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NEW RESEARCH HORIZON ***Review***

Oviductal secretions: will they be key factors for the future ARTs?

Manuel Avilés[1,*], Alfonso Gutiérrez-Adán[2], and Pilar Coy[3]

[1]Department of Cell Biology and Histology, Faculty of Medicine, University of Murcia, Murcia, Spain [2]Department of Animal Reproduction, INIA, Madrid, Spain [3]Department of Physiology, Veterinary Faculty, University of Murcia, Murcia, Spain

*Correspondence address. Tel: +34-868884385; Fax: +34-868884323; E-mail: maviles@um.es

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ABSTRACT: A variety of evolutionary processes has led to the development of different organs to ensure that internal fertilization occur successfully. Fallopian tubes are a particularly interesting example of such organs. Some of the key events during fertilization and early embryo development occur in the oviduct. Knowledge of the different components described in the oviduct is extensive. Oviductal components include hormones, growth factors and their receptors that have important roles in the physiology of the oviduct and embryo development. Other oviductal factors protect the gamete and the embryos against oxidative stress and pathogens. Different proteins and enzymes are present in the oviductal fluid and have the ability to interact with the oocyte and the sperm before the fertilization occurs. Of special interest is the oviduct-specific glycoprotein (OVGP1), a glycoprotein that is conserved in different mammals, and its association with the zona pellucida (ZP). Interaction of the oocyte with oviductal secretions leads us to emphasize the concept of 'ZP maturation' within the oviduct. The ZP changes produced in the oviduct result in an increased efficiency of the *in vitro* fertilization technique in some animal models, contributing in particular to the control of polyspermy and suggesting that a similar role could be played by oviductal factors in human beings. Finally, attention should be given to the presence in the oviductal fluid of several embryotrophic factors and their importance in relation to the *in vivo* versus *in vitro* developmental ability of the embryos.

Key words: oviduct-specific glycoprotein / concept of zona pellucida maturation / oviductal secretions / *in vitro* development / embryotrophic factors

Introduction

In sexual reproduction, whereby male and female give rise to different gametes that must meet and fuse to produce a new organism, two principal strategies have been developed: external and internal fertilization. In the external fertilization model, large numbers of both gametes are usually released into the external aquatic milieu. In the internal fertilization model, the male has developed a specific organ that allows the introduction of the sperm into the female genital tract during copulation. Moreover, different evolutionary processes have led to the development of different organs to ensure that fertilization takes place and that the embryo develops. Fallopian tubes in primates, usually named oviducts in non-primates, are a particular example of such organs, although their specific role in fertilization is controversial. Although Fallopian tubes have long been considered a mere conduit for gametes and embryos, numerous studies performed during recent decades have demonstrated that the oviduct is involved in several important processes (gamete maturation, capacitation, sperm selection, embryo development etc.) that are necessary for the appropriate gamete and embryo physiology (Hunter, 1998). Later, we will focus on some oviductal processes recently described in mammalian species other than humans that contribute to optimal fertilization and early embryo development. These findings could provide useful information for the development of new strategies to improve some of the assisted reproductive techniques currently used in humans.

Oviductal fluid composition

The oviductal secretion is a complex fluid formed by secreted components from epithelial cells and from blood plasma. It contains many metabolic components, including glucose, lactate, pyruvate and amino acids, whose respective concentrations often differ from those of the uterine fluid and plasma (Stanke *et al.*, 1974; Gardner *et al.*, 1996; Tay *et al.*, 1997; Aguilar and Reyle, 2005; Harris *et al.*, 2005; Li *et al.*, 2007; Hugentobler *et al.*, 2008; Leese *et al.*, 2008; Vecchio *et al.*, 2009; Hugentobler *et al.*, 2010). A large number of proteins have been detected in oviduct and/or oviductal secretion, and the list of components is growing each year (Supplementary Table S1; Buhi *et al.*, 2000; Killian, 2004; Georgiou *et al.*, 2007). It was reported that some of these components influence or may contribute to the optimal development of the different processes that take place in the oviduct. Readers are directed to the different references included in Supplementary Table S1 for detailed information on the

role played by these oviductal components. Thus, the components can be classified in different groups as: (i) growth factors, cytokines and receptors, (ii) hormones and receptors, (iii) proteases and inhibitors, (iv) antioxidant protective agents, (v) defense agents, (vi) glycosidases and glycosyl transferases, (vii) other enzymes, (viii) chaperones and heat shock proteins, (ix) other proteins, (x) glycosaminoglycans and proteoglycans and (xi) other components. It was reported that growth factors produced by oviductal epithelium contribute to more efficient embryo development (this aspect is reviewed in more detail later in this manuscript). Other oviductal components are responsible for the protection of gametes and embryos against oxidative stress. It is known that sperm are damaged by reactive oxygen species (Aitken and De Iuliis, 2010). Glycosidases are present in the epididymal fluid and contribute to sperm maturation (Tulsiani *et al*., 1998; Tulsiani, 2006). Glycosidases have been detected in the oviductal fluid of different species (Supplementary Table S1). Therefore, a similar change in the carbohydrates of the sperm plasma membrane could be anticipated in the oviduct; however, this effect and its significance require further studies. These enzymes have the ability to modify the glycoproteins contained in the zona pellucida (ZP), membrane of the epithelial cells and sperm, and consequently these enzymes could affect the sperm binding to the ZP and to the oviduct. Recently, we observed that oviductal fluid exhibits glycosidase activity with specific variations during the estrous cycle, suggesting a specific role in the regulation of the carbohydrate residues present in the oviduct and gametes (Carrasco *et al*., 2008a, b). Some proteins or glycoproteins have been observed to bind to the sperm or the oocyte as osteopontin, glycodelin and oviduct-specific glycoprotein (OVGP1), modifying the gamete physiology and the fertilization (Gabler *et al*., 2003; Chiu *et al*., 2007; Coy *et al*., 2008).

Precise information about the different proteins contained in oviductal fluid is lacking, especially in the case of humans, where obtaining biological samples is more difficult. However, thanks to microarray analysis, extensive information about gene expression in human oviductal mucosa was recently made available, providing a more accurate idea of the probable protein composition of the oviductal fluid (Tone *et al*., 2008). Previously, an analysis of the gene expression in bovine oviductal epithelial cells at estrus and diestrus was performed showing differential gene expression (37 up-regulated at estrus and 40 at diestrus) between them (Bauersachs *et al*., 2004). The oocyte, sperm and embryos are present in the oviduct at different times (cycle phases) and in different places, suggesting that the composition of oviductal fluid is dynamically changing: for example, a different function was observed for the oviductal fluid obtained from the ampulla than from the isthmus (Way *et al*., 1997). As another example, it is important to take into consideration that the oviductal secretion could be modified by the presence of gametes, as it was recently shown in *in vitro* (Kodithuwakku *et al*., 2007) and *in vivo* studies (Georgiou *et al*., 2007). Future improvements and increased efficiency of the analytical methods used will allow the analysis of different samples collected in low amounts and provide detailed information on the genes transcribed and proteins secreted in the oviduct in different physiological conditions and in different anatomical regions. These studies will probably be performed in animal models in the first instance due to the difficulty of collecting samples in humans. Such developments will throw more light on the fertilization and embryo development processes. Additionally, in order to clarify the role played by the different proteins, it will be necessary not only to purify them but also to perform assays in a context that mimics as closely as possible the *in vivo* situation. In the following paragraphs, we will describe some of the recent findings in this field with special focus on OVGP1.

Oviduct-specific glycoprotein

OVGP1 belongs to the glycosyl hydrolase 18 family, which includes proteins with chitin-hydrolyzing activity; however, no enzymatic activity has been described for this oviductal protein (DeSouza and Murray, 1995; Buhi *et al*., 1996; Jaffe *et al*., 1996). *OVGP1* was detected in the genome of different mammals including monotremes (Warren *et al*., 2008), marsupials (Mikkelsen *et al*., 2007) and placentals. The protein expressed by the *OVGP1* gene, known as OVGP1, is also named oviductin or mucin-9 and has been identified in several placental species, including human (Donnelly *et al*., 1991; Arias *et al*., 1994; Sendai *et al*., 1994, 1995; DeSouza and Murray, 1995; Suzuki *et al*., 1995; Buhi *et al*., 1996; Verhage *et al*., 1997; Buhi, 2002; Killian, 2004). However, it was recently reported that horses and rats are special cases because *OVGP1* homolog is a pseudogene and consequently this protein is not expressed by the oviduct (Mugnier *et al*., 2009; Tian *et al*., 2009). The facts that the *OVGP1* is not expressed in these species and that *OVGP1* gene-null mice has apparently a normal fertility (Araki *et al*., 2003) suggest that the role played by this glycoprotein is not essential for fertilization in some species.

Maximum production of OVGP1 is dependent on the plasma estrogen level in cows, baboon, sheep, pig and human (Arias *et al*., 1994; DeSouza and Murray, 1995; Buhi *et al*., 1996; Verhage *et al*., 1997; Lok *et al*., 2002); however, no difference in mRNA expression was observed in the hamster or rabbit oviduct during the estrous cycle (Paquette *et al*., 1995; Merchan *et al*., 2007). OVGP1 shows different amino acid lengths among species (Fig. 1). Additionally, OVGP1 polymorphism has been reported in hamster and rabbit (Merchan *et al*., 2007; Paquette *et al*., 1995). This polymorphism can also be seen in human, mouse and sheep when the databases were analyzed. A comparative analysis of the similarities in the amino acid sequences of different species points to a high degree of conservation in the N-terminal region of the protein (Verhage *et al*., 1997). In contrast, considerable divergence has been observed in the C-terminal region of the protein (Fig. 1); however, little information about the biological role played by the C-terminal region exists (Yong *et al*., 2002). Thus, Yong *et al*. (2002) have reported that the C-terminal region of the OVGP1 protein seems to be responsible for overcoming the 2-cell embryo blockage in rabbits. The future use of recombinant-protein technology capable of producing native forms, truncated and chimera proteins would probably provide important information about these different regions of the proteins.

Gamete interactions with oviductal secretions: oocyte and ZP maturation

Oviduct and its secretion affect the physiology of the gametes. Capacitation, selection and storage of the sperm during its transit in the oviduct have been analyzed in detail previously (reviewed in Yanagimachi, 1994; Suarez, 2007; Suarez, 2008a, b; Talevi and Gualtieri, 2010). For that reason, this aspect will not be addressed in this review. We will focus

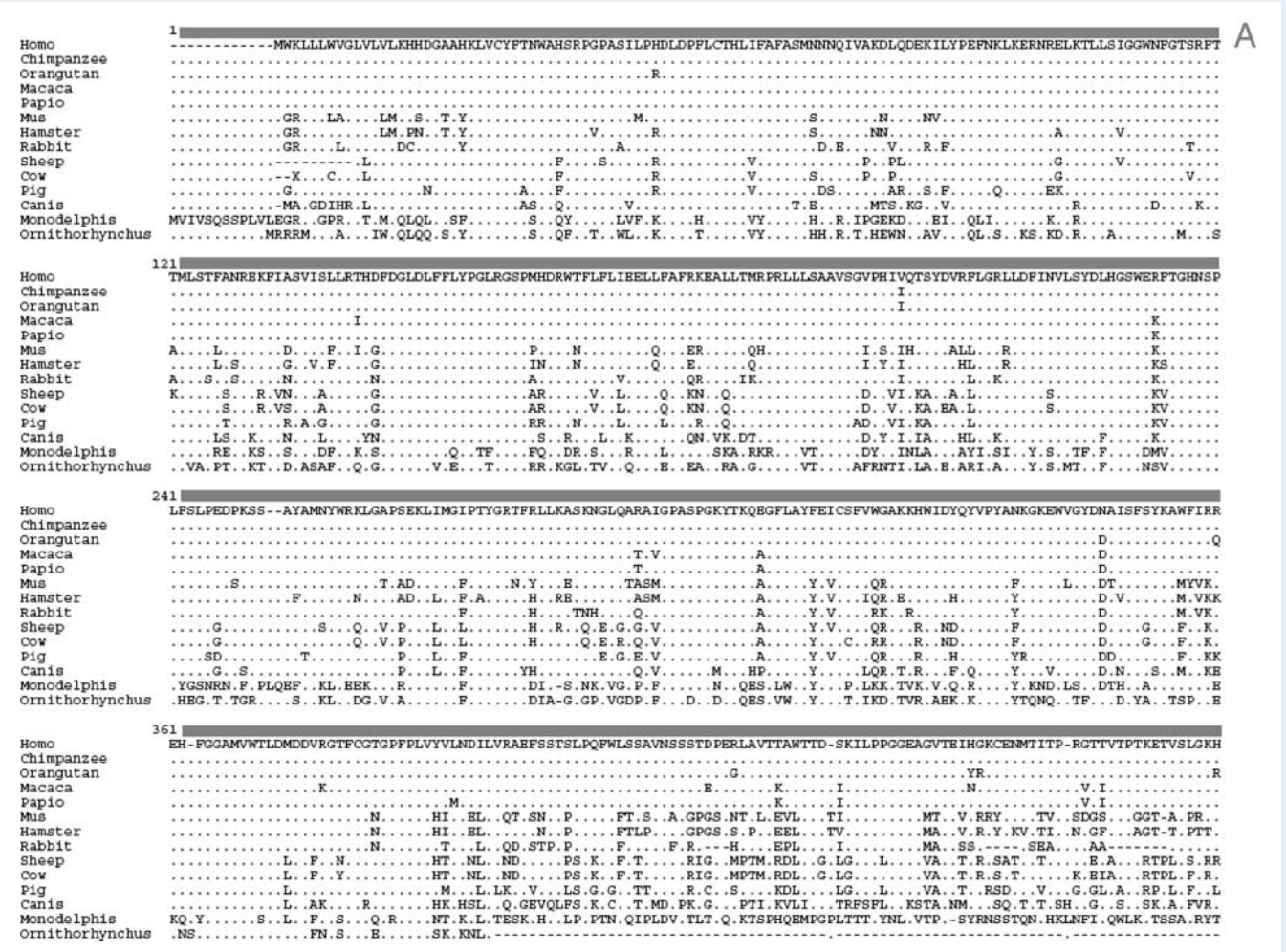

Figure 1 Alignment of deduced amino acid sequences of OVGP1 from different mammals including monotreme (*Ornithorhynchus anatinus*), marsupial (*Monodelphis domestica*) and placentals (Primates, Glires, Carnivora and Cetartiodactyla). Bars indicate gaps inserted to obtain an optimal alignment. A comparison of the amino acid sequences of various mammalian oviductal glycoproteins reveals five distinct regions. The regions A and D are conserved in the different mammals. The region A corresponding to the amino terminal end has a high degree of identity in monotremes, marsupials and placentals. The region B shows a low identity among the different mammals and contains multiple insertion/deletion. The region C is an insertion present only in *Mus* and the region E is typical of the human, chimpanzee and orangutan. Sequences used to perform the analysis: *Homo*, U09550; Chimpanzee, ENSPTRT00000002063; Orangutan, ENSPPYT00000001243; *Macaca*, U87259; *Papio*, M59903; *Mus*, NM_007696; Hamster, D32218; Rabbit, NM_001082105; Sheep, U17988; Cow, D16639; Pig, U43490; *Canis*, XM_847145; *Monodelphis domestica*, XM_001381963; *Ornithorhynchus anatinus*, ENSOANT00000024277.

on other aspects, such as the effect of the oviductal secretions in the oocyte and embryo development.

Oocyte development occurs in the ovary during the follicle growth (folliculogenesis), during that time many changes take place. Previous studies showed that ZP properties are modified during folliculogenesis in several species including humans (Tesarik *et al.*, 1988; Oehninger *et al.*, 1991; Avilés *et al.*, 1999, 2000a, b). These changes have been collectively referred to as zona maturation (Fig. 2). However, little attention has been paid in the literature to the changes produced in the ZP after ovulation. This is mainly due to the difficulty in obtaining these tubal oocytes, especially in species such as human, bovine and porcine. Although ovarian oocytes can be fertilized, they are not exactly the same as their *in vivo* counterparts. Several studies have reported that the extracellular oocyte coat is modified after ovulation during its transit through the oviduct (Oikawa *et al.*, 1988; Robitaille *et al.*, 1988; Kolbe and Holtz, 2005; Lyng and Shur, 2009). Some of these changes have been shown to be necessary and affect sperm–ZP binding as well as the role of the ZP in the control of polyspermy.

Zona maturation and sperm–ZP binding

It has been more than 20 years since the description of how the hamster ZP is modified by an oviductal factor (Robitaille *et al.*, 1988) and how this factor could be involved in fertilization (Sakai *et al.*, 1988; Boatman and Magnoni, 1995). OVGP1s associated with the ZP of ovarian oocytes after ovulation in several species. In humans, there is no direct *in vivo* evidence for any association of the OVGP1 and the ovulated oocyte. An indirect approach using *in vitro*

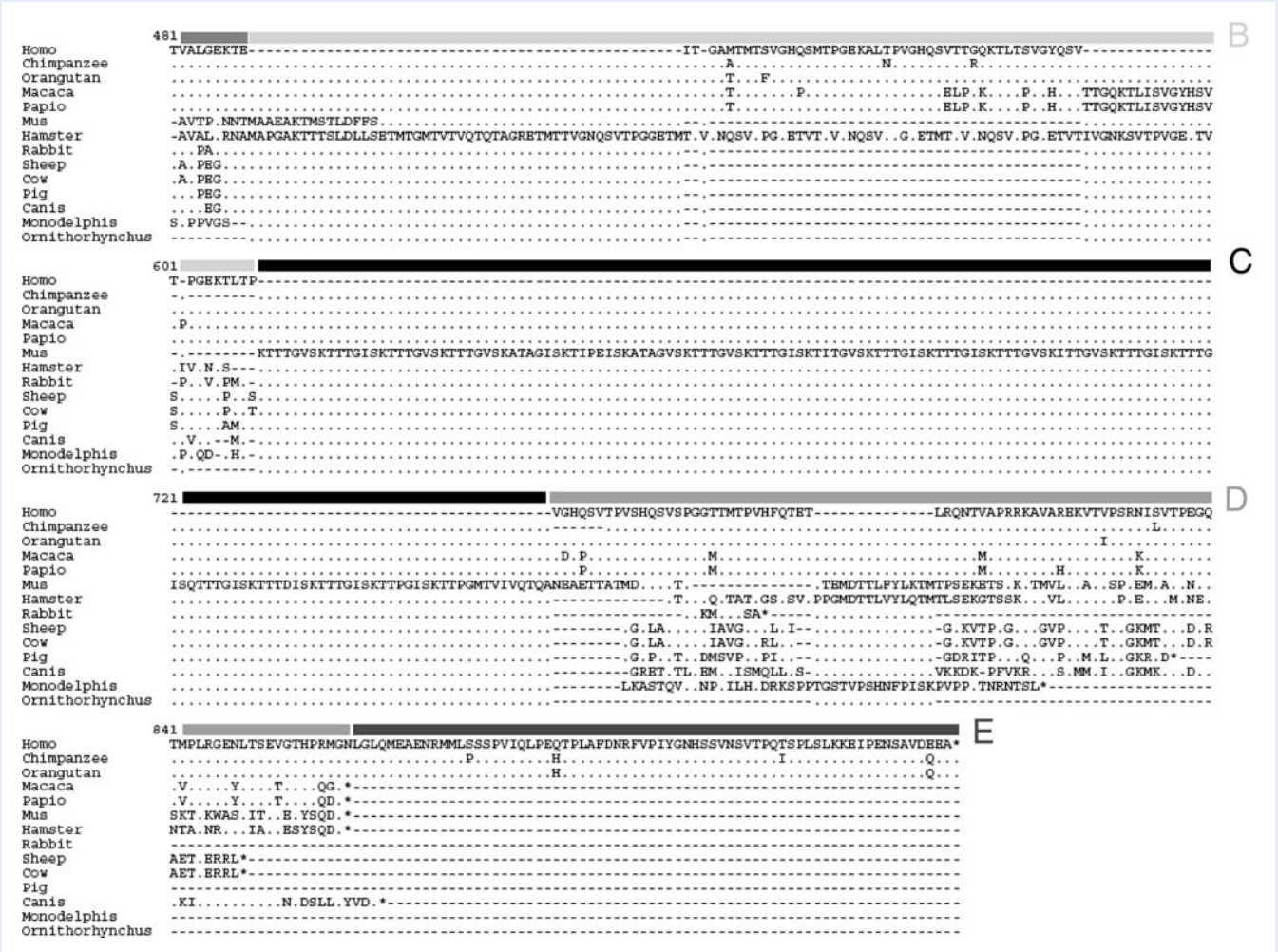

Figure 1 Continued

conditions reported that partially purified human OVGP1 becomes associated with human ZP from an ovarian oocyte isolated from an antral follicle (O'Day-Bowman *et al*., 1996). However, the biological significance of this ZP change in humans remains elusive. Perhaps, this oviductal maturation of the oocyte could be responsible for the sperm selection that improves the fertilization and embryo development as reported in other species (McCauley *et al*., 2003). Future studies using purified human oviductal fluid or recombinant proteins will provide information about the relevance of this process.

It was previously reported that bovine OVGP1 binds to the porcine and bovine ZP (Coy *et al*., 2008), a heterologous interaction that has been also reported between species not closely related, such as humans and hamsters. Thus, human OVGP1 bound to the hamster ovarian ZP *in vitro* (Reuter *et al*., 1994). Baboon OVGP1 can bind human ZP (O'Day-Bowman *et al*., 1996). Partially purified OVGP1 can bind the ZP of both human and baboon ovarian oocytes (O'Day-Bowman *et al*., 1996). The similarities between the different OVGP1 could suggest that a similar role is played by all these proteins; however, this is not always the case. For example, the incubation of porcine or bovine oocytes with oviductal secretions decreased the number of sperm bound to the ZP (Kouba *et al*., 2000; Coy, *et al*., 2008). This result is the opposite of that observed for human and hamster models (Boatman and Magnoni, 1995; O'Day-Bowman *et al*., 1996). Despite the high similarity between human and baboon OVGP1, baboon OVGP1 produces a significant decrease in the number of human sperm bound to the human ZP (O'Day-Bowman *et al*., 1996). The effects produced in the sperm binding to the ZP could be produced by the sterical hindrance of the ZP carbohydrates (decrease) or by the exposure of the OVGP1 glycan needed for the sperm binding (increase).

It has previously been suggested that sperm–oocyte binding is mediated by a multiple complex involving several sperm plasma membrane proteins and several carbohydrates present in the oocyte extracellular matrix (Thaler and Cardullo, 2002; Rodeheffer and Shur, 2004; Lyng and Shur, 2007). These carbohydrates are contained specifically in the ZP proteins and may also be present in the proteins attached to the ZP once the oocyte enters the oviduct after ovulation (Oikawa *et al*., 1988; Rodeheffer and Shur, 2004; Lyng and Shur, 2009). The different carbohydrates from different glycoprotein origins could be responsible for the independent sperm binding sites in the ZP and for the low- and high-affinity sperm binding sites described previously (Thaler and Cardullo, 1996; Johnston *et al*., 1998; Mori *et al*., 2000).

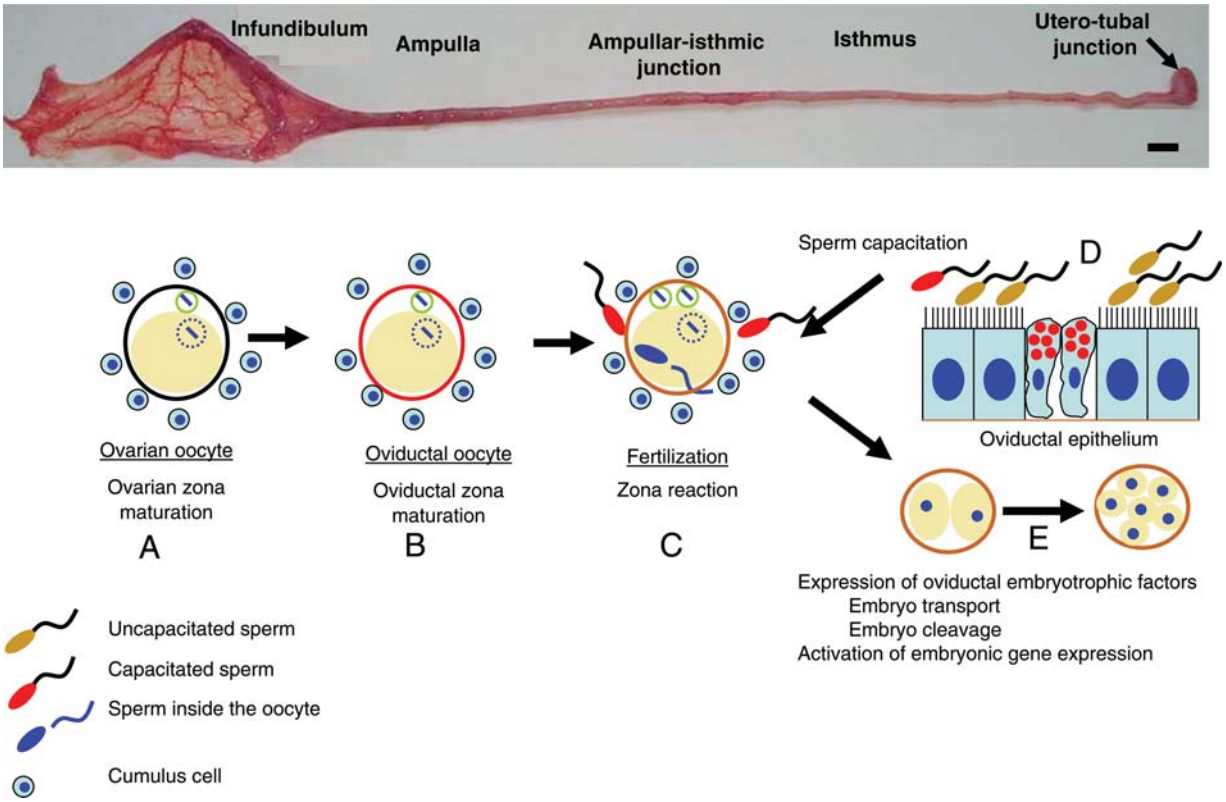

Figure 2 Main events produced during the fertilization in the different anatomical regions of the oviduct. A dissected pig oviduct is showed (bar: 1 cm). (**A**) Ovarian oocytes at the metaphase II stage with expanded cumulus cells are released into the oviductal infundibulum during ovulation. (**B**) Once in the oviductal ampulla and exposed to the oviductal fluid, oocytes undergo an oviductal ZP maturation. This maturation includes a pre-fertilization ZP hardening mediated by OVGP1, at least in the pig and cow species. (**C**) Later, in the ampullar–isthmic junction, the ZP hardening will decrease the possibilities for sperm–ZP binding and reduce the number of sperm capable of penetrating the oocyte. After fertilization, zona reaction is triggered, avoiding the entry of additional spermatozoa. (**D**) Isthmus is recognized in many species as the sperm reservoir, and the region where the last steps of capacitation take place. (**E**) Isthmus is also the region crossed by the early embryo toward the uterus and the secretion of oviductal embryotrophic factors contribute to its physiological development.

Zona maturation: ZP hardening and blockage of polyspermy

Among the functions of the ZP, the prevention of polyspermy during fertilization is a primary concern (Wassarman *et al.*, 2005; Dean, 2007; Hedrick, 2007; Coy and Avilés, 2009); however, this role in farm animals has been demonstrated to be more complex than was previously thought. Changes in ZP regulating sperm entry into the oocyte occur not only after but also before sperm–ZP contact (Coy *et al.*, 2008). We have recently shown that the chemical and the biological properties of the ZP change when porcine or bovine oocytes matured *in vitro* are incubated in oviductal fluid (Coy *et al.*, 2008). On the one hand, the ZP increases its resistance to proteolytic digestion from seconds to hours after only 30 min of contact with oviductal fluid. On the other hand, this modified ZP decreases its affinity for sperm binding and is less penetrable, resulting in reduced levels of polyspermy (Fig. 2). Obviously, passage through the oviduct adds several molecules to this oocyte coat and can alter the terminal moieties exposed for the sperm or enzymes (e.g. proteases). Moreover, according to the view that spermatozoa penetrate the ZP by physical thrust (Bedford, 2004), only those with the ability (or the force) to cross the protease resistant ('hardened') ZP would successfully fertilize the oocyte. This finding stresses the importance of the oviductal secretions in the regulation of polyspermy.

In the above study, it was shown that the molecule responsible for the observed effects was OVGP1 (Coy *et al.*, 2008). However, interesting specific differences between pig and cow were found. For example, in pigs, the strongest effect of the oviductal fluid on ZP resistance to proteolysis was observed when the fluid came from adult animals around ovulation time. In gilts near ovulation, the effect existed but was 4 times lower. In contrast, oviductal fluid from either gilts or sows in the luteal phase of the estrous cycle did not increase ZP resistance to proteolysis, whereas in cattle, almost any oviductal fluid sample consistently affected ZP resistance to digestion (authors' observations). Since it has been shown that OVGP1 secretion is dependent on the estrogen level in plasma in cows and pigs, among others, new questions arise from these observations: for example, why does OVGP1 have this effect throughout the estrous cycle in cows and only during a short temporal window in

pigs? Is this a concentration-dependent effect? Or are any other molecules involved in the role of OVGP1 on ZP modifications?

In mice, ZP resistance to proteases is not acquired in the oviduct (Inoue and Wolf, 1974; Coy *et al*., 2008), but, after fertilization, it arises from the cortical reaction (Barros and Yanagimachi, 1971; Ducibella *et al*., 1990; Vincent *et al*., 1990). Moreover, mouse eggs exposed to bovine oviductal fluid did not acquire resistance to protease (Coy *et al*., 2008); however, very recently, it was demonstrated that a minor fraction of the mice OVGP1 is able to bind the ZP (Lyng and Shur, 2009). This is another example, in a general context, of species-specific differences for the role of the same protein (OVGP1) on the same matrix (ZP).

Returning to the ungulate model, we have demonstrated that, at least in the case of OVGP1, the presence of heparin in *in vitro* experiments is necessary to keep the protein bound to the porcine ZP. Many reports support a role for heparin, a sulfated glycosaminoglycan (S-GAG), in the capacitation process as well as in the sperm–ZP interaction (Bergqvist and Rodríguez-Martínez, 2006). Our recent results introduce a new role for oviductal S-GAGs. Porcine and bovine ZPs from *in vitro* matured oocytes incubated in a medium with heparin and without oviductal fluid did not acquire pronase resistance (authors' observations). Similarly, the presence of heparin in the IVF medium did not reduce sperm–ZP binding. However, heparin acts as a modulator of the ZP modifications described in oviductal secretions. So, the ZP network that contains OVGP1 and other elements surrounding oocytes in the oviduct is stabilized by the binding of S-GAGs, modifying ZP solubility and consequently making it more resistant to sperm penetration. The mean content of total S-GAGs in tubal fluid differs among species and could partially explain the different effects observed in different species (Tienthai *et al*., 2000; Bergqvist and Rodríguez-Martínez, 2006).

In light of this contribution of oviductal secretions to the biological activity of the ZP, we consider that the concept of zona maturation (classically used to describe the changes in the ZP during the folliculogenesis) should be reconsidered to include two different aspects: (i) ovarian maturation and (ii) oviductal maturation (Fig. 2).

How does OVGP1 play a different role in different species?

This question remains unresolved but there are different hypotheses that will need to be tested in the future. First, the different biological activities could be due to the different protein sequence (Fig. 1). Additionally, it was suggested that positive Darwinian selection promotes the divergence of the OVGP1 in different mammals (Swanson *et al*., 2001). Second, the different biological roles played by the OVGP1 could be due to the different grade of glycosylation and/or to different splicing and polymerization forms. Carbohydrates mainly present in O-linked chains are a major OVGP1 component (Malette and Bleau, 1993). Glycosylation differences detected in the estrous cycle could be responsible for a different biological role of the oviductal-secreted glycoproteins (McBride *et al*., 2004, 2005). Thus, only a minor fraction of the mouse OVGP1, recognized by the PNA lectin, is able to bind the ZP (Lyng and Shur, 2009). Recently, we reported that only two bovine OVGP1s of ~75 and 95 kDa have the ability to bind to porcine ZP and are responsible for the hardening observed when the ZPs are incubated in oviductal fluid and for increased monospermy (Coy *et al*., 2008). The exact role played by the different glycoforms in the different species should therefore be addressed. Third, the OVGP1 activity could be affected by ZP composition. The protein composition of the ZP has to be taken into consideration because different mammals have different compositions. In mammals, ZP is formed by three or four proteins (Bleil and Wassarman, 1980; Lefievre *et al*., 2004; Boja *et al*., 2005; Hoodbhoy *et al*., 2005; Goudet *et al*., 2008; Izquierdo-Rico *et al*., 2009). Additionally, in the three proteins' model, it was observed that ZP1 is present in mice; however, in porcine and bovine ZP, ZP4 is present but not ZP1 (Goudet *et al*., 2008). The relevance of the different composition of ZP to the OVGP1 interaction should be investigated in the future. In this context, the use of oviductal fluids and oocytes from different species and different recombinant OVGP1 proteins could provide valuable new information about the role played by the OVGP1 in fertilization, hardening of the ZP and binding to the ZP.

Oviductal secretions and embryo development

The first week of development represents the interval called preimplantation or pre-attachment development (depending on the species), which is a uniquely mammalian phenomenon and encompasses the free-living period of mammalian development during which the early conceptus traverses the oviduct and gains access to the uterine environment. Blastocysts form with two cell types: the trophectoderm, which develops into the embryonic portion of the placenta, and the inner cell mass, which develops into the embryo proper. The embryo in its early stage of development does not need contact with the maternal tract to regulate its own cell division and differentiation. Preimplantational embryos can develop *in vitro* and can produce normal offspring after embryo transfer; however, the development of preimplantation mammalian embryos *in vitro* is compromised compared with those grown *in vivo*. In humans, it was observed that the *in vitro* development of embryos to the blastocyst stage is not an efficient process, ranging from 15% to 26% of success (Fehilly *et al*., 1985; Bongso *et al*., 1989; Dokras *et al*., 1991). Thus, in a previous study after the analysis of more than 550 bipronucleate embryos, it was reported that only 26% of the embryos reached the blastocyst stage (Dokras *et al*., 1993). Other studies performed later have observed an increase in the percentage of blastocyst that can be higher than 50% depending on the culture condition, the age of the oocytes and other parameters (see review Gardner *et al*., 1998; Dumoulin *et al*., 1999; Pantos *et al*., 1999; Schoolcraft *et al*., 1999; Smith, 2002; Van Landuyt *et al*., 2005).

Deprivation of some *in vivo*-produced maternal factors could be responsible for impaired *in vitro* development and viability (Rizos *et al*., 2002) and for some pathological alterations associated with *in vitro*-produced embryos (Fernandez-Gonzalez *et al*., 2007, 2008). However, it is important to take into consideration that other factors such as chromosome defects contribute to the low efficiency of blastocyst formation in addition to the suboptimal culture condition (Gekas *et al*., 2001).

The female reproductive tract modifies its activity in order to provide the optimal environment for the development of the embryo (Buhi, 2002). It has been reported that cannabinoid signaling may coordinate smooth muscle contraction and relaxation for embryo transport in

the oviduct (Wang et al., 2004). In addition to embryo transport, the oviduct produces a number of factors, and many of their corresponding receptors are present in embryos (Kane et al., 1997; Lee and Yeung, 2006). Several studies have identified embryotrophic factors from the oviduct and have analyzed the effects of such factors on the morphological development of embryos during preimplantation (Kane et al., 1997; McCauley et al., 2003; Lee et al., 2006). Some of the oviductal proteins and factors that display embryotrophic activity *in vitro* are described in Supplementary Table S1 and reviewed by Lee and Yeung (2006). In addition, oviductal embryotrophic factors can act during different stages of development. We have recently shown that cleavage and blastocyst development rates in pigs were significantly higher from oviductal fluid-treated oocytes than from untreated oocytes. The oviductal fluid protects the embryo against adverse impacts on mtDNA transcription/replication and apoptosis (Lloyd et al., 2009). However, scarce information exists about the physiological role played by the majority of the proteins present in the oviductal fluid (Supplementary Table S1) and their contributions to the fertilization and embryonic development, especially in humans. Animal models could play an important role in clarifying their roles.

During the secretory phase of the estrus cycle, the oviductal epithelium releases various biomolecules to the lumen to enhance embryo development. This secretory activity of the oviduct is regulated by steroid hormones and also modulated by gametes and embryos. Interaction between preimplantation embryos and the maternal genital tract has been suggested. The preimplantation embryo may reveal its presence even before arrival in the uterus because there is evidence that it can affect both the expression of oviductal genes and its own transport (Lee et al., 2006). It has been reported that some receptors of embryonic factors affecting oviductal physiology, like the receptor for the embryo-derived platelet-activating factor, are present in the oviducts of humans and cows (Tiemann et al., 2001; Velasquez et al., 2001). Oviducts maintain the production of demilune cell parotid protein in the presence of preimplantation mouse embryos, improving subsequent embryo development (Lee et al., 2009). Also, the human oviduct-derived embryotrophic factor-3 contains complement protein-3 (C3), which is not embryotrophic, but is converted into the embryotrophic derivate iC3b. It has been reported that the presence of embryo and steroid hormones regulates the synthesis and secretion of oviductal C3, phospholipid transfer protein and amphiregulin (Lee et al., 2005, 2006, 2009).

Some embryotrophic factors present in the oviduct may not be species-specific. The oviductal environment supports embryonic growth up to the blastocyst stage across a wide range of species following trans-species transfer (Rizos et al., 2007). The use of such intermediate hosts for the culture of zygotes fertilized *in vitro* or *in vivo* is not a recent phenomenon but while in the early days it was a necessary means of achieving development before the development of adequate *in vitro* culture systems (Gandolfi and Moor, 1987), nowadays such systems are used to produce embryos of superior quality (Gutierrez-Adan et al., 2004). For example, the culture of bovine fertilized oocytes in the ewe oviduct does not produce more blastocysts than following culture *in vitro*; however the quality of the blastocysts is improved significantly (Rizos et al., 2002).

Early-cleavage embryos are able to cope with environmental stress and can grow in a wide range of culture conditions, indicating that preimplantation embryos can readily adapt to their culture environment. This adaptive response to the environment operates through the alternative activation or deactivation of developmental gene expression and phenotypes (Fernandez-Gonzalez et al., 2007). Contrary to the view that early embryos are the most fragile stages of life, mammalian preimplantation embryos exhibit remarkable plasticity and will attempt to form blastocysts under a wide range of culture conditions, although, presumably, at some adaptive cost to their post-gestational development program. Such plasticity may turn out to be unsuitable and lead to adult disease (Ecker et al., 2004; Fernandez-Gonzalez et al., 2004). The only optimal microenvironment for embryo development is the oviduct. Understanding the oviductal environment and the factors secreted by the oviduct is important for reproducing the *in vivo* condition *in vitro* and eliminating any long-term effects produced by the *in vitro* conditions.

In humans, it was reported that a better implantation rate (as high as 50%) was obtained by using the blastocyst transfers following *in vivo* fertilization, uterine flushing and embryo donation (Croxatto et al., 1972; Buster et al., 1985). Moreover, a recent study suggests that better results are obtained when blastocysts are transferred to the female uterus compared with the transfer of cleavage-stage embryos (Papanikolaou et al., 2008) probably due to a better synchronization between the embryo and the uterus. The chief advantage of producing a superior embryo lies in the decreased risk of multiple pregnancies. With this in mind, the studies to date suggest that further research will result in the development of an optimal embryo culture medium in the near future.

Concluding remarks

A universal characteristic of the mammalian oocyte is the passage of the cell through the Fallopian tube (oviduct). Much evidence indicates that this complex conduit plays a key role in fertilization and early embryo development *in vivo*. Despite the great advances in assisted reproductive techniques, it seems that the oviduct is necessary for optimal gamete maturation, capacitation, selection and embryo development. Thus, the relevance of the oviducts' contribution seems to differ between animal models; however, key processes are usually conserved in different species. Detailed information about the oviduct secretion and function is lacking, especially in humans due to the difficulty in obtaining appropriate samples. We are convinced that in the near future the detailed knowledge of the oviductal transcriptome and secretome to be achieved through robust technology and the use of appropriate animal models will throw further light on the role played by the oviduct. The use of animal models will provide us detailed information about the different components present in the oviduct, and their effects on the gamete biology, fertilization and embryo development. These experimental approaches will allow us to develop better embryo culture medium and condition to improve the low rate of blastocyst formation and also their quality in humans.

Supplementary material

Supplementary material is available at http://molehr.oxfordjournals.org/.

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