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CAPACITATION OF SPERMATOZOA

In the early 1950s, Austin and Chang independently described the changes that are required for the sperm to fertilize oocytes *in vivo*. These changes were originally grouped under name of "capacitation" and were the first step in the development of *in vitro* fertilization (IVF) in humans. After the ejaculation the sperm cells go through several essential physiological changes during their time in the female genital tract before they, at the end, are able to penetrate the oocyte membrane. It has to do with a physiological maturation process of the sperm cell membranes, which is seen as the precondition for the next step to follow, namely the acrosome reaction. Following these initial and fundamental findings, a remarkable number of observations led to characterization of the molecular steps behind this process. The discovery of certain sperm-specific molecules and the possibility to record ion currents through patch-clamp approaches helped to integrate the initial biochemical observation with the activity of ion channels. This is of particular importance in the male gamete due to the fact that sperm are transcriptionally inactive.

Capacitation is a functional maturation of the spermatozoon. The changes take place via the sperm cell membrane in which it may be that receptors are made available through the removal of a glycoprotein layer. The area of the acrosomal cap is also so altered thereby that the acrosome reaction becomes possible.

Through the membrane alterations, the motile properties of the spermatozoon also change. **Discharging whipping movements of the tail** together with largersideways **swinging movements of the head** take place. This type of motility is designated as hyperactivity. One can therefore say that the visible consequences of capacitation consist in hyperactivity of the spermatozoon. Since it cannot be determined ahead of time when the exact moment is that the oocyte and spermatozoon will meet, the **maturation mechanisms** are so configured that various groups of sperm cells are able to keep their chances of fertilization upright over a relatively long time after cohabitation. For this purpose the ejaculated sperm cells do not all end their capacitation at the same time, thus creating **heterogenous groups** of sperm cells.

The groups have differing histories in terms of their age and their storage conditions. Thus, in what concerns maturation/capacitation, they are not all on the same level. This makes it possible to keep fertilization-able sperm cells, since they mature in such a staggered sequence. One can imagine that at any given time **a small population of spermatozoa may have ended their capacitation** and are thus ready to fertilize an oocyte that has possibly made its way to the ampullary part of the uterine tube.

The most significant aspects are listed below:

a. Human sperm are highly pleomorphic in the sense that a large number of cells in the ejaculate display a great variety of morphological forms.

b. Humans deposit the ejaculate in the vagina.

c. Human sperm are selected in the cervix, where only morphologically normal or slightly abnormal sperm can migrate through this channel. A cohort of sperm immediately passes into the cervical mucus, whereas the remaining sperm population becomes a part of the coagulum. Then, a second round of selection occurs in the uterotubal junction (UTJ).

d. In general, the study of human sperm starts from a semen sample.

e. In humans, the semen is frequently manipulated to isolate the highly motile population of sperm.

f. *In vitro* incubation under capacitating conditions for human sperm ranges from 3 to 24 h. As a **result, a great variability of results is reported in the literature.**

g. The role of the uterus, the oviduct, and their secretions on human sperm capacitation is largely unknown due to practical and ethical limitations. A great number of molecules that are present in the female tract that have also been shown to modify sperm function are usually not included in the *in vitro* capacitation experiments. In addition, uterine contractions facilitate the sperm transport mechanism that is essential for migration within the female reproductive tract.

Sperm Plasma Membrane and Seminal Plasma Cholesterol

The sperm plasma membrane not only serves as the cell boundary but also presents a dynamic structure that has an impact on sperm capacitation. During capacitation, several changes in the sperm membrane have been described:

- Increase in membrane fluidity, lateral movement of cholesterol to the apical region of the sperm head, and cholesterol efflux from the sperm plasma membrane to the extracellular environment.
- The approximate lipid content of mammalian sperm is composed of 70% phospholipids, 25% neutral lipids (cholesterol), and 5% glycoproteins.
- Cholesterol being the main sterol in the cellular plasma membrane (~90%) .
- Desmosterol, a cholesterol precursor, and sulfate derivatives were reported (~10%).
- The cholesterol/phospholipid (C/PL) ratio in sperm varies between species 0.83 in human sperm.
- Davis reported a correlation between the C/PL ratio in sperm and the time required to complete capacitation when comparing different mammalian species: the higher the C/PL ratio, the longer the incubation period for capacitation to be achieved.
- Sperm cholesterol content is finely regulated within the male reproductive tract as the concentration of lipids in blood serum does not correlate with the seminal plasma levels . Cholesterol is found in high abundance in seminal plasma.

Cholesterol Efflux During Capacitation

It has been well demonstrated *in vitro* that capacitation is associated with removal of cholesterol from the plasma membrane. Albumin is the most used cholesterol acceptor in *in vitro* experiments, and it has been described to be in high abundance in the oviduct. The lipid transfer protein-I (LTP-I), a key protein in the human plasma metabolism of the high-density lipoprotein (HDL), is present in the reproductive fluids and it also serves as a cholesterol

acceptor. A capacitation-associated movement, due to cholesterol efflux, of GM1 has been observed during capacitation.

Calcium Requirements during Capacitation

Sperm functional changes that take place during capacitation depend on a combination of sequential and concomitant signaling processes, which includes complex signaling cascades where intracellular Ca^{2+} plays a central role. There are some reports where Ca^{2+} levels were measured and showed an increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) during mammalian sperm capacitation.