

How does the sperm make its way to the egg and how does fertilization take place?

Capacitation, acrosome exocytosis, steps of sperm-egg interaction, egg activation

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Fertilization is a complex, multi-step process. This fascinating biological event actually begins with both sperm and eggs undergoing a series of preparatory steps to make fertilization possible (Fig. 1). At ovulation, the egg (or multiple eggs, depending on the species) leaves the ovary for the oviduct. Concurrently, the egg progresses through meiosis, known as "oocyte maturation" or "meiotic maturation," from prophase I, where it has been arrested since before birth, to an arrest in metaphase II in most species. Sperm are morphologically mature upon leaving the testis, but they must undergo several steps to acquire fertilization competence. During epididymal maturation (Chapter 10), sperm develop the ability to (1) be motile and (2) undergo capacitation (addressed below), largely via reorganization of the sperm surface, that is thought to be important for the sperm's fertilizing capability. Next, upon ejaculation, the sperm are mixed with seminal fluid, which includes buffering components that allow sperm survival in the acidic environment of the vagina. Seminal fluid can also include proteins that attach to the sperm and later will mediate sperm binding to the oviduct (see below).

In the female tract, sperm undergo capacitation, defined as the physiological changes that confer the ability to fertilize an egg. It is notable that the discovery of methods to support sperm capacitation *in vitro* is one of the advances that made *in vitro* fertilization possible. Capacitation-associated changes include the loss of cholesterol from the sperm plasma membrane, activation of a soluble adenylate cyclase in the sperm, generation of the second messenger cyclic AMP, and activation of a number of protein kinases. Capacitated sperm are also now capable of undergoing acrosome exocytosis (addressed below). In many mammalian species, capacitation is associated with a change in the sperm's swimming pattern to a non-progressive, whiplash motion, which characterizes hyperactivated motility.

Sperm can be stored in the female reproductive tract by interacting with epithelial cells that line the oviduct. In most mammals, including humans, sperm can survive in the female tract for up to several days. Possible functions of sperm storage in the female tract include prevention of polyspermy (fertilization of the egg by more than one sperm), maintenance of sperm fertility and viability, and regulation of capacitation and hyperactivated

motility. Eventually, sperm travel to the site of fertilization, the ampulla region or the ampullary-isthmic junction of the oviduct, depending on the species. The transit of the sperm up the oviduct could be mediated by different factors, including contraction of the female tract to push sperm upward, sperm motility propelling migration up the tract, and/or sperm motility possibly directed toward a follicular or egg chemoattractant.

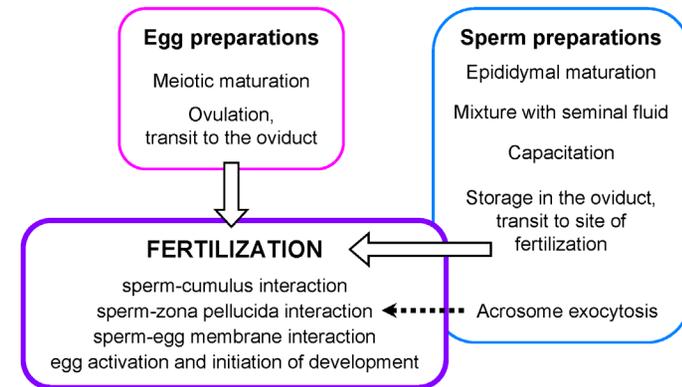


FIG. 1. Schematic diagram showing the steps discussed in this chapter, including the eggs preparatory steps (pink box), the sperm's preparatory steps (blue box), and the steps of fertilization itself (purple box). The dotted line indicates that acrosome exocytosis, the last step of the sperm's preparatory changes, occurs with sperm interaction with the egg's zona pellucida.

Fertilization itself occurs in several steps: (1) sperm-cumulus interactions, (2) sperm-zona pellucida interactions, (3) sperm-egg membrane interactions, and (4) egg activation and initiation of development (Figs. 1, 2). The ovulated egg is surrounded by cumulus (granulosa) cells embedded in an extracellular matrix made of hyaluronic acid. Sperm penetration through this matrix is mediated by the sperm's motile force and perhaps also facilitated by hyaluronidases on the sperm surface.

The sperm next interacts with the egg's coat, the zona pellucida (ZP), which is synthesized by the developing egg during oogenesis and is composed of three or four glycoproteins, depending on the species. The identity of the receptor on the sperm for the ZP has been debated for decades; it is likely not a single protein but a group of proteins. The ZP supports sperm binding in a species-selective manner and induces the sperm to undergo acrosome exocytosis. Also known as the acrosome

reaction, acrosome exocytosis is the liberation of the contents from the acrosome, the large secretory vesicle on the head of the sperm (Fig. 2). The release of these contents is accomplished by the formation of hundreds of fusion pores between the acrosome and the head plasma membrane. Acrosome exocytosis is linked with two critical changes in the sperm: 1) the acrosome releases enzymes to digest a hole in the ZP, and 2) upon completion of acrosome exocytosis, new surfaces of the sperm are exposed, which render the sperm capable of interacting with the egg plasma membrane. Thus, acrosome exocytosis is a necessary prerequisite for the next step of fertilization, gamete membrane interaction (see below). The signal triggering the sperm to undergo acrosome exocytosis is thought to be binding to a specific ZP component, although a recent hypothesis speculates that acrosome exocytosis in mouse sperm is induced by a mechanosensory signal as the sperm moves through the ZP matrix. Downstream from this initial trigger, calcium is a key second messenger that induces the sperm to undergo acrosome exocytosis.

Once the sperm has penetrated through the ZP, it reaches the egg plasma membrane. The interaction of the sperm with the egg plasma membrane is a multi-step process, beginning with adhesion of the sperm to the egg plasma membrane, bringing the membranes in close contact, and culminating in membrane fusion, which creates cytoplasmic continuity between the gametes (Fig. 2). The molecular basis of sperm-egg membrane interactions, like with sperm-ZP interactions, is not completely understood but this process likely involves multiple molecules. Upon formation of cytoplasmic continuity between the gametes, one of the intracellular components introduced into the egg from the sperm is a sperm-specific form of phospholipase C (PLC ζ). This PLC generates inositol triphosphate (IP₃) from phosphatidylinositol 4,5-bisphosphate (PIP₂). IP₃ in turn binds to IP₃ receptors on the egg's intracellular Ca²⁺ stores, the endoplasmic reticulum. This causes release of Ca²⁺ into the cytosol, activating several Ca²⁺-dependent enzymes. The activation of this signaling pathway induces the egg-to-embryo transition, also known as egg activation. The main events of egg activation are the establishment of blocks at the level of the ZP and/or the egg membrane to prevent polyspermic fertilization, the completion of meiosis (exit from metaphase II arrest) and progression to embryonic mitosis.

In sum, the sperm's mission to fertilize the egg and deliver the paternal genome to the future embryo involves a highly orchestrated series of steps that is initiated soon after leaving the testis and continues through the male and female reproductive tract, culminating with gamete fusion, egg activation, and merger of the maternal and paternal genomes.

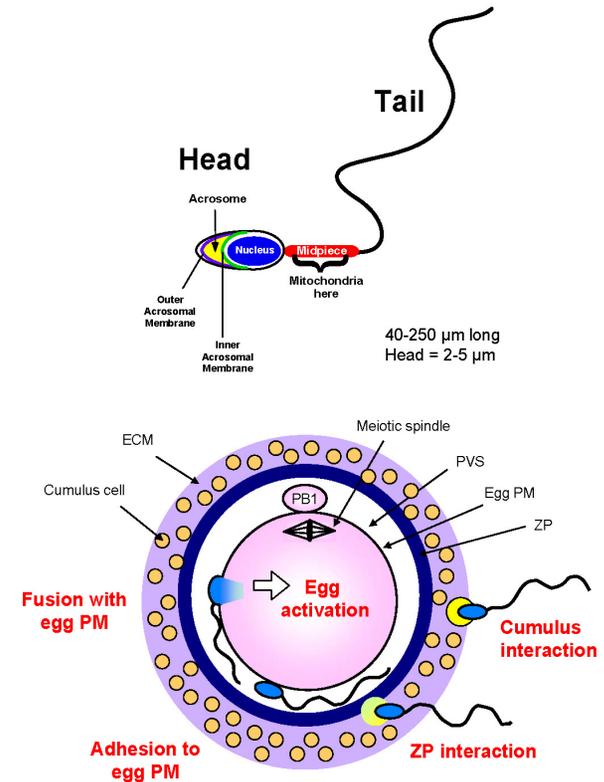


FIG. 2. *Upper panel:* Schematic diagram of a mammalian sperm, indicating the two main domains, the head and the tail. The flagellar tail contains microtubules, and includes the midpiece, which is where the mitochondria are located. The head includes the sperm chromatin in the nucleus (blue), and the acrosome (yellow). Acrosome exocytosis is achieved by the formation of fusion pores between the outer acrosomal membrane (purple) and plasma membrane (black). After acrosome exocytosis is complete, the inner acrosome membrane (green) is exposed on the surface of the sperm. *Lower panel:* Schematic diagram showing the structures of the mammalian egg (black text) and the steps of fertilization (red text). Abbreviations: ECM, extracellular matrix in which the cumulus cells are embedded; ZP, zona pellucida; PM, plasma membrane; PVS, perivitelline space, the space between the zona pellucida and the egg plasma membrane; PB1, first polar body, the product of cytokinesis resulting from the first meiotic division. The second meiotic division will not be completed until egg activation occurs.

Suggested reading

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