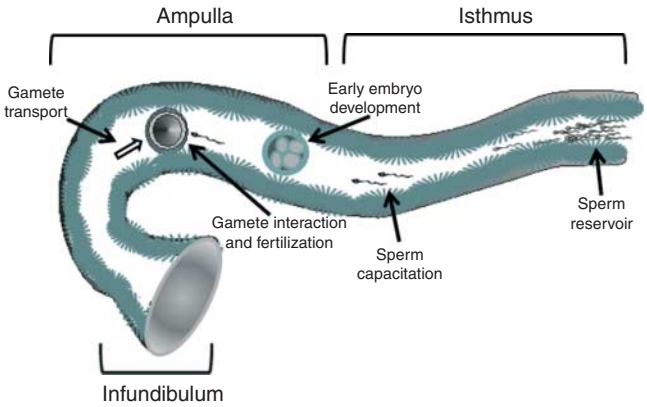

Figure 1 Schematic representation of the oviduct and its suggested involvement in the reproductive process.

The volume and some protein components of the oviductal fluid change throughout the cycle. Part of the complex mixture of proteins that are present in the oviductal fluid come from serum transudate, but there are also specific proteins synthesized and secreted by the oviductal epithelium, and some of them could be regulated by cyclic hormonal changes, with increased biosynthesis at the periovulatory period (Buhi *et al.* 2000, Buhi 2002).

Gamete transport within the oviductal lumen would be a highly controlled process (Suarez 2006, Kölle *et al.* 2009). There is evidence showing that the ciliary activity of the oviductal epithelial cells plays a key role in gamete and embryo transportation. It has been determined that the frequency of ciliary movement of the human oviductal epithelium increases after ovulation (Suarez 2006, Kölle *et al.* 2009).

The following pages will present a review of experimental data that support the central role of the oviduct and its secretion in the reproductive process (Fig. 2).

Sperm–oviduct epithelial cell interaction

Once spermatozoa reach the oviduct, they could follow two pathways. Some of them quickly migrate to the ampulla region, and usually they are not able to fertilize the oocyte, while most of spermatozoa are retained in the isthmus region forming a sperm reservoir, in the presence of the oviductal fluid (Figs 1 and 2; Croxatto 2002, Suarez 2008*a*). Some spermatozoa from the reservoir will retain their viability and their fertilizing ability until ovulation takes place (Suarez 2008*a*).

In different mammalian species, it has been shown that spermatozoa sequestered in the isthmus region could attach to epithelial cells, delaying sperm capacitation until ovulation-associated signals induce their release, allowing their transit to the ampulla. Such interaction would involve the sperm acrosomal region and the apical region of the oviduct epithelial cells, mainly of the ciliated cells (Petrunkina *et al.* 2001, Croxatto 2002, Suarez 2008*a*, Coy *et al.* 2012*a*). In some mammals, such as canine, cattle, and horses, the interaction between spermatozoa and oviduct epithelial cells appears to be associated with sperm survival and capacitation state (Kawakami *et al.* 2001, Suarez 2006, 2008*b*). The molecular and biological mechanisms behind the sperm–epithelium interaction have not been clarified yet.

Different studies have investigated the effects of oviductal molecules that could be involved in the sperm–oviduct interaction. Members of the annexin family of proteins detected in the oviductal epithelium were identified as potential receptors for sperm proteins in bovine and porcine species (Ignotz *et al.* 2007, Suarez *et al.* 2008*a*, Teijeiro *et al.* 2009). Results from a recent study on pigs suggested that sperm binding to oviduct requires the presence of proteins with 6-sialylated biantennary glycans in the membrane of epithelial cells (Kadirvel *et al.* 2012).

Participation of molecules from oviductal secretion in sperm–oviduct interaction

Heparin and other sulfated glycoconjugates, which could be detected in oviductal fluid, were shown to induce the synchronous release of sperm adhering to bovine oviduct epithelium *in vitro*. Heparin-released sperm showed significantly higher intracellular Ca^{++} levels and increased levels of tyrosine-phosphorylated proteins compared with adhering spermatozoa (Gualtieri *et al.* 2005). Another study reported that uncapacitated bovine spermatozoa adhered to the oviduct, and their release was associated with capacitation (Talevi *et al.* 2007). The authors suggested that thiol-reducing agents in the oviductal fluid, such as sulfated glycoconjugates and disulfide reductants, may modulate the redox status of sperm surface proteins, leading to the release of

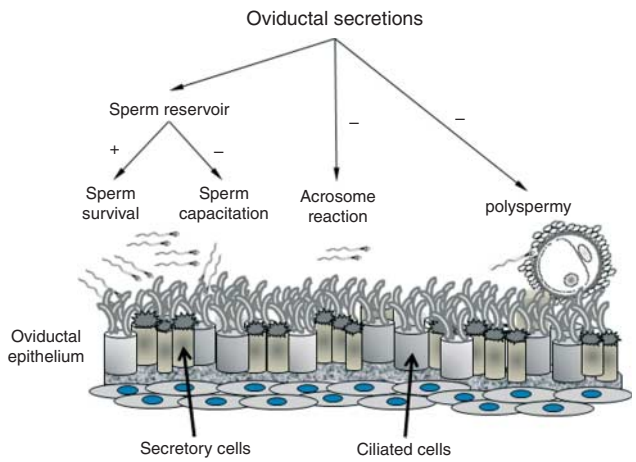

Figure 2 Reported effects of the oviductal secretions on gamete function and gamete interaction in different experimental models. The symbols '+' and '−' indicate stimulatory or inhibitory effects respectively.

spermatozoa from the oviductal epithelium through the reduction of sperm surface protein disulfides to sulfhydryls (Talevi *et al*. 2007, Gualtieri *et al*. 2010).

An endocannabinoid known as anandamide is synthesized in the oviductal epithelia and detected in the oviductal fluid, and binds to cannabinoid receptors. These receptors were detected in mammalian reproductive tissues and male gametes from different species, such as human, porcine, and bovine species (Schuel *et al*. 2002*a*,*b*, Maccarrone *et al*. 2005, Rossato *et al*. 2005, Gervasi *et al*. 2009, Osycka-Salut *et al*. 2012). Gervasi *et al*. (2013) reported that anandamide levels in bovine oviductal fluid varied during estrous cycle, with the highest values detected during the periovulatory period, suggesting that this endocannabinoid levels may be regulated by ovarian hormones. It was reported that anandamide could modulate the bovine sperm–oviductal epithelium interaction, by inhibiting sperm binding and inducing sperm release from epithelial cells (Gervasi *et al*. 2009, Osycka-Salut *et al*. 2012). However, other authors observed that anandamide had no effects on sperm–oviduct binding and sperm release, but might contribute to the oviduct sperm-reservoir function, decreasing motility and capacitation, and prolonging sperm fertile life (Talevi *et al*. 2010).

Oviductal secretion and sperm function

Different experimental approaches have been used in order to assess the effects of the oviductal fluid on gamete function, fertilization, and the initial embryo development.

In some studies, the oviductal fluid was collected by placing a cannula in the oviduct (Leese 1988, Kavanaugh *et al*. 1992, Grippo *et al*. 1995, Way *et al*. 1997, Kumaresan *et al*. 2012).

In addition, the conditioned media from cultures of oviductal cells or tissue explants from different species were used to study the effects of the oviductal secretion on gamete function (Verhage *et al*. 1988, Yeung *et al*. 1994, Yao *et al*. 2000, Quintero *et al*. 2005, Munuce *et al*. 2009, Zumoffen *et al*. 2010).

Numerous studies in mammals have shown that the oviductal secretion or some of its components were able to modulate sperm function, sperm–zona interaction, and the process of fertilization (Fig. 2; Rodriguez-Martinez 2007, Mugnier *et al*. 2009, Killian 2011).

Co-incubation of spermatozoa with oviduct epithelial cells or their conditioned media maintained sperm viability and motility (Zhu *et al*. 1994, Kervancioglu *et al*. 2000, Quintero *et al*. 2005, Munuce *et al*. 2009, Zumoffen *et al*. 2010). However, the mechanisms by which oviductal cells and their secretory products favor the survival of spermatozoa remain unknown.

It has been reported that spermatozoa incubated in the presence of oviductal fluid or co-cultured with oviduct epithelial cells showed a pattern of hyperactivated motility related to the capacitation state, and it would be a preliminary step to undergo the acrosome reaction (Suarez, 2006, 2008*b*). It has also been observed that co-culture of sperm with oviductal cells or incubation in the presence of oviductal fluid showed beneficial effects on the human sperm membrane stabilization (Zhu *et al*. 1994, Yao *et al*. 1999). The decrease in human sperm response to acrosome reaction inducers in the presence of the oviductal cells or their conditioned media suggests that oviductal secretion could exert a stabilizing effect on sperm, contributing to avoid a premature acrosome reaction in the absence of the female gamete (Morales *et al*. 1996, Yao *et al*. 1999). Results from our laboratory indicated a significant decrease in the ionophore-induced acrosome reaction in human sperm incubated previously in the presence of a conditioned medium from human oviductal tissue cultures (Quintero *et al*. 2005). Another study showed that the exposure of boar sperm to porcine oviductal fluid collected in the follicular phase of the estrous cycle promoted boar sperm viability and acrosomal integrity (Coy *et al*. 2010). A recent study has reported that incubation of boar sperm in the presence of pre-ovulatory oviductal fluid caused a significant increase in sperm protein tyrosine phosphorylation compared with incubation with post-ovulatory oviductal fluid or the control medium (Kumaresan *et al*. 2012). In addition, the observed phosphorylation patterns appeared to be individual dependent in porcine species.

Numerous research studies have investigated the oviductal factors that could be involved in the reported effects. The presence of adequate levels of bicarbonateand calcium seems to be essential in regulating sperm capacitation, motility, and acrosome reaction (Rodriguez-Martinez 2007, Leese *et al*. 2008, Abou-haila & Tulsiani 2009, Lishko *et al*. 2012). Hyaluronan and sulfated glycosaminoglycans, such as heparin, have been detected in oviductal fluid from different mammalian species (Kawakami *et al*. 2000, Tienthai *et al*. 2000, 2004, Bergqvist & Rodríguez-Martínez 2006). Glycosaminoglycans were involved in modulating sperm viability and capacitation in some species (Kawakami *et al*. 2000, Tienthai *et al*. 2000, Bergqvist & Rodríguez-Martínez 2006).

Transuded serum proteins, such as albumin and HDLs, are found in the oviductal fluid and would be involved in the cholesterol efflux from sperm membrane during capacitation (Travis & Kopf 2002, Leese *et al*. 2008, Abou-haila & Tulsiani 2009).

Involvement of oviductal proteins in sperm function

The oviduct synthesizes and secretes proteins whose functions have not been clarified with certainty (Leese *et al*. 2008, Killian 2011). Notorious differences in the proteomic profiles of the oviduct between follicular and luteal phases of the reproductive cycle in pig were

reported (Seytanoglu *et al*. 2008). In addition, the presence of gametes appears to alter the pattern of protein synthesis and secretion of the oviductal cells. Supporting this idea, the binding of equine spermatozoa to homologous oviductal cells could change the pattern of protein secretion of the epithelial cells (Thomas *et al*. 1995*a*). The authors suggested that, during this interaction, spermatozoa would be exposed to oviductal protein factors that would maintain their viability and motility and would also facilitate the elimination of deleterious metabolic products (Thomas *et al*. 1995*b*). Georgiou *et al*. (2005, 2007) also showed that the presence of spermatozoa in the pig oviduct could alter the expression and secretion of specific oviductal proteins.

Recently, we have shown that proteins from conditioned media of oviduct tissue culture decreased the follicular fluid-induced acrosome reaction and the phosphorylation in tyrosine residues of human sperm proteins in a dose-dependent manner (Zumoffen *et al*. 2010).

In the last 30 years, several investigations have been directed to identify proteins from the oviductal fluid to analyze their potential effects on the reproductive process. Some of these oviductal proteins and their reported actions will be described as follows.

Oviductins

The production and secretion of high-molecular-weight (MW 70–130 kDa) glycoproteins from the oviductal epithelium seem to be associated with hormonal changes during the ovulatory cycle in different species (Buhi *et al*. 2000, Buhi 2002, Leese *et al*. 2008, Avilés *et al*. 2010). Oviductins, also known as oviduct-specific glycoproteins, have been found in the oviducts of every mammalian species studied to date, and the cDNA sequences for these glycoproteins indicated that they show a high homology among species (Donnelly *et al*. 1991, Arias *et al*. 1994, Sendai *et al*. 1995, Buhi *et al*. 1996). Bovine oviductin, referred to as an estrus-associated protein, was isolated from the oviductal fluid and was able to bind to the head and middle piece of spermatozoa (King & Killian 1994). Bovine oviductin has been shown to promote *in vitro* sperm capacitation and maintain both the viability and motility of spermatozoa compared with the control medium without any added protein and these effects were dose dependent (King *et al*. 1994, Abe *et al*. 1995). Mouse oviductin has been shown to bind to the equatorial and acrosomal regions of mouse sperm heads (Lyng & Shur 2009). Other studies indicated that hamster oviductin bound to the anterior acrosomal region of the sperm and enhanced sperm capacitation (Kimura *et al*. 1994, Saccary *et al*. 2013). In addition, it was reported that the sperm-binding sites of hamster oviductin were related to the sperm capacitation status and the acrosome reaction (Kan & Esperanzate 2006).

Osteopontin

This phosphoprotein, which contains repetitive amino acid sequences of arginine–glycine–aspartic acid (RGD), was detected in the bovine oviductal secretion and shown to have a variable expression throughout the estrous cycle (Gabler *et al*. 2003). Glycoproteins containing the RGD recognition sequence, which would be ligands of integrins, could be present on the extracellular cover of bovine oocytes and sperm (Ikawa *et al*. 2010). A study by Souza *et al*. (2008) revealed that distribution of sperm-binding sites of osteopontin changed after incubation in the bovine oviductal fluid, and the authors suggested that the protein could participate in sperm–oocyte interaction. Another study has reported that osteopontin increased bovine sperm capacitation (Monaco *et al*. 2009).

Glycodelins

These glycoproteins have been detected in the human oviduct at least in four isoforms, namely glycodelin S, glycodelin A, glycodelin F, and glycodelin C, based on the differences in glycosylation (Yeung *et al*. 2006, Chiu *et al*. 2007*a*, *b*). Glycodelins are highly homologous to beta-lactoglobulins, which were detected in the female reproductive tract from several species (Huhtala *et al*. 1987). Glycodelin A is produced and secreted by the oviductal epithelium. Recombinant glycodelin A was shown to inhibit capacitation of human and hamster spermatozoa (Dutta *et al*. 2001). Glycodelin F is expressed in the human oviductal epithelium and in granulosa luteal cells and was shown to bind to the acrosomal region of human sperm head and suppress the progesterone-induced AR (Yeung *et al*. 2006). Thus, it was suggested that glycodelin F could help to prevent a premature acrosome reaction, before the human spermatozoa contact the zona pellucida (ZP; Yeung *et al*. 2007). Glycodelin C, generated from glycodelins A and F in oocyte cumulus cells, has been shown to bind to sperm head, mainly in the equatorial region (Chiu *et al*. 2007*b*).

Atrial natriuretic peptide

This peptide is expressed in the pig oviductal epithelium and is present in the oviductal fluid. Its receptor was detected in spermatozoa (Zhang *et al*. 2006). The pre-incubation of boar spermatozoa with atrial natriuretic peptide has been shown to induce the acrosome reaction (Zhang *et al*. 2006).

Sperm adhesion molecule 1 (SPAM1)

This protein is a hyaluronidase also known as PH-20 present in sperm membrane. It has been found to be secreted in the female reproductive tract (including the oviduct) and it can bind to sperm (Griffiths *et al*. 2008). It was shown that hyaluronic acid interacts with the

PH-20 protein anchored on the macaque and human sperm membrane increasing the basal levels of intracellular calcium and promoting the induced acrosome reaction (Sabeur *et al*. 1998, Cherr *et al*. 1999).

Lactoferrin

This glycoprotein was isolated in our laboratory from the conditioned medium of human oviductal tissue culture based on its binding ability to sperm membrane and was further identified as human lactoferrin (Zumoffen *et al*. 2013). It was detected in tubal fluid and appeared to be estrogen regulated in human oviduct epithelial cells (Zumoffen *et al*. 2013). Results of our study indicated that lactoferrin presents different binding patterns to sperm related to the capacitation status and the acrosome reaction, suggesting that the protein could participate in sperm–oocyte interaction (Fig. 3; Zumoffen *et al*. 2013). In addition, lactoferrin was able to modulate some sperm functions related to capacitation (C Zumoffen and S Ghersevich unpublished observations).

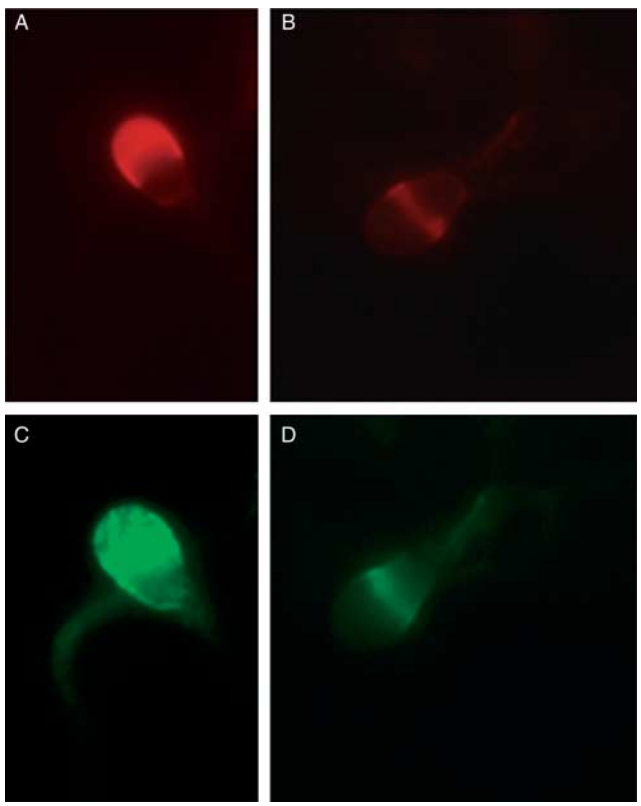

Figure 3 Fluorescence micrographs showing the acrosomal staining (detected with *Pisum sativum*-rhodamine) and the binding of FITC-conjugated lactoferrin in human spermatozoa incubated under capacitating conditions. (A) Intact acrosome sperm. (B) Acrosome-reacted sperm. (C) Lactoferrin localized to the sperm head in the same cell as (A). (D) Lactoferrin was detected mainly in the equatorial segment in the same spermatozoon as (B).

Involvement of oviductal secretion in gamete interaction

Numerous studies have investigated the effects of the oviductal secretion on gamete interaction. Experiments conducted on cows have shown that the presence of nonluteal oviductal fluid or fluid collected from the isthmic oviductal region increased more sperm–zona binding than the fluid collected in the luteal stage of the estrous cycle or the fluid from the ampulla respectively (Grippo *et al*. 1995, Way *et al*. 1997). The authors suggested that the effects of bovine oviductal fluid on gamete function and interaction depended on the oviductal region and the stage of the estrous cycle (Grippo *et al*. 1995, Way *et al*. 1997). Taitzoglou *et al*. (2007) reported changes in exposed saccharide residues of bovine sperm during capacitation in the presence of oviductal fluid and they suggested that these modifications could influence sperm–zona binding, zona penetration, and interaction with the oolemma.

It has been reported that the exposure of hamster oocytes to the oviductal environment increased sperm–zona binding, zona penetration and fertilization (Boatman *et al*. 1994). In accordance with the previous results, incubation of hamster oocytes in the presence of oviductal fluid improved both sperm–zona binding, zona penetration and fertilization (Kito & Bavister 1996).

A study conducted on dogs reported that incubation in the presence of oviductal fluid increased the sperm–ZP binding (Kawakami *et al*. 1998). Another study revealed that co-culture of equine gametes with homologous and heterologous (porcine) oviductal cells increased equine IVF rates (Mugnier *et al*. 2009). Coy *et al*. (2010) reported that exposure of boar spermatozoa to pre-ovulatory porcine oviductal fluid increased zona binding and polyspermy during IVF.

In the case of human species, co-incubation with oviductal cells or their conditioned media was found to reduce the human sperm binding to ZP (Morales *et al*. 1996, Yao *et al*. 1999).

It has been shown that exposure of ZP to oviductal fluid increased ZP resistance to proteolysis. This effect was associated with reduced polyspermy by decreasing sperm–ZP binding in porcine and bovine species (Coy *et al*. 2008). The increased ZP resistance to proteolysis by oviductal fluid seems not to be species specific, at least among ruminants and rabbits (Katska *et al*. 1989, 1999). Supporting this suggestion partially, the presence of human oviductal fluid increased ZP resistance to proteolysis in rabbit, sheep, pig, and bovine species, but not in human species, suggesting that this effect could depend on the species (Mondéjar *et al*. 2013*a*).

Involvement of oviductal proteins in gamete interaction

Experimental evidence supports that proteins play a central role in modulating gamete interaction. Once the

spermatozoon detects the oocyte, it must cross two barriers, the cumulus cells and the ZP, before it could contact the female gamete plasma membrane (Ikawa *et al*. 2010, Coy *et al*. 2012*a*; Fig. 2). The ZP is a glycoprotein cover that surrounds the oocyte in mammals and would be responsible for the species specificity of gamete interaction (Wassarman *et al*. 1999).

It has been suggested that species-specific zona adhesion is not mediated by a single receptor. Instead, sperm–zona binding would involve a multiplicity of receptor–ligand interactions and would require the coordinated action of different proteins (Nixon *et al*. 2005, Gahlay *et al*. 2010, Clark *et al*. 2011, Avella *et al*. 2013). The initial mouse sperm–zona binding could also involve components of the ZP acquired in the oviduct after ovulation (Lyng & Shur 2009).

Experimental evidence suggested that there is a dynamic aggregation of zona proteins believed to be important in sperm–ZP recognition to the regions of sperm that mediate this binding event (Gahlay *et al*. 2010). In addition, a recent study has demonstrated that mannose, fucose, and β-*N*-acetylglucosamine were terminal carbohydrates on the mouse oocyte ZP involved in cross-linking or aggregation with receptors on the sperm membrane (Wu & Sampson 2014). It has been suggested that mouse sperm receptors for zona proteins interact with both the glycans and the protein backbone of the ZP (Clark *et al*. 2011).

It has been proposed that the interaction between integrin-like proteins on the oolemma and disintegrins of transmembrane proteins that contains a disintegrin and metalloprotease domain (ADAM), found on the sperm membrane would be involved in the gamete fusion process (Ikawa *et al*. 2010, Inoue *et al*. 2011). However, this idea is mainly supported by results obtained from studies on the fusion of gamete membranes carried out in mouse models.

Different experimental approaches have demonstrated that oviductal proteins could interact with gametes and affect gamete interaction (Fig. 2). A previous study has reported that six proteins from the bovine oviductal fluid were attached to the homologous ZP (Staros & Killian 1998). In a study carried out in our laboratory, the presence of proteins from the conditioned media of human oviductal tissue culture resulted in a dose-dependent inhibition of the sperm–ZP binding and decreased the detection of sperm D-mannose-binding sites, which are associated with gamete interaction (Munuce *et al*. 2009).

Some of the oviductal proteins suggested to be involved in modulating gamete interaction have been identified and their reported effects are described below.

Oviductins

These glycoproteins secreted by the oviductal epithelium were shown to interact with the oocyte ZP in different species. O'Day-Bowman *et al*. (1996) reported that incubation of human or baboon spermatozoa in the presence of the oviductin increased hemizona binding and penetration to hamster oocytes. The presence of oviductin also increased the *in vitro* sperm fertilizing ability in bovine species (King *et al*. 1994, Martus *et al*. 1998). Oviductins were suggested to participate in the initial sperm–zona adhesion in mice and were found to be associated with both the ZP and the perivitelline space of mouse oocytes (Ensslin *et al*. 2007, Lyng & Shur 2009). Despite the results mentioned above, a study using *Ovgp1*$^{-/-}$ mice indicated that fertility of *Ovgp1*$^{-/-}$ females was within the normal limits, suggesting that, at least in mice, the protein was not essential for the process of *in vivo* fertilization (Araki *et al*. 2003).

An early study demonstrated that hamster oviductin was bound to the ZP during transit of the oocyte in the oviduct (St-Jacques *et al*. 1992). However, the exposure to oviductin was shown to decrease the sperm–zona interaction and inhibit IVF of cumulus-free oocytes in hamsters (Kimura *et al*. 1994, Saccary *et al*. 2013). It has been reported that exposure to porcine oviductin before and during IVF decreased the incidence of polyspermy in pig oocytes and reduced the number of bound sperm (Kouba *et al*. 2000, McCauley *et al*. 2003). Oviductin and heparin-like glycosaminoglycans have been implicated in the pre-fertilization ZP hardening in cows and pigs, which could affect sperm binding and would contribute to prevent polyspermy (Coy *et al*. 2008). In addition to oviductin, proteins from the heat shock protein family and the protein disulfide isomerase A4 appear to be involved in ZP hardening in bovine species (Mondéjar *et al*. 2013*b*).

Osteopontin

A study on bovine species demonstrated the binding of osteopontin (which is secreted by the oviductal epithelium) to the ZP (Gonçalves *et al*. 2008). It has also been reported that the pre-incubation of spermatozoa or oocytes with oviductal fluid pre-treated with antibodies against osteopontin reduced sperm–ZP binding and IVF (Gonçalves *et al*. 2007, 2008). Another study has demonstrated that the exposure to osteopontin during IVF decreased polyspermy in pigs (Hao *et al*. 2006, 2008). In addition, it has also been demonstrated that exposure to osteopontin during IVF also increased the fertilization efficiency in pigs and slightly increased the IVF rates in equine species (Hao *et al*. 2006, 2008, Mugnier *et al*. 2009).

Glycodelins

Exposure to glycodelin A has been shown to decrease human gamete interaction *in vitro* (Oehninger *et al*. 1995). This effect would result from blocking the binding of the sperm fucosyltransferase 5 (suggested to be the sperm glycodelin A receptor) to the ZP (Chiu *et al*. 2007*a*). The presence of glycodelin F has also been reported to reduce gamete interaction (Chiu *et al*. 2003).

Glycodelin C would remove the previously attached glycodelins A and F from spermatozoa, enhancing the zona-binding capacity of sperm passing through the cumulus oophorus (Chiu *et al*. 2007*b*).

HSPA5

This protein also known as GRP8 was first isolated from the plasma membrane of oviduct epithelial cells and its expression in these cells changed throughout the estrous cycle and would be under hormonal control (Bauersachs *et al*. 2004, Boilard *et al*. 2004). The presence of this protein was detected in human oviductal fluid and the conditioned medium from tubal tissue cultures (Marín-Briggiler *et al*. 2010). Recombinant GRP78 was found to bind to spermatozoa and was able to decrease sperm–zona interaction in a dose-dependent manner (Marín-Briggiler *et al*. 2010).

Atrial natriuretic peptide

It has been shown that pre-incubation of spermatozoa with this peptide increased the oocyte penetration rate and decreased the polyspermy rate and the average number of sperm per penetrated oocyte in pigs (Zhang *et al*. 2006).

S100A11

The expression of this protein, which belongs to the S100 family of proteins, was detected in the oviductal epithelium, mainly in the ampullary region of the mouse oviduct and at the estrous stage of the estrous cycle (Hanaue *et al*. 2011). S100A11 was also detected bound to the plasma membrane of cumulus cells surrounding the oocytes. Pre-treatment of the cumulus cell–oocyte complex with recombinant S100A11 significantly reduced the efficiency of IVF in mice. The authors suggested that the effect could be mediated through the binding of S100A11 to the plasma membrane of the cumulus cells (Miwa *et al*. 2010, Hanaue *et al*. 2011).

Deleted in malignant brain tumors 1 (DMBT1)

This protein was shown to be expressed by the oviductal epithelium and was localized to the ZP and the cytoplasm of oocytes in equine and porcine species (Ambruosi *et al*. 2013). Pre-incubation of oocytes with recombinant deleted in malignant brain tumors 1 (DMBT1) increased the monospermic IVF rate in pigs (Ambruosi *et al*. 2013). The reported effect was also observed when oviductal fluids were used instead of the recombinant protein, but there was no effect when an antibody against DMBT1 was previously added to the oviductal fluid (Ambruosi *et al*. 2013).

Glycosidase enzymes

These enzymes have been detected in hamster, porcine, and bovine oviductal secretion (Tulsiani *et al*. 1996, Carrasco *et al*. 2008*a*, *b*). It has been suggested that these enzymes could affect the protein and carbohydrate distribution on the sperm and the ZP surface and could modulate sperm–oocyte binding and gamete–oviductal epithelium interaction, both suggested to be carbohydrate-mediated events occurring in the presence of the oviductal fluid (Carrasco *et al*. 2008*a*, *b*).

Proteases

Plasminogen activators were detected in porcine and bovine oviductal flushing and their relative concentrations were found to change during the ovulatory cycle (Roldán-Olarte *et al*. 2005). Plasminogen is present in the oviductal fluid through the estrous cycle (Mondéjar *et al*. 2012). Plasminogen activators and their main substrate, plasminogen, were also found in the cumulus cell extracellular matrix and oocyte ZP (Roldán-Olarte *et al*. 2005, Mondéjar *et al*. 2012). A recent study has demonstrated that the presence of plasminogen in the IVF medium decreased sperm penetration of oocytes in porcine and bovine species (Mondéjar *et al*. 2012). It has been suggested that sperm binding to oocytes triggers the releasing of plasminogen activators from the oocyte and the generated plasmin causes sperm detachment from the ZP (Coy *et al*. 2012*b*). Supporting this idea, it has been reported that, after fertilization, plasminogen and plasminogen activator immunolabeling decreases in the oocyte, suggesting its conversion into plasmin (Mondéjar *et al*. 2012).

Sperm adhesion molecule 1

This hyaluronidase, together with other enzymes, has been implicated in assisting the sperm penetration through the cumulus cell layer surrounding the ZP (Lin *et al*. 1994). It has also been involved in the binding of acrosome-reacted sperm to the ZP (Myles & Primakoff 1997, Redgrove *et al*. 2013).

Lactoferrin

In a recent study, human lactoferrin was shown to bind to ZP. In addition, the presence of the protein caused a dose-dependent decrease in the human sperm–zona interaction (Zumoffen *et al*. 2013). Lactoferrin was also shown to reduce the availability of sperm D-mannose receptors (C Zumoffen and S Ghersevich, unpublished observations). The latter effect could partially explain the inhibition of sperm–zona binding in the presence of the protein.

Involvement of oviductal secretion in embryo development

Some studies have suggested that co-culture of gametes or embryos with oviduct epithelial cells benefits IVF rate and embryo development respectively (Liu *et al*. 1995, Wiemer *et al*. 1995, Romar *et al*. 2001, Kattal *et al*. 2008,

Mugnier *et al*. 2009). However, these results were not supported by studies on other mammalian species (Izquierdo *et al*. 2002, Kidson *et al*. 2003, Shirazi & Motaghi 2013). The difference in the mentioned results may reflect the fact that every study was performed under very different conditions. However, potential species-specific effects of co-culture with oviductal cells on embryo development could not be ruled out, but they remain to be demonstrated yet.

It has been proposed that co-culture with oviduct epithelial cells would reduce the undesirable factors in the culture medium and this would benefit embryo development. It is possible that epithelial cells, through their metabolic capacity, reduce the atmospheric oxygen pressure and the levels of substances such as glucose, which act as inhibitors of embryonic development *in vitro*. Another possible mechanism would involve the production of embryotropic factors, such as certain growth factors, whose presence in the oviduct has been clearly documented. Growth factors in the oviduct were suggested to be involved in preimplantation embryo development (Dalton *et al*. 1994, Einspanier *et al*. 1999, Pushpakumara *et al*. 2002, Wijayagunawardane *et al*. 2005, Itoh *et al*. 2006, Sun *et al*. 2006, Kawamura *et al*. 2007, Weng *et al*. 2009, Swangchan-Uthai *et al*. 2011).

It has been reported that the condition of the oviduct where bovine embryos were placed until reaching the blastocyst stage influenced their gene expression patterns, especially for those genes that regulate metabolic activity (Gad *et al*. 2011). Thus, factors from the oviductal secretion could affect the embryo gene expression.

In addition, Lee *et al*. (2005, 2006) have analyzed the interaction between embryos and oviduct in mice and their results suggested that the presence of the embryo could affect the protein expression of the mouse oviductal epithelium, as shown for the phospholipid transfer protein (PLTP) and the demilune cell and parotid protein.

Phospholipid transfer protein

In the presence of an embryo, the mouse oviductal epithelium secretes PLTP, which showed a higher expression in the embryo-containing oviduct than in the control oviduct (Lee *et al*. 2005). As *Pltp* mRNA increased in the oviductal epithelia of pregnant mice, the authors suggested that it could be involved in *in vivo* preimplantation embryo development (Lee *et al*. 2005).

Demilune cell and parotid protein

This protein was also highly expressed in mouse oviductal lumen in the presence of embryos (Lee *et al*. 2006). Demilune cell and parotid protein was shown to stimulate the growth of preimplantation embryos, suggesting that it may participate in embryo–maternal dialog (Lee *et al*. 2006). Other proteins present in the oviductal secretion suggested to be involved in modulating embryo development are mentioned below.

Oviductins

They were localized to the perivitelline space and the membrane of embryos from different species before the implantation. Their densely glycosylated mucin-type domains would act as a protective shield around the oocyte and the early embryo and would be important for early stages of embryo development (Malette *et al*. 1995, Boatman 1997, Velasquez *et al*. 2001, Buhi 2002, Wolf *et al*. 2003, Gonçalves *et al*. 2008). Porcine oviductin increased post-cleavage embryo development to blastocyst (Kouba *et al*. 2000, McCauley *et al*. 2003). In a study on goats, Pradeep *et al*. also reported that oviductin increased the cleavage rate, and morula and blastocyst formation (Pradeep *et al*. 2011).

Osteopontin

A study on bovine species reported that pre-incubation of oocytes with oviductal fluid pre-treated with antibodies against osteopontin reduced the *in vitro* embryo development when compared with the oviductal fluid alone (Gonçalves *et al*. 2008). Supporting the mentioned results, the presence of osteopontin improved the efficiency of *in vitro* embryo production in bovine species (Monaco *et al*. 2009). In addition, the exposure to osteopontin during IVF has also been shown to improve *in vitro* development of porcine embryos (Hao *et al*. 2006, 2008).

Human oviduct-derived embryotropic factor 3

This factor contains complement protein 3 (C3) and its derivatives C3b and inactivated complement 3b (iC3b) (Lee at al. 2004). C3 is produced and secreted by human and mouse oviductal cells. Both derivatives, but not C3, were embryotropic, while iC3b was most efficient in enhancing the mouse blastocyst development, with larger size and higher hatching rate (Lee at al. 2004). Oviductal cells possess C3 convertase activity converting C3 to C3b (Tse *et al*. 2008). It has been shown that the mouse preimplantation embryos may cooperate with oviductal cells to produce embryotropic iC3b (Tse *et al*. 2008). The levels of C3 and iC3b in mouse oviductal fluid were highest on day 3 of pregnancy, when they could enhance the blastocyst development and result in larger size and higher embryo hatching rate *in vitro* (Lee *et al*. 2009). Based on these data, it has been suggested that the oviduct produced C3/C3b, which could be converted into iC3b in the presence of the embryo stimulating its development.

Concluding remarks

Until a few decades ago, the oviduct was considered as a simple passive conduit that provided an optimal microenvironment in terms of temperature, pH, osmotic pressure, nutrients, and oxygen pressure, enabling both

the fertilization process and the early stages of embryo development (Pauerstein & Eddy 1979). The accumulated experimental evidence reviewed in the present work supports that the oviduct is actively involved in the reproductive process, considering that its secretion contains molecules capable of modulating gamete functions and interaction. It would also contribute to regulate the early stages of embryo development.

Based on the reported data in different mammalian species, it has been considered that spermatozoa in the oviduct interact with factors that would help select subpopulations of male gametes that remain viable while developing an optimal fertilizing ability. The oviductal environment would also contribute to decrease the number of sperm that could interact with the oocytes.

Numerous studies have identified specific molecules, most of which are proteins, in the oviductal environment that could be involved in modulating different stages of the reproductive process. The expression of certain protein components of the oviductal secretion would be subject to cyclic changes of sex steroids. In addition, the presence of gametes or embryos could affect the protein expression from oviductal epithelial cells. It could be thought that the resulting effect of the oviductal secretion, either inhibitory or stimulatory, on the reproductive process would result from the dynamic cooperative action of multiple factors present in the oviduct at different stages of the ovulatory cycle (Fig. 4). The combined action of these factors, either inducers or repressors, could contribute to the regulation of the complex mechanism of reproduction in the oviduct. The balance between the stimulatory and inhibitory effects would result from the regulation of the expression of these oviductal factors, which could be dependent on the ovulatory cycle and the oviductal region, induced by the presence of gametes or embryos, constitutive, or even influenced by individual characteristics or by certain disorders. Thus, the deficiency of a given molecule might not impair fertility capacity because its action could be compensated by another factor with similar functions. However, any alteration in this balance could affect some stages of the reproductive process and could perhaps impair fertility.

Therefore, the complexity of the reproductive process warrants a continuous research effort to unveil the mechanisms and oviductal factors behind its regulation.

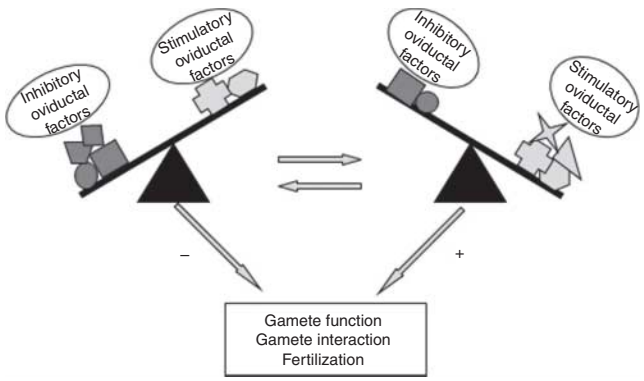

Figure 4 Drawing showing the suggested actions of the oviductal secretion in different stages of the reproductive process. The effect of the oviductal secretion would result from the combined action of several factors, either stimulatory or inhibitory. The balance between the stimulatory and inhibitory effects would result from the regulation of the expression of these oviductal factors, which could be dependent on the ovulatory cycle and the oviductal region, induced by the presence of gametes, constitutive, or even associated with a given disorder. Among oviductal proteins from different species with potential inhibitory actions, the following ones could be mentioned: glycodelins A and F, GRP78, S100 A11, and lactoferrin. On the other hand, proteins such as oviductins, osteopontin, atrial natriuretic peptide, glycodelin C, and sperm adhesion molecule 1 were reported to have some stimulatory effects *in vitro*. The symbols '+' and '−' indicate stimulatory or inhibitory effects respectively.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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