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Regulation of sperm storage and movement in the mammalian oviduct

SUSAN S. SUAREZ*

Department of Biomedical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY, USA

ABSTRACT The oviduct plays a vital role in ensuring successful fertilization and normal early embryonic development. The male inseminates many thousands or even millions of sperm, but this alone does not ensure that fertilization will be successful. The female tract, particularly the oviduct, provides filters that select for normal vigorously motile sperm. In conjunction with molecules in the seminal plasma and on sperm, the female tract regulates how and when sperm pass though the tract to reach the site of fertilization. Various regulatory processes control sperm passage into and through the oviduct. In some species, the uterotubal junction opens and closes to regulate when sperm may enter; furthermore, passage through the junction requires certain proteins on the sperm surface. Most of the sperm that manage to enter the oviduct soon become trapped and held in a reservoir. In marsupials and insectivores, this involves trapping sperm in mucosal crypts; while in most other mammalian species, this involves binding sperm to the oviductal epithelium. As the time of ovulation approaches, the sperm in the reservoir undergo capacitation, including motility hyperactivation. Capacitating sperm shed proteins that bind them to the mucosal epithelium, while hyperactivation assists the sperm in pulling off of the epithelium and escaping out of mucosal pockets. The process of sperm release is gradual, reducing chances of polyspermic fertilization. Released sperm may be guided towards the oocyte by secretions of the oviduct, cumulus cells, or oocyte. Hyperactivation likely assists sperm in penetrating the cumulus matrix and is absolutely required for penetrating the oocyte zona pellucida and achieving fertilization.

KEY WORDS: *sperm, fallopian tube, uterine tube, oviduct*

The oviduct consists of three segments, each with different functions: the uterotubal junction, the isthmus, and the ampulla. The uterotubal junction provides a barrier to infectious microbes that might enter the oviduct from the uterus. It also regulates which sperm may enter and when. The isthmus serves as a sperm storage organ and the ampulla provides an environment conducive to fertilization and early embryonic development. The movements of sperm are regulated by these three segments in different ways so as to fulfill those functions.

The uterotubal junction regulates sperm movement from uterus to oviduct

The anatomy of the uterotubal junction indicates that it is constructed to restrict entry of infectious organisms and leukocytes from the uterus and to regulate entry of sperm (Fig. 1A). In many species, mucosal folds fill most of the lumen and these folds can further occlude the lumen by contraction of smooth muscle in the wall and/or by fluid engorgement of the connective tissue in the wall (Wrobel *et al.,* 1993; Hafez and Black 1969). In the cow, mucosal folds form cul-de-sacs that face back towards the uterus (Yaniz *et al.,* 2006).

In the mouse, the junction is patent shortly after coitus, but tightly closed about an hour later (Zamboni 1972; Suarez, 1987). Electron micrographs reveal close apposition of epithelium and interdigitation of microvilli (Zamboni 1972). Very little is known of the signals that regulate smooth muscle contraction or wall fluid engorgement to open and close the junction.

In some species, the narrow lumen of the uterotubal junction is

Abbreviations frequently used in this paper: ADAM, a disintegrin and metalloprotease; BSP, bovine seminal plasma; LTL, lotus teragonolobus; tACE, testis-specific angiotensin converting enzyme.

***Address correspondence to:** Susan S. Suarez. Department of Biomedical Sciences, T5-002B Veterinary Research Tower, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, USA. e-mail: sss7@cornell.edu

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filled with mucus. Mucus has been found in the uterotubal junction in humans (Jansen, 1980), as well as in rabbits (Jansen, 1978; Jansen and Bajpai, 1982), pigs (Hunter, 2002; Suarez *et al.,* 1990), and dairy cattle (Suarez *et al.,* 1997). In humans, mucus is produced primarily during the periovulatory period and is thought to serve as a selective conduit for sperm (Jansen, 1980).

Although the uterotubal junction may become more patent during estrus or when stimulated by coitus, sperm may not readily pass through it unless certain proteins are present on the sperm head plasma membrane. Male mice that are null mutants for the genes encoding ADAM2 (Cho *et al.,* 1998), calmegin (Ikawa *et al.,* 1997; Yamagata *et al.,* 2002), or testis-specific angiotensin converting enzyme (tACE) (Hagaman *et al.,* 1998, Krege *et al.,* 1995) are infertile because their sperm cannot pass through the uterotubal junction nor bind to the zona pellucida. In these null mutants, both the motility and morphology of the sperm appear normal. ADAM2 (also known as fertilin β) is localized on the plasma membrane overlying the acrosome on mature sperm (Cho *et al.,* 1998). Null mutant sperm for ADAM2 also have abnormally low levels of ADAM3 (cyritestin) as well as other ADAMs on mature sperm (Kim *et al.,* 2006; Nishimura *et al.,* 2007). In the case of calmegin, this is a chaperone protein, which is active in testicular spermatogenic cells where it lies in the lumen of rough endoplasmic reticulum and assists in the proper folding of some nascent polypeptides destined for sperm plasma membranes. Male mice that are null mutants for calmegin lack ADAM3 on mature sperm (Yamaguchi *et al.,* 2006). In the case of tACE null mutants, there is strong evidence that the missing tACE normally acts to release GPI-anchored proteins from the sperm plasma membrane (Kondoh *et al.,* 2005; Metayer *et al.,* 2002). Male mice that are null mutants for tACE show abnormal distribution of ADAM3 in sperm membranes (Yamaguchi *et al.,* 2006). Altogether, these null phenotypes implicate ADAM3 in providing passage of sperm through the uterotubal junction, although this remains to be tested and other ADAMs may be involved instead or as well. The role of ADAMs in enabling sperm to pass through the uterotubal junction may be to allow sperm to gain footholds on the wall lining the junction and thus move ahead by sticking lightly to the epithelium.

Formation of the oviductal sperm storage reservoir

In mammals, sperm are held in a storage reservoir in the oviduct until the time of ovulation draws near. In marsupial mammals and some insectivores (Bedford *et al.,* 1999; Bedford *et al.,* 1997a; Bedford *et al.,* 1997b; Taggart, 1994), sperm are stored in special mucosal crypts or bulbous pockets. In some cases the sperm appear to be held in the crypts by suppression of flagellar motility (Bedford and Breed, 1994).

In contrast to the marsupials and insectivores, most other species of mammals create an oviductal sperm storage reservoir by binding the sperm to the epithelial surface (Harper, 1973, Hunter, 1981; Hunter and Nichol, 1983; Overstreet and Cooper, 1978; Suarez, 1987; Wilmut and Hunter, 1984; Yanagimachi and Chang, 1963). There are no specific structures like crypts; however, many of the bound sperm are found down in pockets formed by mucosal folds (Fig. 1B). Binding sperm to the epithelium plays a role in preserving sperm fertility while they are stored and also serves to reduce incidence of polyspermic fertilization by releasing sperm very gradually during the periovulatory period. While oocytes have one or more mechanisms for blocking polyspermy (Hedrick, 2007; Wortzman-Show *et al.,* 2007), further protection from polyspermy is provided by the gradual release of sperm from the reservoir. In the pig, when sperm numbers were artificially increased at the site of fertilization, the incidence of polyspermy was increased (Day and Polge, 1968; Hunter, 1973; Hunter and Leglise, 1971; Polge *et al.,* 1970).

Identification of oviduct binding proteins on sperm

Carbohydrate moieties are key components of oviductal receptors for sperm. Specific mono- and oligo-saccharides have been shown to competitively inhibit sperm binding to oviductal epithelium in various species (hamster, DeMott *et al.,* 1995; horse, Dobrinski *et al.,* 1996a; pig, Green *et al.,* 2001, Wagner *et al.,* 2002).

Competitive binding inhibition assays identified fucose, particularly in the trisaccharide Lewis-a, as the key component of the oviductal receptor for bull sperm (Lefebvre *et al.,* 1997; Suarez *et al.,* 1998). Affinity purification using Lewis-a as the trap identified PDC109 (also known as BSPA1/A2) as a protein responsible for binding bull sperm to oviductal epithelium (Gwathmey *et al.,* 2003; Ignotz *et al.,* 2001). PDC109 is a small (approximately 16 kDa) acidic, heparin-binding protein, consisting primarily of two fibronectin type II domains. It is secreted by the seminal vesicles and coats the periacrosomal plasma membrane of sperm by associating with membrane choline phospholipids (Desnoyers and Manjunath, 1992; Muller *et al.,* 1998; Ramakrishnan *et al.,* 2001). Epididymal bull sperm bind oviductal epithelium in very low numbers, but when they are coated with PDC109 purified from seminal plasma, their binding increases to the level of ejaculated bull sperm (Gwathmey *et al.,* 2003).

PDC109 is a member of the bovine seminal plasma (BSP) family of proteins. Two other proteins in the family, BSP30K and BSPA3, have also been shown to dramatically enhance binding of epididymal bull sperm to epithelium (Gwathmey *et al.,* 2006). Like PDC109, these are also seminal vesicles secretions that bind heparin and coat the sperm head over the acrosomal region; however, they are present in seminal plasma at only about 1/10 the level of PDC109 (Nauc and Manjunath, 2000). Each one alone is sufficient to raise binding to the level of ejaculated sperm, so it is unlikely that they are required together in a complex. The redundancy of oviduct binding proteins, likely arising through gene duplication, implies that formation of the reservoir is key to reproductive success. Proteins homologous to the BSPs have been identified in several other species. Some of the homologs have also been demonstrated to bind heparin and membrane phospholipids (Calvete *et al.,* 1997; Fan *et al.,* 2006; Leblond *et al.,* 1993).

Binding of epididymal bull sperm to epithelium does occur at a low level. This could be a nonspecific interaction or it could be due to more recently discovered members of the BSP family predicted to be expressed in the epididymis (Fan *et al.,* 2006). In other species, epididymal homologs of the BSP family may be primarily responsible for binding sperm to oviductal epithelium. BSP homologs in the mouse are identified from the EST database as epididymal proteins (Fan *et al.,* 2006). Hamster

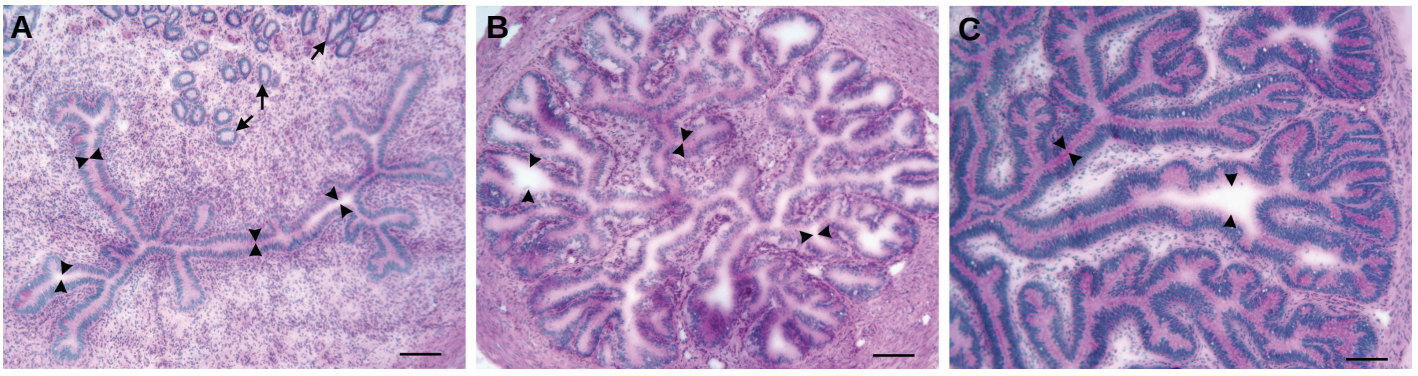

Fig. 1. Frozen cross sections of the uterotubal junction (A), isthmus (B), and ampulla (C) of a preovulatory bovine oviduct, stained with Periodic Acid Schiff to show mucopolysaccharides and with hematoxylin to stain nuclei *(see Suarez* et al.*, 1997). The oviduct was frozen for sectioning to avoid shrinkage associated with embedding tissue in plastic or paraffin. All images were taken at the same magnification (bar, 100 μm). Arrows indicate uterine glands in the wall of the uterotubal junction, which open into the uterine lumen. Arrowheads indicate the oviductal lumen, much of which is as narrow as a sperm head and filled with mucus. Only about half of the diameter of the ampulla is shown. The bovine oocyte, which measures about 125 μm, would take up only a small area of the lumen.*

epididymal sperm infused into oviducts bind to the epithelium (DeMott *et al.,* 1995), indicating that hamster homologs may be expressed in testis or epididymis.

Identification of oviductal receptors for sperm proteins

Oviductal receptors for the BSP proteins were isolated from extracts of bovine apical plasma membrane epithelium using purified BSP proteins as traps. They were identified as four members of the annexin (ANXA1,-2,-4,-5) family of proteins (Ignotz *et al.,* 2007). Antibodies to each of the ANXAs localized them to the apical surfaces of mucosal epithelium in sections of oviduct and also inhibited sperm binding to explants of oviductal epithelium. Western blots confirmed the presence of ANXAs in apical plasma membranes. Because fucose had been determined to be a critical component of the bovine oviductal receptor, the ANXAs were immunoprecipitated from solubilized apical plasma membranes and probed with Lotus tetragonolobus (LTL) lectin to verify the presence of fucose (Ignotz *et al.,* 2007). Thus, these ANXAs are strong candidates for the sperm receptors on bovine oviductal epithelium.

ANXAs comprise a large family of proteins whose functions are poorly understood. They have been localized within cells, in secretions, or on cell surfaces (Rescher and Gerke, 2007). Although ANXAs lack signal peptides to direct them to the cell surface, other mechanisms have been identified that transport ANXAs from cytoplasm to the plasma membrane (Deora *et al.,* 2004). ANXA4 and ANXA5 have been localized to the apical regions of rat oviductal epithelium (Kaetzel *et al.,* 1989), while ANXA1 was detected in extracts of rabbit oviduct epithelium (Tsao *et al.,* 1995). ANXA1 and ANXA2 are associated with cilia of quail oviduct epithelial cells (Chailley and Pradel, 1992). Cell surface ANXA2 mediates cell adhesion between lymphocytes and endothelial cells (Tressler *et al.,* 1993), which might occur via a similar mechanism as that of binding sperm to oviductal epithelium.

ANXA5, conjugated with fluorescein, binds to the acrosomal region of bull and boar sperm (Chaveiro *et al.,* 2007; Gadella and Harrison, 2002). Although ANXA5 is commonly used as a probe to detect cells undergoing apoptosis, other markers of apoptosis showed that ANXA5-labeled boar sperm were not apoptotic, indicating that normal, live boar sperm can bind ANXA5 (Gadella and Harrison, 2002).

Interestingly, ANXA1 is secreted in fairly high amounts by the human prostate gland into the seminal plasma (Christmas *et al.,* 1991). It is not known whether human sperm carry the seminal plasma ANXAs into the oviduct, where they might be replaced by the ANXAs on the oviductal epithelium.

Whereas BSPs have been shown to work individually to enhance sperm binding to epithelium, it is not yet known whether each ANXA alone can act as a receptor for sperm.

The involvement of multiple species of BSPs and ANXAs in sperm binding underscores the importance of holding sperm in the oviductal reservoir. During evolution, when gene duplication occurs and multiple closely related versions of genes are maintained in the genome, all of which actively produce protein products, it is likely that these gene products serve important functions and provide reproductive advantages to the individuals that produce them. The differences among the duplicated gene products can ensure that the system is functional under a variety of conditions. An example of this is isoenzymes, which provide catalytic activity under a broad range of conditions (Campbell and Heyer, 2003). The BSP proteins differ from each other in distribution of surface electrostatic charge (Gwathmey *et al.,* 2006). This bestows the BSPs with different binding affinities for the surface of sperm on one face of the molecule and for the oviductal epithelium on the opposite face. Similarly, the various ANXAs on the oviductal epithelium must have different binding affinities and kinetics for the BSPs on sperm. Thus, the duplication of BSP and ANXA proteins on the sperm side and the oviduct side of the interaction, respectively, can provide a finely tuned regulatory system to ensure that sperm are held and kept fertile in the reservoir and then released gradually at the appropriate time to ensure that fertilization (but not polyspermy) takes place.

Preservation of sperm fertility during storage

Sperm binding to epithelium somehow preserves their fertility during storage. Sperm incubated with epithelium *in vitro* remain viable longer than when they are incubated in medium alone

(Suarez *et al.,* 1990; Pollard *et al.,* 1991; Ellington *et al.,* 1993; Kawakami *et al.,* 2001). Viability of sperm can be extended by incubating them with vesicles prepared from the apical membranes of isthmic epithelium, indicating that the epithelium alone can produce the effect (Dobrinski *et al.,* 1996b; Smith and Nothnick, 1997; Gwathmey *et al.,* 2006; Murray and Smith, 1997). Equine sperm binding to oviductal epithelium or membrane vesicles maintain low levels of cytoplasmic Ca^{2+}, compared to free-swimming sperm or sperm incubated with vesicles made from kidney membranes (Dobrinski *et al.,* 1997; Dobrinski *et al.,* 1996b). Human and equine sperm incubated with membrane vesicles capacitate more slowly than sperm incubated in capacitating medium alone (Dobrinski *et al.,* 1997; Murray and Smith 1997). Possibly, viability is maintained by preventing capacitation and its concomitant rise in cytoplasmic Ca^{2+}. The mechanism for preventing rises of cytoplasmic Ca^{2+} in sperm are not known, but one suggestion is that catalase, which has been detected in the bovine oviduct, serves to protect against peroxidative damage to the sperm membranes, perhaps preventing increased inward leakage of Ca^{2+} (Lapointe *et al.,* 1998).

The oviductal binding protein on bull sperm, PDC109, probably acts to stabilize sperm membranes. PDC109 reduces membrane fluidity and immobilizes cholesterol in phospholipid membranes, including those of epididymal sperm (Greube *et al.,* 2001; Muller *et al.,* 2002). PDC109 could also contribute to membrane stability by inhibiting the activity of phospholipase A_2 (Manjunath *et al.,* 1994; Soubeyrand and Manjunath, 1997). Thus, PDC109 may play a role in preserving bull sperm fertility while they are stored in the reservoir.

Release of sperm from the reservoir

Theoretically, either a loss of binding sites on the oviductal epithelium or a change in sperm could be responsible for release of sperm from the reservoir. Changes in the hormonal state of oviductal epithelium related to impending ovulation were not seen to affect the density of binding sites for sperm in a number of species (Suarez *et al.,* 1991a; Lefebvre *et al.,* 1995; Thomas *et al.,* 1994). On the other hand, there is strong evidence that changes in sperm that are associated with capacitation are responsible for releasing sperm.

Loss of oviduct-binding proteins from the sperm plasma membrane, or their modification, could reduce affinity of sperm for the oviductal epithelium. Capacitated bull sperm show reduced binding to oviductal epithelium as well as to the carbohydrate ligand involved in sperm binding (Ignotz *et al.,* 2001; Revah *et al.,* 2000). This can be accounted for by a shedding of the adsorbed seminal plasma protein PDC109 from the sperm head during capacitation, because binding can be restored in capacitated sperm by adding back purified PDC109 to sperm (Gwathmey *et al.,* 2003).

Heparin is used to capacitate bull sperm *in vitro* (Galantino-Homer *et al.,* 1997; Parrish *et al.,* 1988). The BSP proteins PDC109, BSP30K, and BSPA3 possess heparin-binding sites—(Calvete *et al.,* 1999; Chandonnet *et al.,* 1990; Wah *et al.,* 2002) and incubation with heparin has been shown to remove PDC109 from sperm (Gwathmey *et al.,* 2003). Addition of heparin to bull sperm bound to cultured oviductal epithelium enhances their release (Bosch *et al.,* 2001). Parrish and colleagues (Parrish *et al.,* 1989) showed that heparin-like molecules account for the capacitating activity of bovine oviduct fluid *in vitro*. Thus, increased secretion of glycosaminoglycans into oviduct fluid late in estrus could release sperm from the reservoir. It is interesting that ANXAs, the oviductal receptors for the BSPs, also bind heparin (Ishitsuka *et al.,* 1998; Shao *et al.,* 2006), suggesting that heparin (or a similar glycosaminoglycan) could enhance sperm release by two mechanisms: inducing loss of BSPs from sperm and interfering with binding of BSPs to ANXAs.

During capacitation, sperm also become hyperactivated. Hyperactivated sperm show increased flagellar bend amplitudes, usually on one side of the flagellum, which causes the flagellum to beat asymmetrically (Suarez and Ho, 2003)(Fig. 2). The power of the increased bend amplitude can provide the force necessary for overcoming the attraction between sperm and epithelium. Oviducts removed from mated female mice can be transilluminated in order to examine the behavior of sperm within the reservoir. Under these conditions, hyperactivated sperm can be seen yanking themselves free from the oviductal epithelium. It was noted that only hyperactivated sperm detached from the epithelium (DeMott and Suarez, 1992).

In summary, during capacitation, a combination of shedding extrinsic proteins and hyperactivation likely serves to free sperm from the oviductal epithelium. The epithelium may play a role in sperm release by secreting capacitation factors.

Sperm movement after release from the oviductal storage reservoir

As discussed above, hyperactivation assists sperm in escaping from the reservoir. Hyperactivation assists sperm in other ways as well. Sperm that are hyperactivated are better able to penetrate viscoelastic substances (Quill *et al.,* 2003; Suarez and Dai, 1992; Suarez *et al.,* 1991). Mucus fills the uterotubal junction and extends well into the isthmus in humans (Jansen, 1980), rabbits (Jansen, 1978), pigs (Suarez *et al.,* 1991a), and cows (Suarez *et al.,* 1997); therefore, hyperactivation may assist sperm in swimming through the mucus to escape from the isthmus.

Observations of sperm moving within the mouse oviduct indicate that hyperactivation also endows sperm with greater flexibility for turning around in the pockets between mucosal folds so as to move out into the center of the lumen (Suarez and Osman, 1987).

Hyperactivation may also play a role in chemotaxis. Sperm are equipped with a mechanism for turning towards the oocyte in response to chemotactic factors; that is, they can switch back and forth between symmetrical flagellar beating and the asymmetrical flagellar beating of hyperactivation. Hyperactivation is reversible (Suarez *et al.,* 1987), which enables sperm to alternate between

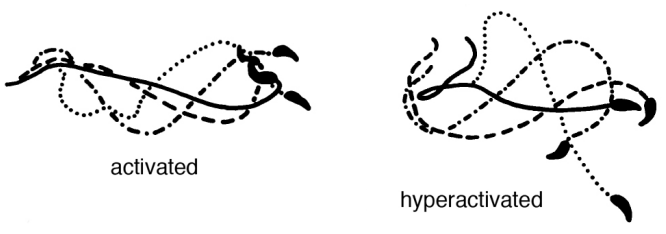

Fig. 2. Movement patterns of activated and hyperactivated mouse sperm *(modified from Suarez and Dai, 1992).*

turning and swimming straight ahead. Mammalian sperm, particularly human sperm, have been reported to turn towards, or accumulate in, a gradient of follicular fluid (Cohen-Dayag *et al.,* 1995; Fabro *et al.,* 2002; Ralt *et al.,* 1994) or medium conditioned by cumulus cells or oocytes (Sun *et al.,* 2005).

Odorant receptors have been localized to a spot in the base of the flagellum or to the flagellar midpiece of human (Spehr *et al.,* 2003), canine (Vanderhaeghen *et al.,* 1993), and rat sperm (Walensky *et al.,* 1995). Placing human sperm in a gradient of the odorant bourgeonal caused a fraction of them to orient into the gradient and triggered rises in cAMP and Ca^{2+} (Spehr *et al.,* 2004). However, odorant-like molecules have not yet been identified in follicular fluid or secretions of the cumulus cells or oocytes.

Despite these intriguing reports of chemotaxis, a chemotactic agent has yet to be identified with certainty in the oviduct, follicular fluid, cumulus matrix, or oocyte. Furthermore, *in vitro*, only a small percentage of sperm (usually less than 10%) are seen to respond chemotactically to physiological secretions, making the identification of active agents difficult (reviewed by M Eisenbach in this volume and Kaupp *et al.,* 2007).

Because hyperactivation occurs in the caudal isthmus, which is a considerable distance from the site of fertilization, sperm may already be hyperactivated when they come under the influence of chemotactic signals. Chemotaxis may therefore involve modulation of hyperactivation to turn sperm towards the oocyte. In the mouse, the cumulus mass fills the ampulla and thus makes an easy target for sperm. In this case, sperm may require guidance to reach oocytes within the large cumulus mass. In humans, cattle, and other large species, the cumulus mass occupies only a small area in the maze-like lumen of the ampulla (Fig. 1C). In these species, sperm might need additional guidance to reach the cumulus mass within the ampulla.

Once sperm reach the cumulus mass, they are usually obliged to swim through the cumulus matrix to reach the oocyte zona pellucida. The matrix is viscoelastic, primarily due to long flexible molecules of hyaluronic acid, which are linked by proteins (Zhuo *et al.,* 2001; Fulop *et al.,* 2003; Salustri *et al.,* 2004). Whereas hyperactivation would assist sperm in penetrating the matrix, the presence of a hyaluronidase on the sperm surface (Kim *et al.,* 2005) must aid in the process. Sperm penetration of the cumulus matrix is reviewed by T. Baba in this volume.

Upon reaching the zona pellucida, sperm require hyperactivation in order to penetrate it. When hyperactivation was blocked in capacitated, acrosome-reacted hamster sperm bound to the zona, they were unable to penetrate it (Stauss *et al.,* 1995). Sperm from male mice that are null mutants for CatSper genes and cannot hyperactivate also cannot penetrate the zona (Quill *et al.,* 2003; Ren *et al.,* 2001).

Conclusions

Although many thousands, or even millions, of sperm are inseminated, this alone does not ensure that sperm will pass into and through the oviduct to reach the oocyte. The ascent of sperm is regulated by the female and successful sperm must be equipped with specific proteins for passing into the oviduct and remaining viable until ovulation. Sperm must also be able to hyperactivate in order to release themselves from the storage reservoir and to penetrate the cumulus matrix and oocyte zona pellucida. The oocyte, cumulus, or some secretion of the female tract may also provide chemotactic guidance to sperm.

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