Minireview

The Modulation of Sperm Function by the Oviductal Epithelium

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During their sojourn in the female tract, sperm come into contact with the epithelial cells that line the tract and their secretions. In the past, much attention has been given to the nature and composition of uterine and oviductal fluid [1–3] with the aim of understanding what components of these fluids may affect the events associated with fertilization and preimplantation embryo development. A number of secretory glycoproteins have been identified in reproductive tract fluids of several species [3]. However, with the exception of two estrus-associated oviductal glycoproteins that may play a role in the capacitation [4, 5] and/or motility [6] of bovine sperm, the function of these glycoproteins in relation to sperm physiology remains unclear.

One remarkable aspect of sperm behavior, widely observed across species, is a tendency to directly contact and adhere to the epithelial cells that line the tract. Evidence is accumulating that such contacts are physiologically significant. Thus, examination of the role of direct contact between sperm and the epithelial cells that line the tract may provide additional insight into the mechanisms that control sperm biology in vivo. Although sperm come into contact with cervical and uterine epithelial cells during passage through the tract, oviductal epithelial-sperm cell interactions are of particular importance. In many species, the isthmic region of the oviduct is an important site of sperm storage prior to fertilization [7]. While resident in the lower isthmus, many sperm adhere to the apical plasma membrane of the ciliated and secretory epithelial cells that line this region. For all species studied so far, adhesion is specific to the rostral region of the sperm head. Sperm adhesion to isthmic epithelial cells is temporary, and adherent sperm are capable of detaching from the epithelium and reaching the oviductal ampulla to participate in fertilization [8]. Current evidence indicates that temporary adherence to the oviductal epithelium has a beneficial effect on sperm viability both in vivo [9] and in vitro [10–15].

The ability of sperm to adhere to and detach from the epithelium appears to be related to their capacitation status. Capacitated hamster and bull sperm bind to oviductal epithelial cells with much lower frequency than uncapacitated sperm [8, 16, 17]. This may be due to changes in the head plasma membrane that occur during capacitation or due to hyperactivated motility associated with the capacitated state that causes the sperm to detach within a short time after making contact. Since some of the capacitation process occurs in the oviduct at a time coincident with sperm-epithelial interaction, it is likely that some aspects of capacitation are modulated through this interaction.

During sperm-epithelial interaction in vivo, sperm adhere to the apical plasma membrane of oviductal epithelial cells. The presence of a heavily sialylated glycocalyx on the apical plasma membrane of oviductal epithelial cells renders this membrane unique among cellular membranes and allows it to be isolated by differential centrifugation [18]. With this technique, apical plasma membrane fractions have been obtained from the oviductal epithelium of rabbits, horses, and humans [19–21]. When these apical plasma membrane fractions were suspended in aqueous media, they formed closed, roughly spherical vesicles ranging in diameter from 30 to 300 nm. Staining with ruthenium red revealed that the majority (~85%) of these vesicles formed right side out. When rabbit [19], equine [20], or human [22] sperm were incubated with homologous oviductal apical membrane vesicles (oAMV) derived either from preovulatory does and mares or from premenopausal women, oAMV were observed by electron microscopy to bind exclusively to the plasma membrane of the rostral (periaxosomal) region of the sperm head.

During prolonged incubation with oAMV, rabbit sperm agglutinated head-to-head in groups of approximately 2–20 (Fig. 1). Rabbit sperm heads were stacked on one another with the oAMV apparently forming the "glue" that held them together. No such regular, head-to-head agglutination pattern was observed in the presence of rabbit kidney AMV (tissue control) or in the absence of AMV (medium control). When equine sperm were incubated in the presence of oAMV and antigen-binding fragments (Fab) derived from polyclonal antiserum raised to the periacrosomal plasma membrane of equine sperm [22], oAMV binding was greatly diminished. These data suggest that binding between sperm and oAMV involves specific molecular interactions [20].

When rabbit, equine, and human sperm were incubated in vitro with homologous oAMV from either preovulatory does and mares or premenopausal women, a significantly higher number of sperm remained viable in culture compared to those incubated in the presence of kidney AMV, anovulatory oAMV, postmenopausal oAMV, or culture medium alone [19–21]. These experiments suggest that direct

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SPERM-OVIDUCT INTERACTION

FIG. 1. Transmission electron micrograph of agglutinated rabbit spermatozoa after 1-h incubation in the presence of apical plasma membrane vesicles isolated from preovulatory oviductal epithelial cells. Vesicle binding is restricted to the rostral region of the sperm head. x27 500. Adapted from Smith and Nothnick, Biol Reprod 1997; 56:87, Figure 3 [19].

Interaction with the isolated apical plasma membrane, in the absence of intact oviductal cells and/or their secretions, is sufficient to maintain sperm viability in vitro in a manner analogous to that occurring in vivo. Moreover, the effects of oAMV on sperm viability were tissue specific and were related to the hormonal status of the oviductal tissue at the time of collection. In addition, the viability-maintaining effect of equine oAMV was significantly reduced in the presence of antibody fragments that reduced oAMV binding to sperm [20], thus suggesting that a specific interaction between sperm and oAMV is required to mediate this effect (Fig. 2).

Direct contact between sperm and the apical plasma membrane of oviductal cells also appears to slow the rate of sperm capacitation. When equine sperm were incubated with oAMV derived from preovulatory isthmic oviductal epithelial cells, the percentage of capacitated sperm was significantly lower at 6 and 24 h than that of sperm incubated in capacitating medium alone or with oAMV in the presence of Fab that reduce oAMV binding to sperm [20] (Fig. 3). When human sperm were incubated with oAMV derived from premenopausal women for up to 48 h, a similar pattern was observed [21]. Under these conditions, human sperm capacitation was delayed by approximately 24 h but eventually reached control levels. These data suggest that sperm interaction with the apical plasma membrane of oviductal epithelial cells may provide a mechanism through which the timing of capacitation can be modulated in vivo. The biochemical basis for this modulation is unclear but is probably related to the regulation of sperm intracellular calcium.

Recently, Dobrinski and coworkers [22] demonstrated

FIG. 2. Percentage of viable equine spermatozoa incubated with or without isolated isthmic oAMV in the presence or absence of antibody fragments (Fab) raised against equine periacrosomal sperm plasma membrane or antibody fragments from nonimmunized rabbit serum (cFab). Medium for culture was Tyrode's albumin lactate pyruvate medium (TALP). Means ± SD, n = 6 ejaculates. Transformed data (1/sqrt[x]) were analyzed by ANOVA for the effects of time, treatment, and interactions. Pair-wise comparisons of means were made using Tukey's studentized range test (HSD). Means with different letters are significantly different (p < 0.05). Adapted from Dobrinski et al., Biol Reprod 1997; 56:866, Figure 5a [20].

FIG. 3. Percentage of capacitated equine spermatozoa incubated with or without isolated isthmic oAMV in the presence or absence of antibody fragments (Fab) raised against equine periacrosomal sperm plasma membrane or antibody fragments from nonimmunized rabbit serum (cFab). Medium for culture was Tyrode's albumin lactate pyruvate medium (TALP). Means ± SD, n = 6 ejaculates. Transformed data (1/sqrt[x]) were analyzed by ANOVA for the effects of time, treatment, and interactions. Pair-wise comparisons of means were made using Tukey's studentized range test (HSD). Means with different letters are significantly different (p < 0.05). Adapted from Dobrinski et al., Biol Reprod 1997; 56:866, Figure 5b [20].

FIG. 4. Intracellular calcium concentration ([Ca 2+ i]) in equine spermatozoa incubated with either isthmic oAMV, antibody fragments (Fab) raised against equine periacrosomal sperm plasma membrane, or oAMV and Fab combined. Medium for culture was Tyrode's albumin lactate pyruvate medium (TALP). Least-squares means ± SEM, n = 6 ejaculates. Data were analyzed by ANOVA for the effects of time, treatment, and interactions. Pair-wise comparisons of means were made using Tukey's studentized range test (HSD). Means with different letters are significantly different (p < 0.05). Adapted from Dobrinski et al., Biol Reprod 1997; 56:866, Figure 6 [20].
that the intracellular calcium concentration ([Ca$^{2+}$]) of equine sperm attached to oviductal epithelial cells was maintained at levels 2- to 3-fold lower than in free-swimming sperm. However, it was not clear from this study whether sperm cells with lower [Ca$^{2+}$], preferentially bound to oviductal epithelial cells or whether [Ca$^{2+}$] remained low as a result of binding. When equine sperm were incubated with oAMV from preovulatory isthmic epithelial cells, a situation akin to being continuously attached to oviductal epithelial cells but still free to swim unimpeded, [Ca$^{2+}$] was maintained at low levels in all sperm [21]. This observation supports the notion that direct contact with the apical plasma membrane of oviductal epithelial cells results in the maintenance of low intracellular calcium. Furthermore, maintenance of low [Ca$^{2+}$] was not observed in the presence of Fab that reduce oAMV binding to sperm, suggesting that a specific molecular interaction between sperm and oAMV was responsible for maintaining low [Ca$^{2+}$]. (Fig. 4).

In sum, the available evidence suggests the following: on route to the site of fertilization, sperm temporarily adhere to the apical plasma membrane of the epithelial cells that line the oviductal isthmus. During the period of adherence, sperm viability is maintained and capacitation proceeds at a slower rate. This prolongs the fertilizable life span of the sperm and maximizes the probability of conception when ejaculation is not coincident with ovulation. These effects on viability and capacitation are likely to be mediated, at least in part, through the maintenance of low intracellular calcium within the sperm. Although much has yet to be determined regarding the molecular mechanisms underlying such effects, direct oviductal epithelial-sperm interactions clearly play an important role in the success of the reproductive process.

REFERENCES