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Minireview

Epididymosomes and Prostasomes: Their Roles in Posttesticular Maturation of the Sperm Cells

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The occurrence of membrane vesicles along the male reproductive tract and in the ejaculated semen appears as a common feature among different species, including humans. Indeed, prostasomes (prostate-derived vesicles) were first described in human semen in 1978 (Ronquist et al, 1978), and vesicular structures similar to prostasomes were also found in the seminal plasma of rabbit (Davis, 1978), ram (Breitbart and Rubinstein, 1982), and stallion (Arienti et al, 1998; Minelli et al, 1998). Furthermore, "prostasome-like" particles are present in the epididymal fluid of rat (Fornes and De Rosas, 1991), hamster (Yanagimachi et al, 1985), and bull (Frenette and Sullivan, 2001) and are also secreted by the bull seminal vesicles (Agrawal and Vanha-Perttula, 1987). The biochemical composition of prostasomes purified from human semen has been well documented. These are multilamellar lipoprotein membrane particles with a diameter of 50 to 500 nm. Their cholesterol-phospholipid ratio reaches 2, sphingomyelin being the major phospholipid. Many proteins are associated with prostasomes, some of them having a catalytic activity (Review: Kravets et al, 2000; Ronquist and Nilsson, 2002).

This review will focus on the physiological implication of these membranous structures with regard to the posttesticular sperm maturation.

Epididymosomes and Epididymal Maturation

Epididymal transit confers the mammalian sperm cells their fertilizing ability, a process that is under androgenic control (Cooper et al, 1986). Among the complex modifications that spermatozoa undergo in the epididymis is the process whereby proteins are produced by the epididymal epithelium and then secreted and transferred to the sperm cells, thereby generating functional male gametes

(Jones, 1998). However, there is evidence that proteins without any signal peptide are also acquired by sperm cells during their epididymal transit, implying an unusual secretion pathway. In fact, a family of orthologous epididymis-specific proteins was characterized in different mammalian species and named P26h, P25b, and P34H in hamster, bull, and man, respectively (Sullivan, 1999). Each of them is acquired by the sperm cells during epididymal transit, and the hamster protein, P26h, has no signal peptide as deduced from its mRNA sequence. This hamster protein is located on the sperm surface, is attached via a glycosyl-phosphatidylinositol (GPI) anchor, and is involved in the zona pellucida recognition (Sullivan, 1999). The epididymal membranous particles present in the lumen, "prostasome-like particles" or epididymosomes, are responsible for anchoring the P26h to the sperm surface (Légaré et al, 1999). Furthermore, epididymosomes of the Chinese hamster have been shown to interact in vivo with the sperm plasma membrane (Yanagimachi et al, 1985; Figure 1). Epididymosomes are thus directly involved in the epididymal maturation process of the sperm cells.

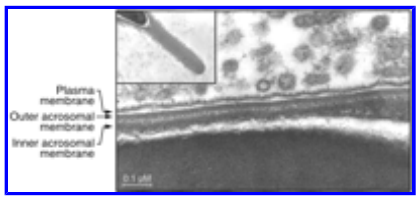

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Figure 1. Electron photomicrographs showing Chinese hamster epididymosomes surrounding the plasma membrane of a spermatozoon. The inset shows the general appearance of the acrosome surrounded by these vesicles. Original photos were kindly provided by Dr Yanagimachi (University of Hawaii).

Like P26h, the bovine ortholog protein P25b is GPI anchored, and its transfer from the epididymal epithelial cells to spermatozoa also implies the intervention of epididymosomes (Frenette et al, 2002). The transfer of P25b was demonstrated between epididymosomes isolated from the cauda epididymidis and spermatozoa from the caput epididymidis, on which the initial quantity of P25b was null. This transfer is fundamental for the fertility of the animals, as bull subfertility is associated with low levels of P25b (Parent et al, 1999). In order to test the hypothesis of possible transfer of other proteins from the epididymosomes to sperm cells in the bull epididymis, the proteins exposed at the surface of epididymosomes from the cauda epididymidis can be biotinylated and then incubated with caput spermatozoa. After 4 washing steps to get rid of the residual epididymosomes, the sperm proteins are extracted and Western blotted with peroxidase-conjugated neutravidin. Under these conditions, only a fraction of the proteins associated with epididymosomes are transferred to spermatozoa (Frenette et al, 2002). This transfer of selected proteins can either mean that only these proteins possess the ability to be transferred or that epididymosomes are not transferred totally, as an intact entity, on spermatozoa. Another possibility is that the population of epididymosomes is heterogeneous, with a different protein composition, as has already been reported for rat epididymal vesicles (Fornes et al, 1995). Protein transfer is dependent on the pH and the zinc concentration: indeed, it is optimum at a pH of 6.0 to 6.5, the variation being 2.5-fold between pH 6.0 and 7.5 (Frenette et al, 2002). This is in accordance with the fact that the fusion between human prostasomes and ejaculated spermatozoa is favored at a slightly acidic pH (Arienti et al, 1997a), thus showing a tendency toward a conserved mechanism. Zinc is also important for the transfer, favoring this process when ranging between 0.1 and 1.5 mM, whereas magnesium and calcium have no effect. Considering that the epididymal intraluminal pH is 6.5 and that high zinc concentrations are found in the epididymis, it is apparent that these are the physiologically relevant conditions for the in vitro transfer of protein.

The biotynilated proteins of epididymosomes are transferred to the acrosomal cap and the midpiece of spermatozoa, with this transfer being temperature-dependent (the maximum transfer occurs between 32 °C and 37 °C). These facts may reflect the importance of the lipid composition and the membrane fluidity of spermatozoa and/or epididymosomes. Thus, the transfer would only be possible on certain microdomains of the sperm plasma membrane, which undergoes important composition modifications during epididymal transit (Parks and Hammerstedt, 1985). The evolution of the structure and composition of the sperm plasma membrane during the transit would permit the acquisition of important proteins, via the epididymosomes, at the right time and location in the excurrent duct.

The mechanism responsible for the protein transfer via the vesicles has not yet been elucidated. However, different hypotheses have been proposed for the cell-to-cell transfer of GPI-anchored molecules and have been reviewed by Ilangumaran et al (1996). Briefly, the acquisition could be mediated in one of 3 ways: 1) by the intervention of plasma lipid-carrier proteins, 2) by interactions between a donor and an acceptor membrane via a "flip-over" phenomenon, or 3) by vesicles that could be processed by endocytosis and the carried proteins sent back to the plasma membrane of the acceptor cell. The 2 latter propositions would be in complete accordance with the epididymosomes – spermatozoa interaction.

The identity (or identities) and precise function(s) of the transferred protein(s) remain to be investigated but could lead to a better understanding of the complex process of epididymal sperm maturation. A number of proteins other than P25b and its orthologs, generally with no signal peptide, are also secreted by the mammalian epididymis or other organs from the male genital tract and are associated with vesicular structures closely resembling the epididymosomes (Table). The direct relation between these proteins and fertility has not always been demonstrated but confirms the importance of the mechanism, the purpose of which could be to protect important proteins from proteolytic digestion, as suggested by several authors (Sutovsky et al, 2001; Rejraji et al, 2002).

Because of the availability of a large amount of biological material, the bull model allows researchers to characterize more precisely the implication of epididymosomes in the mammalian epididymal sperm maturation process. The study of such mechanisms in humans is very difficult from a technical point of view because of the quasi-impossibility of disposing of human epididymis in sufficient amounts to purify both epididymosomes and epididymal spermatozoa. However, the P26h/P25b human ortholog protein P34H is also related to fertility and has been proposed as an indicator of the sperm fertilizing ability (Sullivan, 1999). We can thus hypothesize that the same mechanisms, or relatively close ones, also occur in the human epididymis. Membranous vesicles are important mediators in the epididymis-related maturational events of mammalian spermatozoa. The involvement of epididymosomes in the acquisition of new proteins by the male gamete during epididymal transit can explain why many of these surface proteins behave as integral membrane proteins (Cooper, 1998).

View this table: [in this window] [in a new window]	*Characteristics of selected proteins associated with vesicles secreted by the male genital tract of different mammalian species*

Prostasomes and Postejaculatory Sperm Modifications

As mentioned earlier, the first described vesicles were reported by Ronquist et al in 1978 and were isolated from human seminal plasma by an ultracentrifugation method. Figure 2 shows an electron

photomicrograph of prostasomes purified from human seminal plasma. Further studies showed that these so-called "prostasomes" are secreted by the human prostate and mixed in the semen at the moment of ejaculation. The precise physiological function of these vesicles still remains unclear, but many different in vitro functions have been related to them, such as blood coagulation activity (Fernandez et al, 1997), antibacterial activity (Carlsson et al, 2000), serine-protease activity via the enzyme dipeptidyl-peptidase IV (CD26, Arienti et al, 1997b), and antioxidant activity (Saez et al, 1998, 2000). Many different proteins have been shown to be present on prostasomes, some of which possess enzymatic properties (Review: Kravets et al, 2000; Ronquist and Nilsson, 2002).

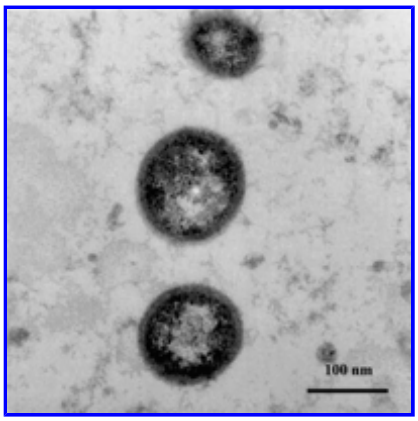

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Figure 2. Electron photomicrographs of prostasomes purified from human semen. Three prostasomes appear as electron-dense material and show their size heterogeneity. The original photo was kindly provided by Dr Kemeny and Dr Guy (Centre Hospitalier Universitaire de Clermont-Ferrand, 63000 France).

The effects of prostasomes on the posttesticular maturation of spermatozoa include an immunosuppressive activity (Rooney et al, 1991, 1993, 1996), an enhancement of sperm motility (Stegmayr and Ronquist, 1982; Fabiani et al, 1994a,b; Carlsson et al, 1997), and an influence on the sperm capacitation process (Cross, 1996a,b; Cross and Mahasreshti, 1997).

The immunosuppressive activity of prostasomes arises from the presence of several complement inhibitory molecules (eg, CD55 [decay accelerating factor] and CD46 [membrane cofactor protein], both of which inhibit the C3-convertase) and from the presence of CD59 (protectin), which inhibits the formation of the membrane attack complex. CD55 and CD59 are GPI-anchored proteins, whereas CD46 is a transmembrane protein. Prostasomes have the ability to transfer CD59 to spermatozoa in vitro, and this mechanism also exists between prostasomes and red blood cells or fibroblasts (Rooney et al, 1993, 1996). It has also been demonstrated that the transfer of CD59 from prostasomes to CD59-deficient red blood cells resulted in protection against complement-mediated hemolysis, thus showing that the functional protein is transferred (Babiker et al, 2002). The transmembrane protein CD46 is also transferred from prostasomes to red blood cells, with the same efficiency, thus showing a complex mechanism, as both GPI-anchored and transmembrane proteins can be transferred (Rooney et al, 1993). The possible role of these molecules would be to protect spermatozoa, once in the female genital tract, from being phagocytosed by the white blood cells. It should be noted that the human epididymal protein HE5 (CD52), which is also a GPI-anchored protein, is acquired by sperm cells during their epididymal transit in humans as well as in cynomolgus monkeys (Yeung et al, 1997). This protein was previously shown to be present on prostasomes (Rooney et al, 1996), thus suggesting an intervention of epididymosomes in the transfer of this protein from epithelial cells to spermatozoa.

Prostasomes also have an influence on sperm motility under several conditions in vitro. First, they enhance the progressive motility of spermatozoa, measured after 1 washing step of whole semen (Stegmayr and Ronquist, 1982). This effect could be due to the modifications of the sperm microenvironment by prostasomes, since these vesicles contain a calcium-dependent ATPase. Second, prostasomes favor the recovery of sperm motility after their immobilization by NaCl washes (Fabiani et al, 1994b). Finally, prostasomes also stimulate the rate of motile sperm recovery following the swim-up technique (Fabiani et al, 1994a). This effect is higher than the effect of albumin and seems to be dependent on the particular lipid composition of the prostasomes, since they keep these properties after a heat treatment of 5 minutes at 100 °C. This enhancement of motile sperm recovery after swim-up is also applicable if the semen has been submitted to freezing and thawing according to classical cryoconservation protocols (Carlsson et al, 1997). The molecular mechanism underlying these effects still remains unclear but is an important part of the prostasomes' action. Indeed, sperm motility and movement quality are important factors in the movement of sperm in the female genital tract (eg, crossing the cervical mucus as well as penetrating the zona pellucida). If prostasomes keep the same functions in vivo, they could promote these various steps by their effects on sperm motility.

Another effect of prostasomes on sperm function is that they have an influence on the capacitation step, a prerequisite for fertilization to occur. Indeed, one of the known inhibitory factors of capacitation, as determined by sperm response to progesterone, is cholesterol (Cross, 1996a). Prostasomes are very rich in cholesterol and represent approximately 40% of the total cholesterol present in seminal plasma. They were shown to inhibit the progesterone-stimulated acrosome reaction of human spermatozoa in vitro (Cross, 1996b). According to Cross and Mahasreshti (1997), the most likely hypothesis is that cholesterol could transfer from prostasomes to the sperm cells. Whatever the mechanism, the particular lipid composition and structure of the prostasomes are related to this function and, as mentioned earlier, could also be involved in the protein transfer within certain precise membrane domains of the sperm cells.

Taken together, the different functions of prostasomes seem to have the common aim to protect spermatozoa after ejaculation in order to preserve them in the most proper state, with their full functional capacities, prior to their encounter with the oocyte.

Epididymosomes and Prostasomes: An Unusual Secretion Pathway?

The transfer of proteins to spermatozoa thus appears as a common feature of epididymosomes and prostasomes. Several of these proteins do not possess a signal peptide or are GPI anchored and transferred with their functional anchor, which implies an unusual secretion pathway. One possibility is that epididymosomes and prostasomes are released in the intraluminal compartment by apocrine secretion. In contrast to mesocrine secretion, this type of secretion does not involve the Golgi apparatus or the fusion of secretory vesicles with the plasma membrane prior to protein secretion. Apocrine secretion implies the formation of apical blebs containing selected organelles, including vesicles of various sizes. These blebs detach from the cell surface, and one hypothesis is that their content could be released when the blebs undergo fragmentation (Hermo and Robaire, 2002). They could also appear as whole entities in the luminal fluid and show properties similar to those of the isolated vesicles or represent 2 different types of secretion. This blebbing phenomenon was first studied in the rat coagulating gland, as well as in the prostate and seminal vesicles (Aumuller, 1979; Aumuller and Adler, 1979), and was also very well documented, in terms of photographic studies, in the bull reproductive tract (Agrawal and Vanha-Perttula, 1988). The studies by Aumuller were undertaken to test whether the apical blebs secreted by these organs (apocrine secretion) were real or just artifacts due to tissue fixation problems. However, the improvement of

fixation techniques could not get rid of these blebs, thus suggesting a real phenomenon. Two enzymes, transglutaminase and carbonic anhydrase II, are secreted in an apocrine way by the rat coagulating gland and do not possess a signal peptide (Seitz et al, 1991; Wilhelm et al, 1998). This secretion pathway thus seems to be specific for certain proteins, mainly GPI-anchored proteins and proteins without a signal peptide.

Apical blebs have also been described as a feature of principal and narrow cells of the epididymis of many mammalian species, including humans. As mentioned earlier, the occurrence of prostasomes or epididymosomes in the lumen of the different ducts could derive from the fragmentation of the released "blebs," thus allowing their interaction with spermatozoa (Hermo and Robaire, 2002). It is very likely that proteins of the cytoskeleton (mainly actin) are involved in the mechanism of apocrine secretion at the step of bleb release, although much work still needs to be done to define this precisely (Aumuller et al, 1999). This secretion pathway is very common in the reproductive tract but is also present in the mammary glands and sweat glands (Aumuller et al, 1997).

The maturation of sperm cells in the epididymis or after ejaculation is thus related to the presence of vesicles in their environment, which is probably the result of apocrine secretions by the male genital tract organs. This process seems to be involved in the constant development of the sperm plasma membrane, playing a major role in the acquisition of particular proteins by spermatozoa.

Conclusion

The occurrence of extracellular vesicular structures in the biological fluids surrounding spermatozoa is a characteristic of the male reproductive tract. These vesicles are present as early as the epididymal transit, when they are tightly related to the sperm maturation process and the acquisition of fertilizing ability. Then, after ejaculation, prostasomes coming from the prostate or from other organs, depending on species, are mixed together in semen. This new environment protects spermatozoa and keeps them functional in association with other soluble factors. A common feature of these different vesicles is their ability to transfer new biologically active proteins to spermatozoa and, also, probably new lipids such as cholesterol. During their journey from the testis to the female genital tract, the development of the complex lipid and protein pattern of the sperm plasma membrane relies at least in part on these vesicles. Their maturation properties in the epididymis are changed to a "reservoir" function concerning the prostasomes.

Prostasomes and epididymosomes can therefore be considered a new insight in the posttesticular maturation process of the mammalian spermatozoa.

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