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Sperm selection in the female mammalian reproductive tract. Focus on the oviduct: Hypotheses, mechanisms, and new opportunities

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ABSTRACT

Research over the past 3 decades has caused a major shift in the way that the oviduct, or fallopian tube, is perceived. Previously, it was regarded as little more than the anatomic site for fertilization, where spermatozoa and oocytes meet as they travel in opposite directions. However, this view has been radically altered by the realization that both spermatozoa and oocytes elicit changes in the biochemical composition of oviductal fluid through the induction of novel gene expression. Moreover, it has also been shown that only a privileged sperm population, selected on the basis of multiple criteria, is permitted to enter the oviduct, where they are subjected to even more selection processes that control their motility and capacitation status, thus either inhibiting or facilitating their progress toward the oocyte. Even more recently, it has become apparent that the oviduct has some ability to differentiate the genetic signatures of X- and Y-bearing spermatozoa. Although how exactly this is achieved is unknown, it prompts us to speculate that the oviduct may also be capable of distinguishing other genetically encoded properties of individual spermatozoa and that there must ultimately be a huge payoff in terms of selective animal breeding.

1. Introduction

Sperm transport in the mammalian female reproductive tract has long been regarded as a race toward the oocyte(s), so that fertilization rate is biased in favor of the fastest swimmers. However, over the past 10 to 20 years, there has been a growing realization that the process of sperm transport is mediated by a far more complex series of interactions between the spermatozoa and the female reproductive tract and that the "sperm race" is no longer a tenable hypothesis. *In vitro* and *in vivo* studies have revealed that sperm behavior is modulated by physical and biochemical interactions with the cells lining the female reproductive tract and the mucous fluids that constitute the environment. The high viscosity of these fluids is of special significance because they can either inhibit or permit the passage of spermatozoa by altering the characteristics of their flagellar movement [1] and their beat frequency. The high viscosity also tends to make the spermatozoa swim near to available surfaces, and the female tract architecture has evolved multiple folds and grooves through which the spermatozoa can swim. In fact, recent evidence has demonstrated that the combined effects of viscous fluids and microgrooves in parts of the female reproductive tract provide significant degrees of selectivity, allowing the passage of spermatozoa but preventing infectious microorganisms from reaching the oviduct [2,3]. Shortly after insemination, the female reproductive tract responds to spermatozoa by altering the suite of proteins it produces, thus also changing the physiological and biochemical environment. In fact, when spermatozoa enter the female reproductive tract, they elicit feedback

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responses from the adjacent epithelial cells, which in turn affect sperm storage, motility, survival, and capacitation.

The female reproductive tract is highly differentiated into distinct anatomic regions, and it is therefore clear that individual spermatozoa must experience interactions with different environments as they make their way toward the oocyte. Sperm deposition in pigs occurs directly into the uterus and involves the ejaculation of a large fluid volume (approximately 2–300 mL) over a period of 5 to 10 minutes. After ejaculation, the vaginal region of the cervix is believed to act as a filter-barrier against the external environment [4], and peristaltic uterine contractions push the spermatozoa toward the uterotubal junction (UTJ). At this stage, some components in seminal plasma exert direct effects on the ovaries, advancing the onset of ovulation by several hours [5]. Even before they reach the UTJ, the spermatozoa are eliciting local immunologic responses and some degree of sperm selection takes place, mediated, among other factors, *via* polymorphonuclear leukocytes (PMN) [6].

2. Sperm selection at the uterotubal junction and oviductal isthmus

Once the spermatozoa reach the UTJ, which represents a physical barrier, the next stage of their journey toward the oocyte(s) involves entering the oviduct and experiencing up to 40 hours of storage in contact with epithelial cells of the oviductal isthmus. In fact, the UTJ itself represents a significant sperm storage region in pigs, and it is likely that a further degree of sperm selection also takes place here. As pointed out by Hunter [7], viscous glycoproteins accumulate in the porcine caudal isthmus before ovulation and form a mucus-like plug which does not disperse until ovulation occurs. The mucus thus acts as a physical barrier to the further progress of spermatozoa, which are forced into narrow crypts and grooves in the local epithelia [2]. Unlike the uterine environment, where the spermatozoa interact extensively with PMNs [6], leukocytes are less common or even absent within the environment provided by the oviductal isthmus [2], which is widely regarded as a safe and protective environment for the privileged sperm population that reaches it [8]. Only uncapacitated spermatozoa are stored in the oviductal isthmus, and in fact, only uncapacitated spermatozoa are capable of binding to epithelial cells [9]. Capacitation is inhibited while the spermatozoa remain in the oviductal sperm reservoir before ovulation [10], despite the abundant presence of bicarbonate (35–90 mM) [11], which would normally be sufficient to induce capacitation and rapid flagellar activity *in vitro*. Sperm–oviduct binding involves species-specific, molecular interactions mediated principally by oligosaccharides [12,13] and by specific sperm-binding proteins [14,15] expressed by the oviductal cells. Refined control of sperm binding and release also appears to involve the redox modulation of sulfated glycoproteins [16–18].

Sperm entry into the oviductal isthmus from the UTJ is a highly selective process. A recent assessment of the distribution of spermatozoa in the porcine female reproductive tract [19] 24 hours after artificial insemination found 142,500 spermatozoa in the UTJ but less than 2000 spermatozoa in the oviductal isthmus. Similarly, a previous study [20] found 75,923 spermatozoa in the UTJ of preovulatory pigs but less than 3000 in the isthmus. Studies of sperm migration in dogs also found that the UTJ effectively controlled the progress of spermatozoa into the oviducts from binding sites situated in the uterus [21]. These studies imply that the UTJ prevents about 90% of uterine spermatozoa from reaching the oviducts. The precise nature of the sperm selection process is not known, but by analogy with other species, it is likely to involve not only active and progressive sperm motility but also the involvement of molecular recognition systems. Some of the relevant information about sperm entry into the oviduct has been gathered from genetic studies in mice, where motile and morphologically normal spermatozoa are prevented from reaching the oviduct if they lack certain proteins [22–26]. These include a family of A disintegrin and metalloprotease (ADAM) proteins, which are expressed during spermiogenesis and primarily located on the sperm head, as well as other proteins such as calmegin and calsperin. Indeed, a recent study has further shown that failure to process ADAM precursors during spermiogenesis, owing to the lack of a specific serine protease, also led to infertility through inadequate sperm migration through the UTJ [27].

The relevance of sperm motility in migration through the UTJ was highlighted by Cox et al. [28], who distinguished two groups of male goats, termed high and low migration, on the basis of the ability of their spermatozoa to penetrate columns of cervical mucus in the laboratory. Correlative counts of spermatozoa in the oviducts of females that had been artificially inseminated with semen from the high- and low-migration goats produced dramatic results The numbers of spermatozoa in the oviducts of females inseminated by the high- and low-migration samples were 1233 and 28.8, respectively. This study emphasized that sperm motility is an informative surrogate for sperm transport through the UTJ; however, it also demonstrated the importance of using viscous media when making such measurements. The motility measurement technique used in the study of goat spermatozoa involved determining the distance traveled by “vanguard” spermatozoa over a fixed time, i.e., the distance traveled by the spermatozoa that covered the furthest distance within the tube. This approach is the basis of the “sperm penetration” or “Kremer test”, used for evaluating human sperm interactions with cervical mucus [29], where antisperm antibodies may inhibit motility. Several researchers have elaborated and standardized the human sperm penetration test, substituting hyaluronic acid or acrylamide polymers for cervical mucus [30,31], and the method has also been used to predict outcomes of the zona-free hamster egg penetration test [32]. The technique has also been applied to the assessment of semen in agricultural species, where it distinguished between two groups of bulls classified as “high” or “low” fertility [33,34] and selected both bull and ram spermatozoa on the basis of high progressive motility, high acrosomal and plasma membrane integrity [35] as well as superior sperm head morphology [36]. This approach is a significant departure from studies that have only measured sperm parameters in the bulk sample and tends to imply that the small population of vanguard