

Sperm-oocyte interaction

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The fusion of the two gametes, sperm and oocyte, marks the beginning of new life. However, gamete fusion represents only the last step in a series of crucial events ensuring successful fertilization. Sperm chemotaxis serves to guide sperm towards the oocyte and hence represents one of the first levels of sperm-oocyte recognition. To be able to “smell” the oocyte, sperm has to undergo capacitation, which causes chemical changes in the sperm tail resulting in increased sperm motility and rearrangements of sperm head membrane proteins to allow egg coat penetration. Because several chemoattractant/receptor pairs have already been identified, chemoattraction appears to be a complex process in mammals (1-3). As an example, oocyte surrounding cells, the so-called cumulus cells, release progesterone, which activates the human sperm cation channel receptor CatSper (4). Surprisingly, the mouse homolog of human CatSper is insensitive to progesterone, indicating that species specificity may be regulated already at this very early stage of fertilization (5). Besides cumulus cells, chemoattractants may also be directly released by the mature oocyte itself, however the identity of these molecules as well as their cognate receptors remains elusive (6). In non-mammals, sperm chemoattractants range from small molecules, over peptides to proteins and hence chemosensation in these organisms is believed to be even more diverse compared to mammals (7). In summary, molecular guidance of sperm towards oocytes is controlled by sophisticated signalling networks that evolved to ensure species-specific fertilization.

To achieve fertilization, it is generally believed that sperm has to bind to the extracellular coat of oocytes, which marks the first physical barrier and the second level of sperm-oocyte interaction. The mammalian egg coat, also called zona pellucida (ZP), is composed of up to 4 different ZP proteins (ZP1-4), while only certain protein domains of ZP2 and ZP3 are discussed to mediate species-restricted sperm binding in mice and humans (8,9). Initially, ZP-incorporated ZP3 was discovered to induce the acrosome reaction, a process in which fusion of the acrosomal membrane and the sperm plasma membrane releases acrosomal contents essential for fertilization. However, this concept is questioned by the observation that acrosome reaction was shown to appear even without physical contact of sperm to the ZP (10). Besides ZP3, the N-terminal domain of ZP2 was shown to possess sperm receptor activity, while the corresponding cognate molecule on sperm remains unknown (9). On the sperm side, sperm-head protein sp56 was postulated to bind to ZP3 and maintain fertilization (11,12). Moreover, zonadhesin was shown to mediate species-restricted binding to the ZP; however the counterpart molecule in the ZP has not yet been identified (13). Besides sp56 and zonadhesin, many other proteins also possess ZP binding activity (1-3). Hence, it appears likely that a multimeric zona recognition complex rather than a single sperm protein facilitates species-specific binding to the ZP (14).

Following chemosensation and ZP binding, the third level of sperm-oocyte interaction requires sperm to physically penetrate the μ m-thick ZP. During acrosome reaction, zona lytic enzymes are released, which are believed to digest the ZP locally and thereby allow sperm penetration. For a long time, the enzyme acrosin was believed to be the key player in this process. However, in light of the fact that acrosin knockout mice remain fertile, acrosin is dispensable for zona lysis in mice (15). Nevertheless, sperm of acrosin knockout mice display a selective disadvantage compared to normal sperm as fertilization is delayed, indicating that acrosin contributes to ZP lysis in mice (16). Besides enzymatic zona lysis, ZP penetration may also be achieved by mechanical force. In favour of this concept, capacitation renders sperm

to become hyperactive and acrosome reaction induces a morphological change of the sperm head, which together may facilitate ZP penetration even without enzymatic digestion of the ZP. Recently, a novel sperm penetration mechanism has been suggested in molluscs in which electrostatic repulsion of the egg coat protein VERL is achieved through its binding to the sperm protein lysin (17).

Having penetrated the ZP barrier and reached the perivitelline space, the interaction between the plasma membranes of the two gametes marks the next level of the sperm-oocyte interaction. A remarkable breakthrough was achieved when oocyte plasma membrane protein Juno was shown to directly interact with sperm plasma membrane protein Izumo1 (18,19). Strikingly, Juno-deficient oocytes as well as Izumo-deficient sperm display impaired sperm-oolemma binding (20,21). In addition, sperm plasma membrane proteins ADAM1, ADAM2 and ADAM3 (a Disintegrin and Metalloprotease) also known as fertilin α , fertilin β and cyritestin were discovered to be important for sperm-oolemma binding. Male mice deficient for either of these proteins displayed impaired sperm binding (22,23). Integrins were reported to serve as potential counterpart molecules for ADAMs (1-3) present in the plasma membrane of oocytes, but because conflicting results were obtained by different groups, the role of integrins in the sperm-oolemma binding process remains largely elusive (1).

Following sperm-oolemma binding, fusion between the two gamete plasma membranes marks the last step in the fertilization process. One of the first proteins that were shown to be important for gamete fusion was the membrane protein CD9 (24). CD9-deficient oocytes show normal sperm binding but impaired fusion and hence CD9 appears to be important, however not essential for fusion. Together with CD9, also tetraspanins CD81 and CD151 were reported to play complementary roles in sperm-egg fusion (2). Tetraspanins are well known to form extensive intermolecular interaction networks and hence it appears very likely that these molecules do not directly facilitate gamete fusion but are essential to form oolemma raft-like microdomain structures. In this way, fusogens can not only be enriched on either side but can also be brought into close spatial proximity to ultimately enable fusion between the two gametes. In addition to integral membrane proteins, GPI-anchored proteins were shown to be important for gamete fusion. Oocyte-specific disruption of the synthesis of GPI-anchored proteins was demonstrated to result in a phenotype similar to CD9-deficient mice (25). On the sperm side, the plasma membrane protein DE, also known as cysteine-rich secretory protein 1 (CRISP1), was shown to be important for gamete fusion. Crisp1-deficient male mice are fertile, but sperm of these mice showed impaired fusion (26). In addition, sperm proteins ADAMs are not only important for oocyte binding, but may also be essential for fusion (27).

In summary, the beginning of new life is a complex and highly regulated multi-step process involving several levels of oocyte-sperm interaction. Despite extensive research, we still face a lot of open questions. Therefore, improving our mechanistic understanding of fertilization could provide new opportunities to improve assisted fertilization, not only in human medicine, but for example also in stockbreeding or endangered species. Furthermore, additional discoveries could lead to novel explanations for so far idiopathic infertility.

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