

# Sperm-oviduct interactions: Key factors for sperm survival and maintenance of sperm fertilizing capacity

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## Abstract

**Background:** Although millions or even billions of sperm are deposited in the female genital tract, only very few sperm reach the oocyte, and only one single spermatozoon will successfully fertilize. During the journey of the sperm within the female genital tract, the interactions between spermatozoa and fallopian tube are critical for sperm selection, sperm survival, and maintenance of sperm fertilizing capacity.

**Results:** This review will provide a comprehensive overview of the latest findings regarding sperm transport and behavior of sperm within the oviduct, sperm selection in the oviduct, the formation of the sperm reservoir, and the release of sperm in the presence of the oocyte. It will primarily focus on recent novel insights on sperm-oviduct interactions, which have been obtained by cutting-edge technologies under *in vivo* or near *in vivo* conditions.

**Conclusions:** The comprehensive analysis of the findings to date will elucidate the complex molecular changes in the tubal epithelium, which are induced by the presence of the sperm and will highlight how the epithelial cells of this organ affect transport, behavior, and function of sperm. This knowledge is essential for scientists and clinicians involved in assisted reproductive technologies.

## KEYWORDS

fallopian tube, gameto-maternal interaction, oviduct, sperm fertilizing capacity, sperm, sperm survival

## 1 | INTRODUCTION

Sperm-oviduct interactions play a pivotal role for successful fertilization. Only sperm, which are capable to interact with tubal epithelium, will survive and maintain fertilizing capacity for 4–5 days (human, most mammals), weeks (birds), or even months (bats).<sup>1–3</sup> When the cumulus-oocyte-complex (COC) has reached the oviduct, successful fertilization only occurs when spermatozoa and oocyte meet in the right place (tubal ampulla) and at the right time (within 12–24 h after ovulation).<sup>4</sup> Thus, the timely transport of spermatozoa in the female genital tract

and the maintenance of fertilizing capacity in the oviduct are essential to maximize the chance of fertilization, and at the same time to ensure that only the best spermatozoon will be successful. Sperm-oviduct interactions can be categorized in physical interactions, which include the 3D swimming response to the microarchitecture of the tubal mucosa, and the molecular interactions, which result in the secretion of specific molecules from both the sperm and the tubal epithelium as a result of gameto-maternal interaction.<sup>5</sup> To date, most of the studies investigating sperm movement and sperm-oviduct interaction have been performed under *in vitro* conditions.<sup>6–8</sup> However, in these

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studies, the 3D microarchitecture of the tubal mucosa is lacking, thus making it impossible to analyze the behavioral pattern and swimming responses of the sperm within the oviduct. In relation to molecular interactions, tubal cell cultures and oviductal explants have provided invaluable insights on changes in gene expression and protein secretion after sperm binding.<sup>9–12</sup> However, under *in vitro* conditions, the complex interactions between the epithelium, the underlying connective tissue, and the smooth muscle layers are lacking. Further to that, paracrine signalling between neighbouring epithelial cells is missing. Consequently, specific features of the tubal epithelium in the presence of sperm, such as receptor activation and secretory activity, cannot be explored. In recent years, novel cutting edge technologies such as digital live cell imaging (LCI) of spermatozoa within the tube,<sup>13–16</sup> confocal fluorescence microscopy using a fibre-optic probe to track sperm within the female genital tract,<sup>17</sup> and optical coherence tomography for 3D high-resolution and high speed tracking of sperm<sup>18</sup> have contributed to gain a comprehensive understanding how the dynamic interplay between tubal epithelium and spermatozoa affects sperm motility, sperm behaviour, and sperm survival. All these studies highlight the importance of the fallopian tube for sperm survival, sperm selection, and maintenance of sperm fertilizing capacity.

## 2 | SPERM TRANSPORT AND SPERM BEHAVIOR ON THE WAY TO THE OVIDUCT AND WITHIN THE OVIDUCT

In humans and in the murine, sperm are deposited in the cranial part of the vagina during natural insemination.<sup>19</sup> Some species, such as pigs, are able to deposit the sperm directly into the uterus as the corkscrew formed penis is able to penetrate the cervix.<sup>20,21</sup> If sperm deposition occurs in the vagina, the spermatozoa must pass the cervix, which is the first major barrier for sperm in the female genital tract. Due to increased estrogen levels around ovulation, cervical patency and the hydration of the mucus are increased.<sup>22</sup> Although these two factors facilitate the migration of sperm through the cervix, around 70%–85% of sperm (dependent on the species and the individual) stick to the mucus and consequently are eliminated from the fertilization process. A further reduction of sperm occurs through a considerable flowback of sperm in the human vagina following coitus, which may account for a loss of 35% up to 100% of the sperm.<sup>23</sup> The remaining spermatozoa, which have been able to pass the cervix, enter the uterine cavity and have to pass the narrow uterotubal junction,<sup>24</sup> which is the second major barrier for the sperm on their way to the oviduct. *In situ* observations of sperm behavior within the native oviduct have shown that the motility of sperm is essential to transport them into the middle of the lumen of the oviduct thus avoiding that the sperm get whirled around by the cilia.<sup>13,15,25</sup> However, sperm motility does not primarily contribute to the swimming progress of the sperm within the female genital tract. LCI has proven that *de facto* the sperm are struggling to move forward due to the strong current produced by ciliary beating.<sup>15</sup> This is confirmed by experiments in knockout (KO) mice, which show that sperm motility alone is insufficient for sperm migration.<sup>26,27</sup> Instead,

progression of sperm is mainly achieved by smooth muscle contraction, which is increased around ovulation.<sup>10,15</sup> Additionally, smooth muscle contraction in the caudal part of the female genital tract is locally increased by the presence of prostaglandins in the ejaculate.<sup>28,29</sup> In the oviduct, sperm are also able to increase their own transport speed by triggering prostaglandin secretion in the epithelium.<sup>10</sup>

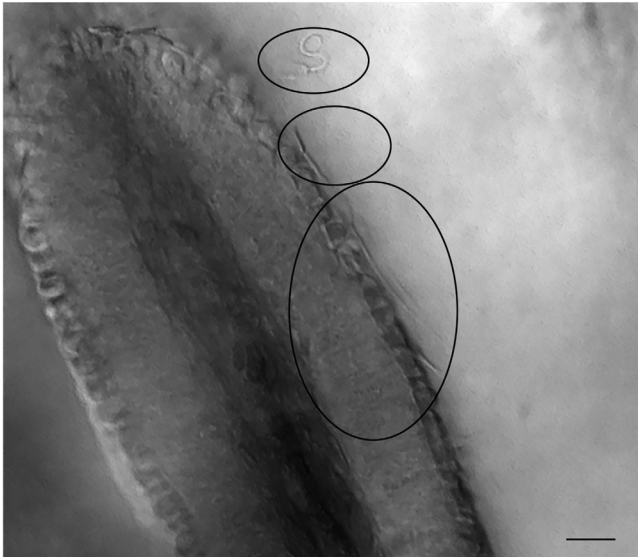
Using a fluid-circulating chamber maintaining the blood circulation and parasympathetic innervation of the murine oviduct Hino and Yanagimachi<sup>30</sup> found that there are active contractions in the oviduct in direction to the ovaries, which result in a rapid transport of luminal fluid. The oviduct secretes fluid continuously.<sup>30</sup> Thus, the oviduct's peristaltic movements and the active upward flow of oviductal fluid in combination with sperm motility enable the sperm ascent, the complete acquisition of sperm fertilizing capacity, and the occurrence of successful fertilization in the oviduct. Importantly, these observations make clear that chemotaxis, rheotaxis, and thertotaxis of spermatozoa are unlikely to be the decisive mechanisms for sperm migration toward the cumulus-oocyte-complex (COC) after ovulation.<sup>30</sup> However, the importance of sperm motility is highlighted by the observation that a few spermatozoa are still able to reach the oviduct when peristaltic movement in the oviduct is blocked using anticholinergic drugs.<sup>31</sup>

During the migration in the female genital tract, sperm undergo capacitation, which allows them to obtain fertilizing capacity.<sup>32</sup> This process involves the removal of glycoproteins, which are attached to the surface of the sperm head.<sup>33</sup> However, the precise molecular mechanisms remain to be fully determined.

When looking at sperm behavior and sperm transport in the fallopian tube, it is important to highlight that every disease in the female genital tract affects sperm transport and sperm behavior. For example, as shown by digital LCI in the bovine model, an inflammation in the female genital tract alters the tubal response and is associated with alterations of ciliary beating frequency, which affects sperm swimming responses.<sup>34</sup> Inflammation also goes along with increased secretion and cellular breakdown, which leads to the sticking of sperm to the dying cells or to mucus or pus, thus eliminating these sperm from the fertilization process.<sup>34</sup> Also, as shown by the use of a wide panel of cutting edge technologies in bovine cystic ovary disease (COD), the cholinergic regulation of smooth muscle contraction in the oviduct is impaired, which is prone to affect a timely sperm transport and successful fertilization.<sup>35</sup> Lastly, all kinds of stress, be it due to inflammatory, mechanical, or chemical triggers, negatively affect the progressive motility of sperm, their velocity, and the ability of hyperactivation,<sup>36</sup> which is an essential prerequisite for fertilization. Similarly, *in vivo* three-dimensional tracking of spermatozoa using optical coherence tomography revealed that spermatozoa exhibit spatial dependence of velocity in the murine oviduct highlighting an intense site-specific interaction between sperm and tubal epithelium.<sup>18</sup>

## 3 | THE SPERM RESERVOIR

When the sperm enter the fallopian tube, spermatozoa bind with their head to the cilia of the tubal epithelium and form a sperm reservoir

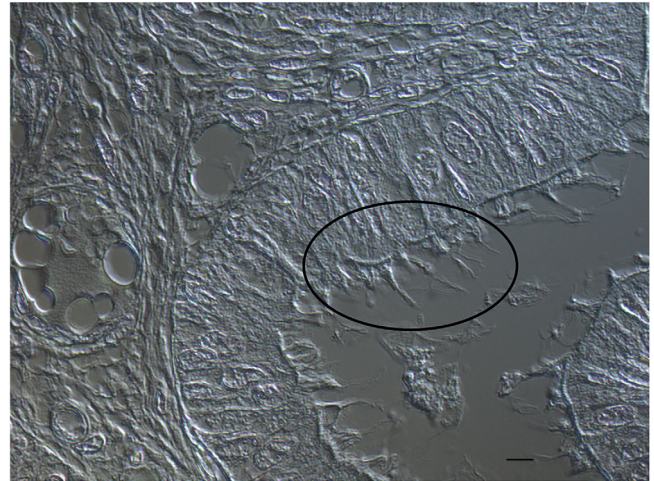


**FIGURE 1** Real-time documentation of sperm bound to the cilia of the bovine ampulla using digital live cell imaging (LCI). Upper circle: floating immotile spermatozoon with coiled tail, middle circle: lagging spermatozoon lying flat on the epithelium, low circle: vital bound spermatozoa with actively moving tail. Bar = 15  $\mu$ m

(Figure 1). The presence of a sperm reservoir has been documented in mice, rats, hamsters, pigs, sheep, cows, and horses.<sup>1,13,15,24,25,37</sup> In humans, it is anticipated that there is a sperm reservoir as intercourse several days before ovulation may result in pregnancy.<sup>38</sup> However, documentation of the formation of a sperm reservoir under *in vivo* conditions is still lacking. The binding to the oviductal epithelial cells enables spermatozoa to maintain their motility and fertilizing capacity for 3–5 days (most mammals), weeks (birds), months (bats), or even years (snakes).<sup>1,3,24</sup>

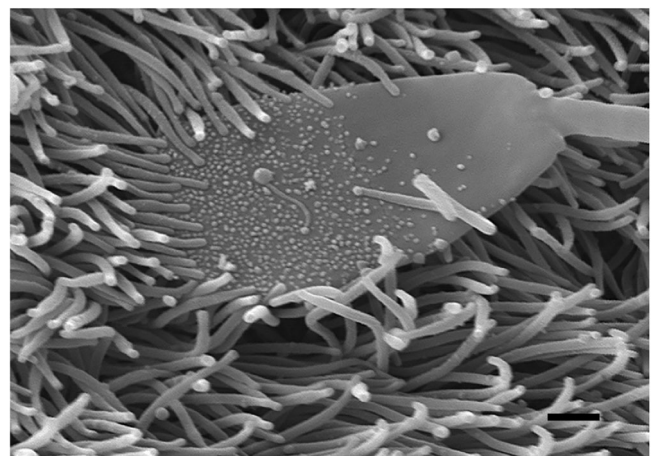
Most sperm bind to the ciliated cells of the isthmus, as this is the first site they encounter. However, several sperm also travel further and are found in the ampulla. Interestingly, most of these sperm bound in the ampulla are located near the COC after ovulation<sup>19</sup> pointing to an important role of the ampulla for sustaining sperm with a high fertilizing capacity. As shown by digital LCI in the bovine model, which allows *in situ* observations of sperm within the oviduct, Camara Pirez et al.<sup>16</sup> demonstrated that sperm binding and sperm behavior in the sperm reservoir are not affected by cycle stage. Real-time LCI in the oviduct also revealed that most bound sperm are agile spermatozoa, which are binding to the tubal cilia (Figure 1, lower circle, Figure 2) at a tangential angle of 30–40° with an actively beating undulating tail.<sup>16</sup> This important feature of sperm binding can also be shown using differential interference contrast microscopy (Figure 2). Scanning electron microscopy reveals that cilia are in direct contact with the sperm head and “hug” the sperm in the acrosomal region (Figure 3).

Importantly, sperm motility is preserved in the sperm reservoir and is sustained by the molecular interactions with the oviduct and secretions such as glycoproteins and acidic mucopolysaccharides, which are produced by the secretory cells of the tubal epithelium.<sup>16</sup> LCI revealed that 5%–15% of the sperm in the reservoir reveal hyperactivation. They



**FIGURE 2** Formation of the sperm reservoir in the bovine oviduct as seen by differential interference contrast microscopy (DIC). Circles indicate bound sperm. Bar = 8  $\mu$ m

show an asymmetrical high amplitude and a whip-like beating of the tail and a rotating head.<sup>16</sup> Hyperactivation is an important key behavior of sperm, which allows them to detach from the tubal epithelium and to penetrate the cumulus oophorus of the oocyte after ovulation.<sup>39,40</sup> Within the sperm reservoir, hyperactivation might also enable sperm to detach and bind to another site of the oviduct.<sup>41</sup> *In situ* observations of sperm within the bovine oviduct also revealed that 10%–20% of the sperm bound in the tubal reservoir are lagging spermatozoa, which are characterized by a decreased binding angle and a reduced motility of the tail.<sup>16</sup> Around 20% of the sperm in the reservoir are immotile sperm, which are lying flat on the tubal epithelium and do not show any movement of the tail (Figure 1, middle circle).<sup>16</sup> Importantly, with ongoing binding time, previously agile sperm may become lagging and then immotile.<sup>16</sup> However, it is important that especially due to freezing and thawing, there is a percentage of sperm, which is immotile or dies already during the migration in the female genital tract. They are



**FIGURE 3** A bovine spermatozoon is bound to the cilia of the ampullar cells (scanning electron microscopy). Bar = 1  $\mu$ m

seen as floating immotile spermatozoa in the oviductal fluid<sup>16</sup> (Figure 1, upper circle).

Sperm binding in the Fallopian tube is mediated by species-specific carbohydrate moieties on the cilia. This involves fucose in the bovine,<sup>42</sup> mannose in the pig,<sup>43</sup> sialic acid in the hamster,<sup>44</sup> and galactose in the horse.<sup>45</sup> In cows and sheep, these carbohydrate moieties on the cilia bind to sperm binder proteins on the sperm head.<sup>1,46</sup> Whereas it is very clear that the molecules mediating the binding between sperm head and tubal epithelium are species-specific, the key factors for sperm survival and maintenance of sperm fertilizing ability are similar in all species. As shown by digital LCI in the oviduct, these key factors include (a) the presence of an intact plasma membrane on the sperm head to enable sperm binding and formation of the sperm reservoir, (b) the establishment of an active communication between sperm and oviductal cells, and (c) the maintenance of sperm motility by nutrients provided by the tubal cells and secretions from the genital tract.<sup>13,15,16,25</sup> Consequently, as soon as the sperm bind to the cilia of the tubal cells, signaling cascades are initiated, which promote the synthesis and secretion of molecules. Especially glycoproteins and mucopolysaccharides play a major role for maintenance of sperm motility.<sup>11,47</sup> Thus, gene and protein expression patterns of the tubal epithelium have been shown to be altered after sperm binding.<sup>9</sup> For example, in the porcine model, both the transcription and the translation of complement C3, oviductal glycoprotein and retinol-binding protein are increased in the presence of sperm.<sup>9</sup> To date, the precise mechanisms of sperm signaling in the oviduct and the specific molecules of these signaling cascades have not been fully clarified. However, there are numerous hints that apocrine and paracrine signaling play a major role. In regard to apocrine signaling, it is widely accepted that the oviductal cells produce extracellular vesicles (EVs), which include exosomes and microvesicles (reviewed by Alminana and Bauersachs and Harris et al.<sup>48,49</sup>). These EVs are key modulators of the communication between spermatozoa and the female genital tract as they are able to transfer different functional molecules such as lipids, proteins, and nucleic acids to the sperm. In the porcine, oviductal EVs have been proven to bind to sperm in a time- and dose-dependent manner and to regulate sperm motility and survival in the sperm reservoir.<sup>50</sup> In murine and feline, EVs have been reported to bind to the membrane of the acrosome and midpiece and to promote capacitation and sperm fertilizing ability.<sup>51,52</sup> In addition to that, it was demonstrated that PMCA4, a Ca<sup>2+</sup> efflux pump, which is essential for sperm fertilizing ability, is secreted by tubal cells in oviductal EVs.<sup>53</sup> As PMSA4 regulates calcium levels, it also promotes sperm hyperactivation and acrosome reaction.<sup>53</sup> Bathala et al. were able to show that EVs play a similar role in the human with fertility-modulating cargo components being conserved, which regulate the expression of proteins required for capacitation and successful fertilization.<sup>52</sup>

However, for a holistic view of sperm-oviduct interactions, it is important to take into account that the composition of the oviductal fluid changes around ovulation due to cyclic hormonal changes,<sup>54</sup> Thus, not only local, but also systemic signals contribute to the creation of an optimal environment for sperm survival.

## 4 | SPERM SELECTION IN THE OVIDUCT

The oviduct is an important organ for sperm selection. Only sperm, which bind to the tubal epithelium, will be able to maintain motility and fertilizing capacity.<sup>15,16</sup> The ability to bind varies considerably from individual to individual but is also very different in one individual over time.<sup>15,16</sup> Alterations of sperm morphology are correlated with reduced sperm binding capacity.<sup>55</sup> Freezing and thawing generally decreases the sperm binding ability in the sperm reservoir,<sup>13,15,16</sup> which might be due to mechanical damage of the sperm plasma membrane and subsequently to the binder proteins on the sperm head. More importantly, as shown by digital LCI, even sperm, which are able to bind, may become immotile over time. These immotile sperm are not able to hyperactivate and detach from the tubal epithelium in the presence of the oocyte.<sup>15</sup> The precise causes have not been elucidated yet. However, these observations show that the formation of the sperm reservoir can be considered as the third selection mechanism of sperm in the female genital tract. This last selection process in the oviduct might be the most sensitive in the whole female genital tract as not only morphological (integrity of the plasma membrane of the sperm head) and mechanical properties (sperm motility, pattern of movement), but also specific molecular features of the sperm head are required for successful sperm binding and survival.

## 5 | RELEASE OF SPERM IN THE PRESENCE OF THE OOCYTE

The release of sperm from the sperm reservoir is triggered as soon as the cumulus-oocyte-complex (COC) arrives in the ampulla.<sup>56</sup> As shown during LCI studies, the oocyte per se is not able to attract sperm.<sup>14,15</sup> The COC needs to attach to the ampullar epithelium with the cumulus cells. This binding within a very short time initiates a signaling cascade in the tubal epithelium, which leads to the release of specific molecules attracting the sperm.<sup>15,25</sup> This is confirmed during routine IVF procedures, in which the oocyte alone in the petri dish is not able to attract sperm. The nature of these molecules, which signal the sperm the presence of the oocyte, is still unknown.

The release of sperm is driven by hyperactivation, which is characterized by high-amplitude, asymmetrical beating of the tail, as well as by molecular changes of the sperm head, which reduces binding affinity to the tubal epithelium.<sup>24,57</sup> Hyperactivation is induced by an increased influx of Ca<sup>2+</sup> ions through the cation channels of sperm (CatSper). This results in increased intracellular sperm calcium concentrations enabling vigorous movement of the sperm tail.<sup>58</sup> In humans, like in most mammals, CatSper channels play a pivotal role for sperm motility.<sup>59–61</sup> Thus, mutations in CatSper channels have been shown to be correlated with human infertility.<sup>62</sup> In mice, spermatozoa from CatSper1 KO mice are not able to migrate through the oviduct.<sup>32</sup> Progesterone, which is synthesized by the cumulus cells of the COC, has been shown to activate CatSper channels in humans and to increase Ca<sup>2+</sup> influx.<sup>61,63,64</sup>

Interestingly, this is not the case in the mouse<sup>63</sup> pointing to species-specific variations in signaling pathways for activation of CatSper channels and induction of sperm movement.

## 6 | CONCLUSION

The numerous mechanical and molecular interactions between spermatozoa and tubal epithelium are crucial for timely sperm transport, for sperm selection, and for maintenance of sperm fertilizing ability. The precise molecular mechanisms and signaling pathways between spermatozoa and the tubal cells still need to be elucidated. If these pathways are known, this knowledge holds promise to provide novel concepts for new therapeutic strategies for treatment of infertility, such as the application of specific molecules for sperm guidance in the female genital tract. It will also help to further improve the outcome of assisted reproductive technologies as oviductal factors, which are currently missing during IVF might be added to improve sperm quality and fertilizing ability.

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## CONFLICT OF INTEREST

The author declares no conflict of interest.

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