Molecular events involved in the acquisition of fertilizing ability in mammalian male gametes

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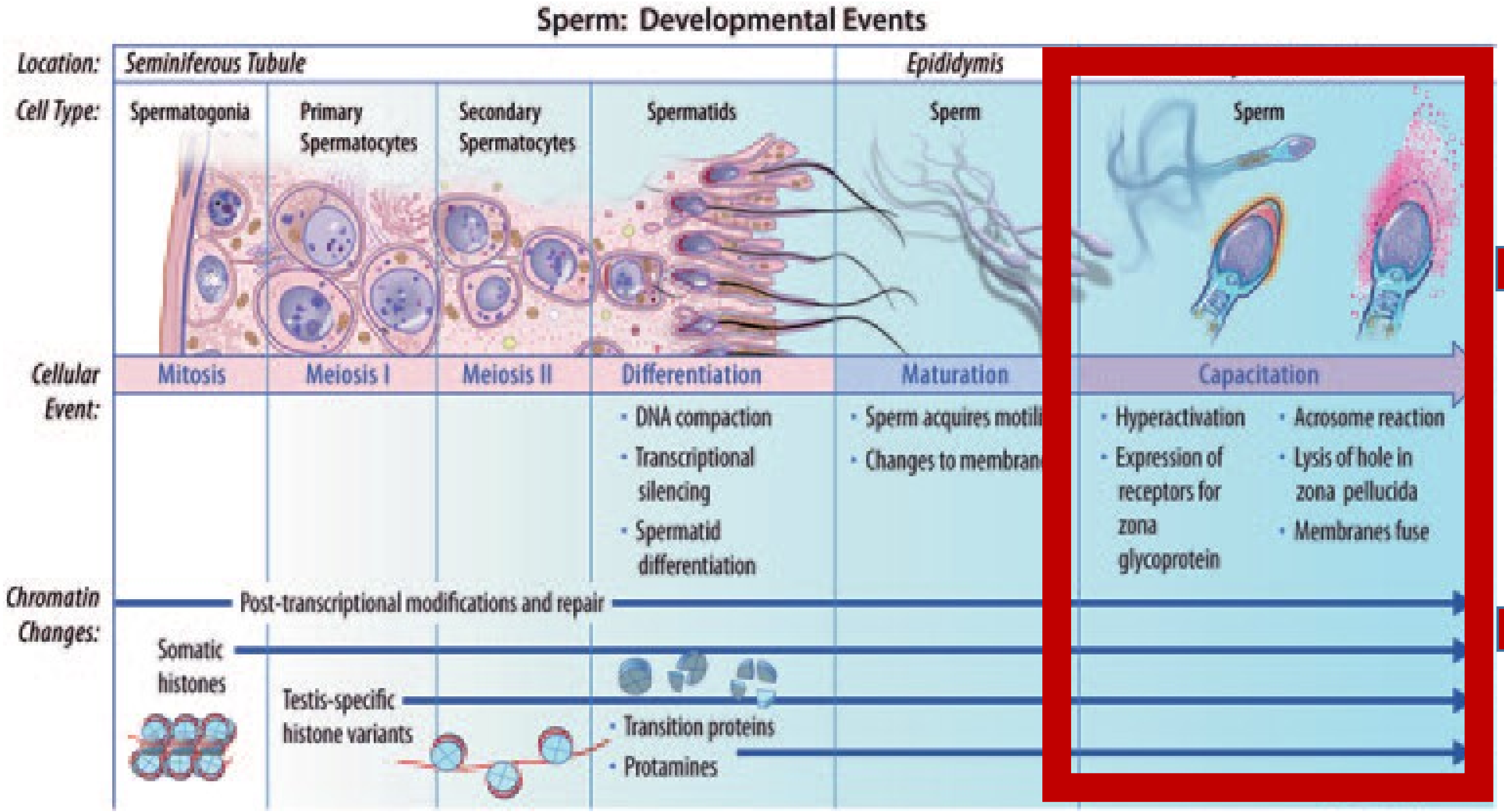
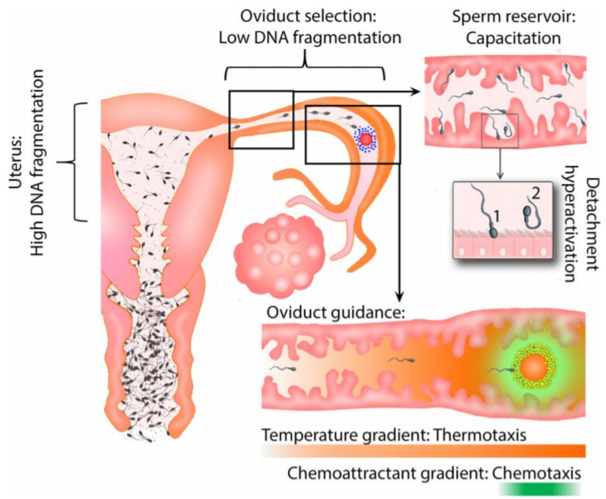
Mammalian spermatozoa maturation



Durairajanayagam et al. Sperm Biology from Production to Ejaculation. 2015

In Vivo



Perez-Cerezales S. et al. BOR, 2018, 98(3), 262–276

In Vitro

In Vitro Capacitation

- It is very different from in vivo capacitation
- It takes some hours
- It involves a low percentage of sperm cells
- It is a discontinous (and reversible?) process
- It is driven by the balance of activating and inhibiting factors
- It makes the spermatozoa prone to biochemical damages (epigentic risk)

Possible implemenatations:

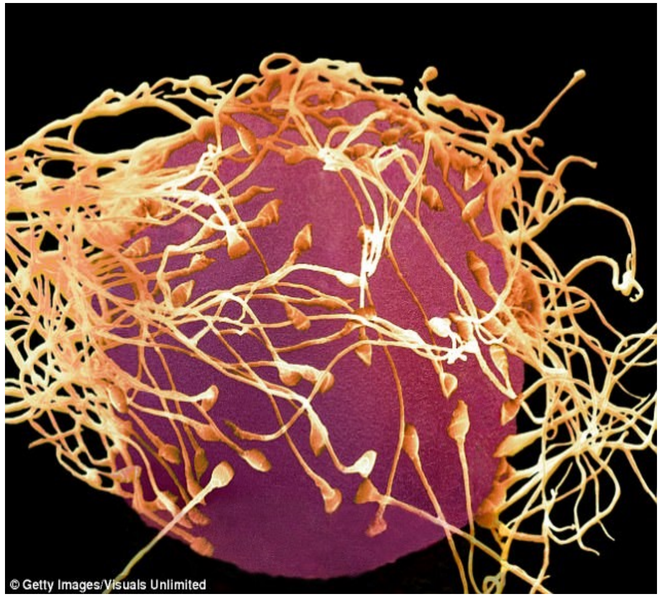
More physiological systems
Biomaterials

Capacitation

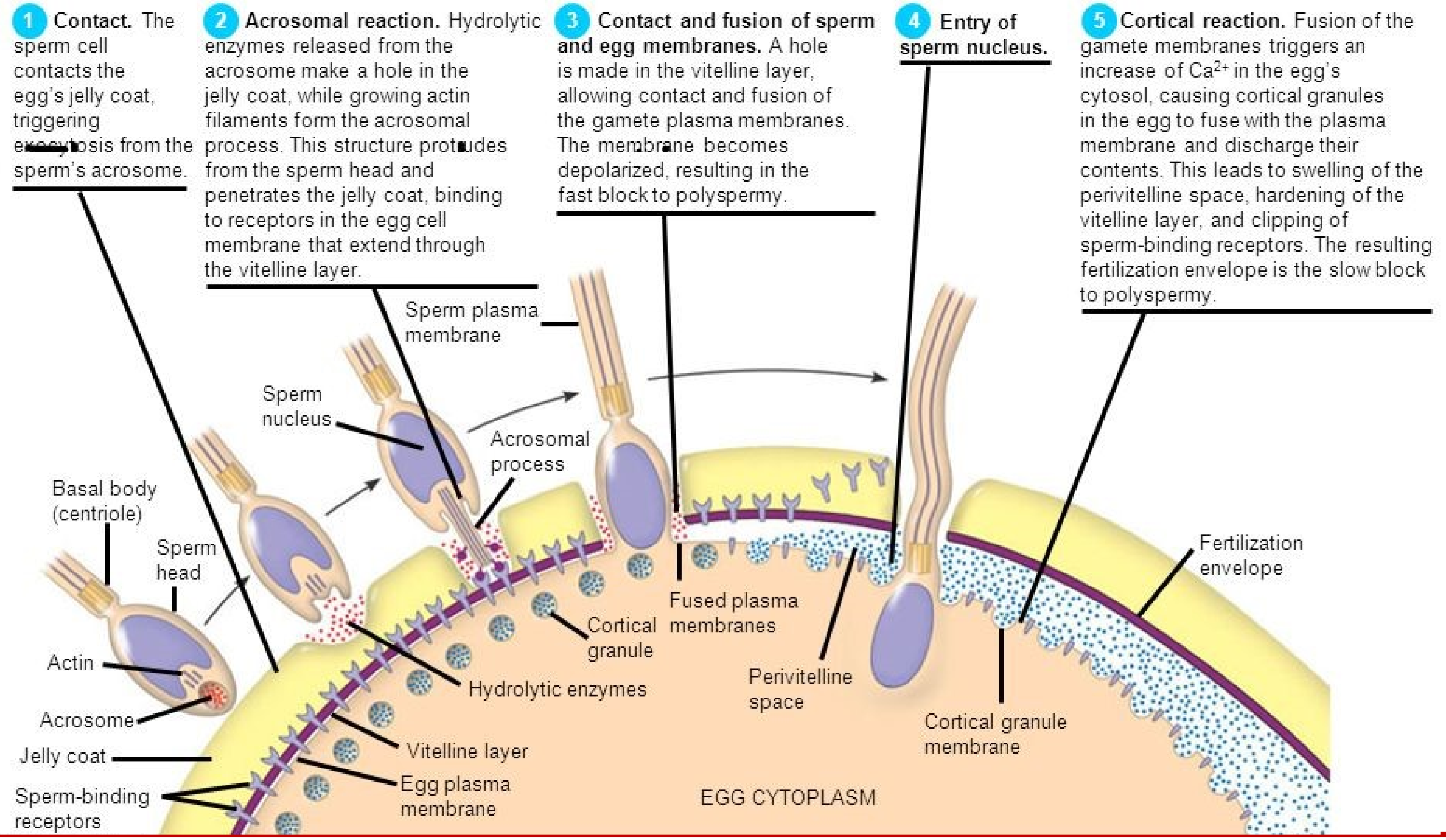
Sperm membrane remodelling

Cytoskeleton reorganization

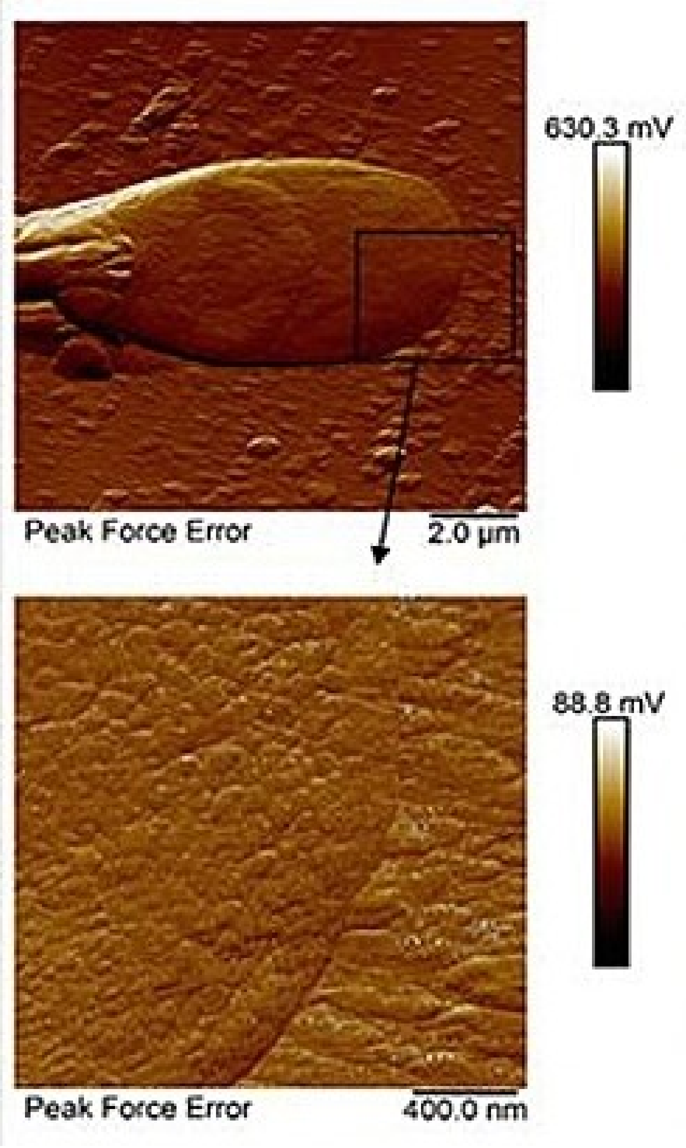
Cytosolic signaling

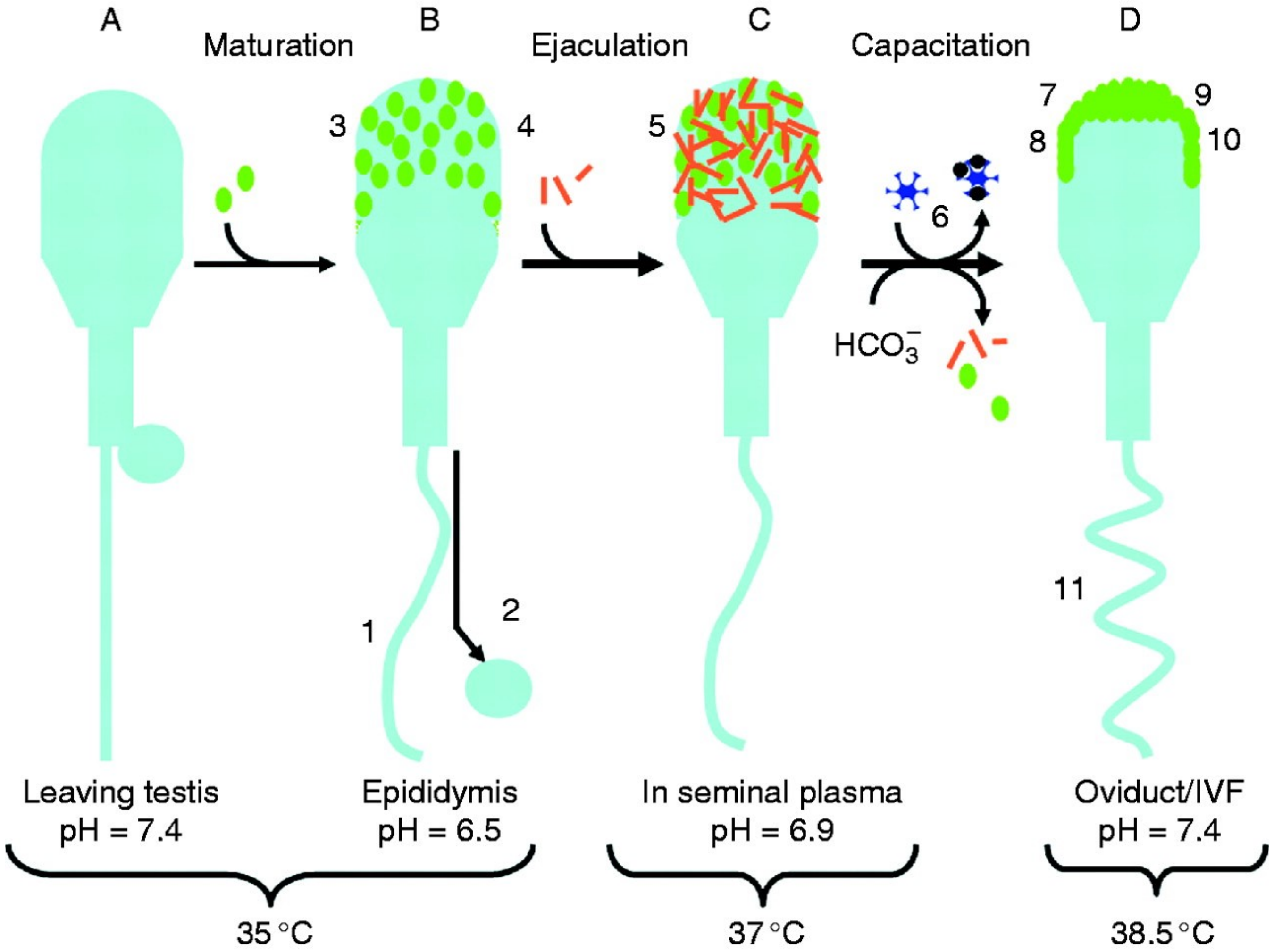


Capacitation, Acrosome Reaction and Fertilization



Sperm head domains





Bernabò et al., Carbon Volume 129, April 2018, Pages 428-437.

Leahy and Gadella, Reproduction (2011) 142 759–778.

Cholesterol and mebrane remodelling

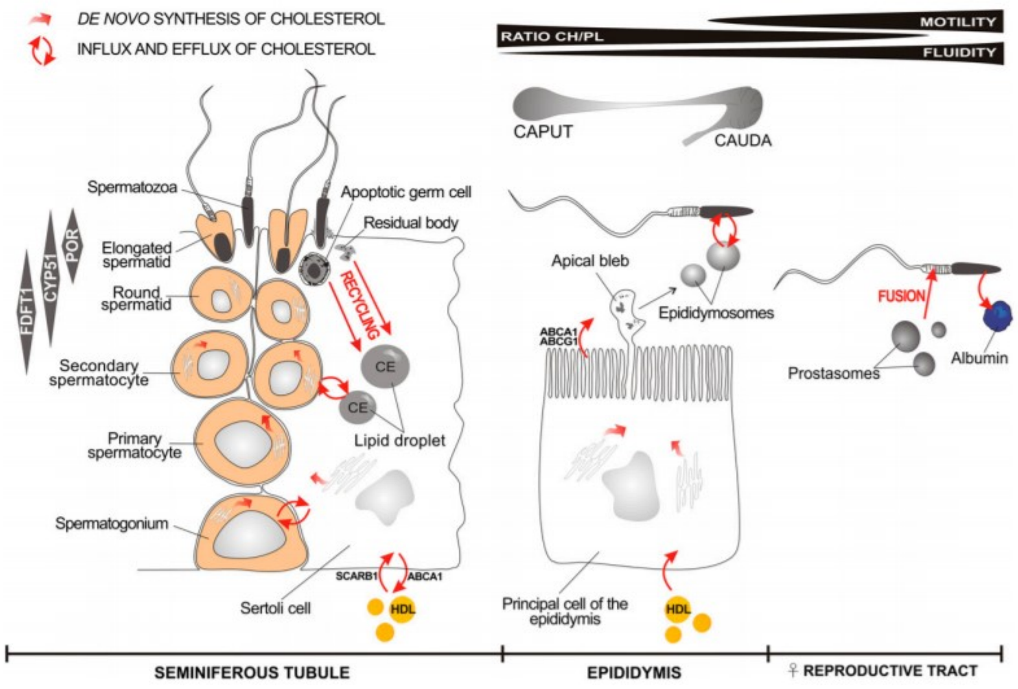
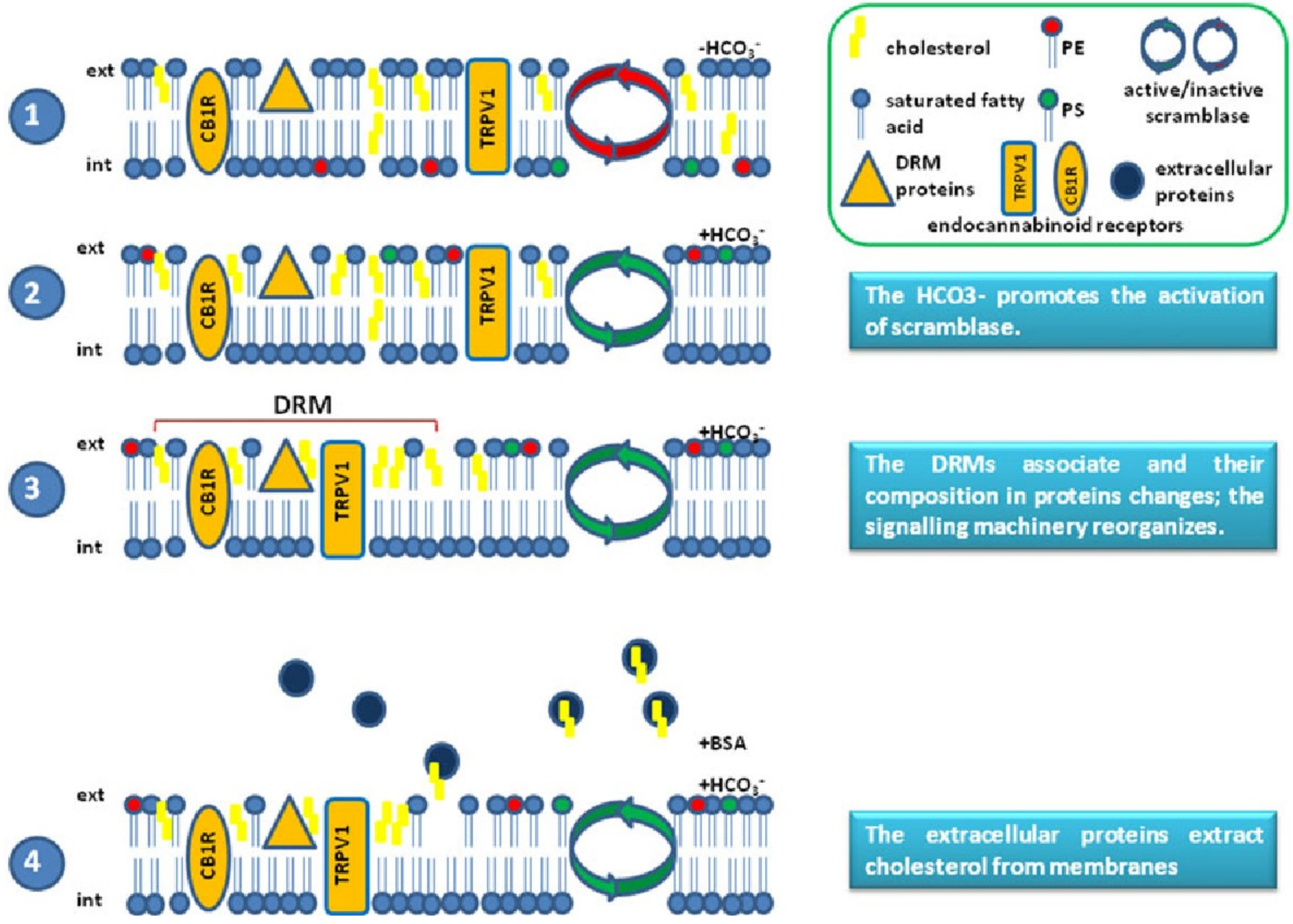


Fig. 2. Schematic representation of major cholesterol synthesis and trafficking sites during sperm maturation. A limited quantity of cholesterol required to synthesize new plasma membranes during spermatogenesis in seminiferous tubules originates from de novo synthesis in spermatocytes (34). The stage-specific expression of cholesterogenic enzymes farnesyl diphosphate farnesyl transferase 1 (FDFT1), CYP51, and POR during spermatogenesis is displayed in gray boxes (left) (24). Supporting Sertoli cells provide an additional source of cholesterol for spermatogenesis. Sertoli cells acquire cholesterol by de novo synthesis from acetate (35) or import external cholesterol from HDL (37) by specialized cholesterol transporters (36). Another important source of cholesterol in Sertoli cells might be from the recycling of lipid-rich residual bodies and apoptotic germ cells (39). Excess cholesterol can be esterified to cholesterol esters (CE) and stored in lipid droplets, serving as cholesterol reservoirs (40). Some cholesterol can be effluxed to HDL by reverse cholesterol transport (41). Spermatozoa formed in the testis enter the caput epididymis and progress to the caudal region. The epididymis possesses the ability for de novo cholesterol synthesis (51), or it can import cholesterol from the circulation (59). Cholesterol might be effluxed into the epididymal lumen by ABCA1 and ATP-binding cassette sub-family G member 1 (ABCG1) (53). The principal cells of the epididymis secrete small membranous vesicles known as epididymosomes, which could serve as a source for cholesterol exchange with maturing sperm cells (128). The cholesterol content of sperm membranes is decreased during epididymal transit in several species, resulting in the decreased ratio of cholesterol (CH) to phospholipids (PL) (48). The loss of cholesterol results in an increase in sperm membrane fluidity and sperm motility (71). The content of cholesterol in the sperm membrane is further decreased in the female reproductive tract, mostly by the process of capacitation. Albumin serves as a cholesterol acceptor during capacitation. Prostasomes present in the ejaculate are able to fuse with the membranes of spermatozoa, to increase motility, and to prevent early acrosome reaction (73). Individual data were obtained from in vitro and in vivo experiments on different mammalian species and used to collate this scheme.

Keber et al.,Journal of Lipid Research Volume 54, 2013

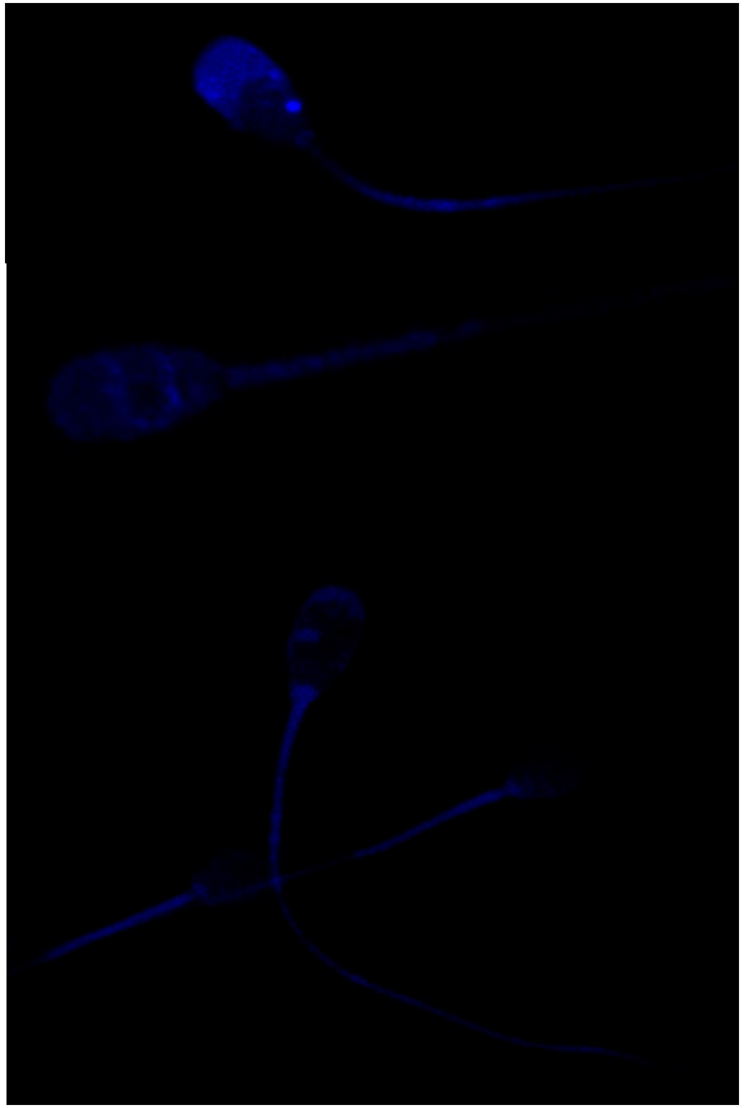
Bicarbonate and DRMs



The HCO3- promotes the activation of scramblase.

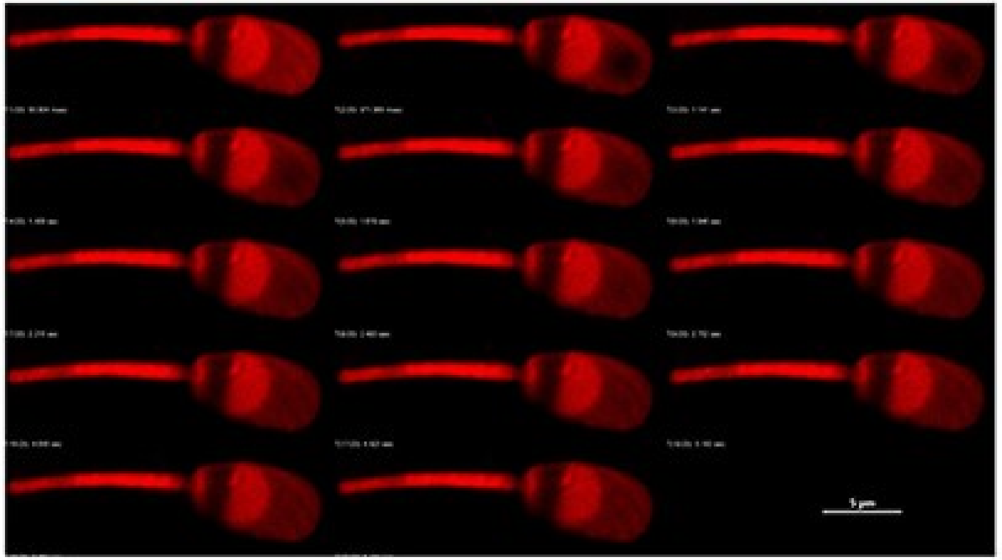
The DRMs associate and their composition in proteins changes; the signalling machinery reorganizes.

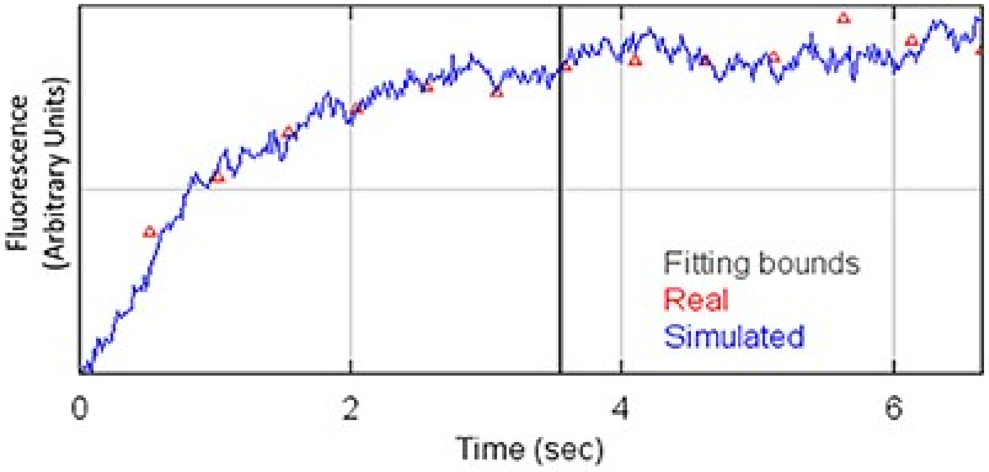
The extracellular proteins extract cholesterol from membranes



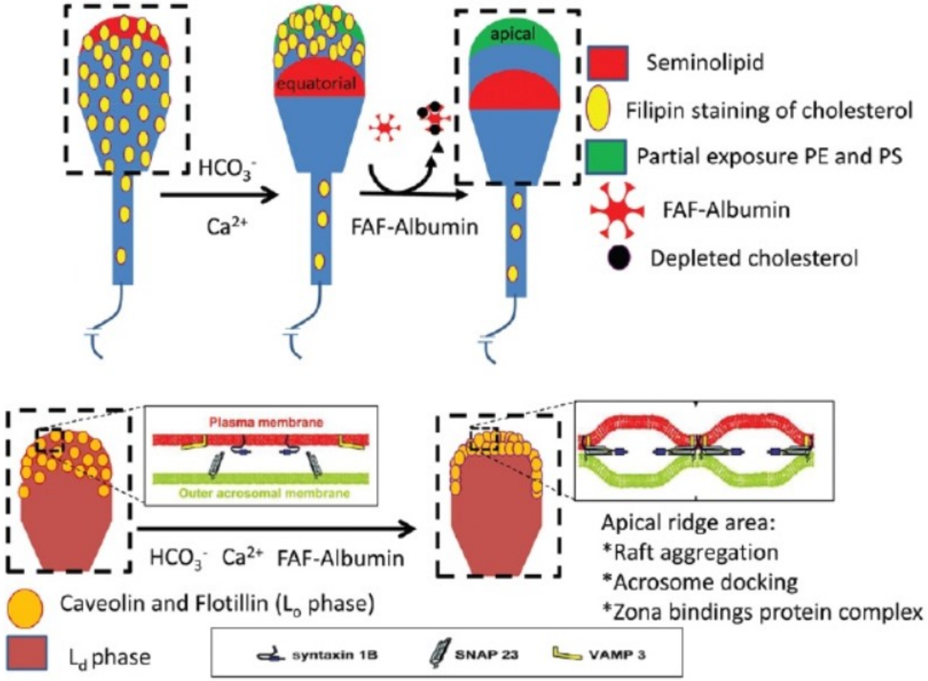
Botto et al., Journal of Membrane Biology 2010 238(1-3), 33-41.

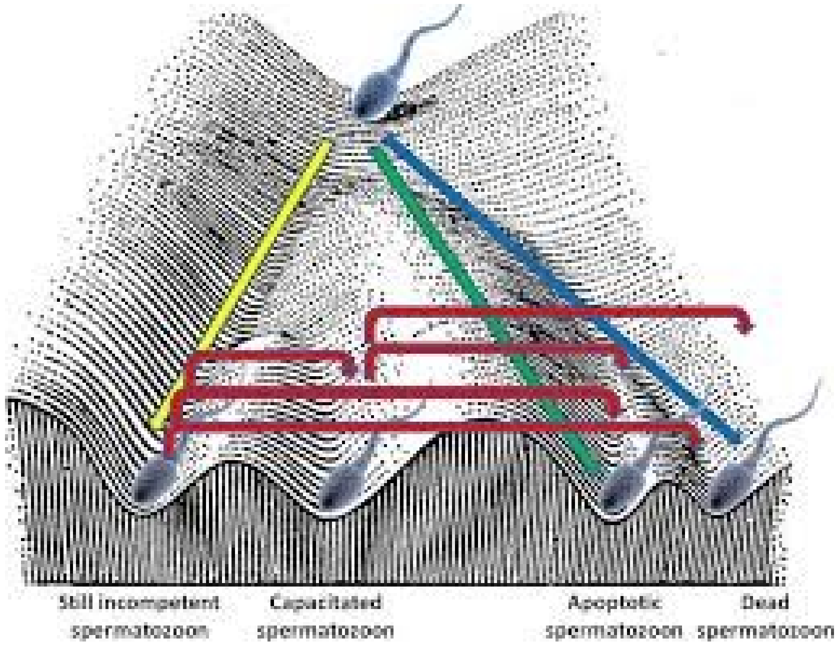
Membrane fluidity





Membrane fusogenicity and sperm fate

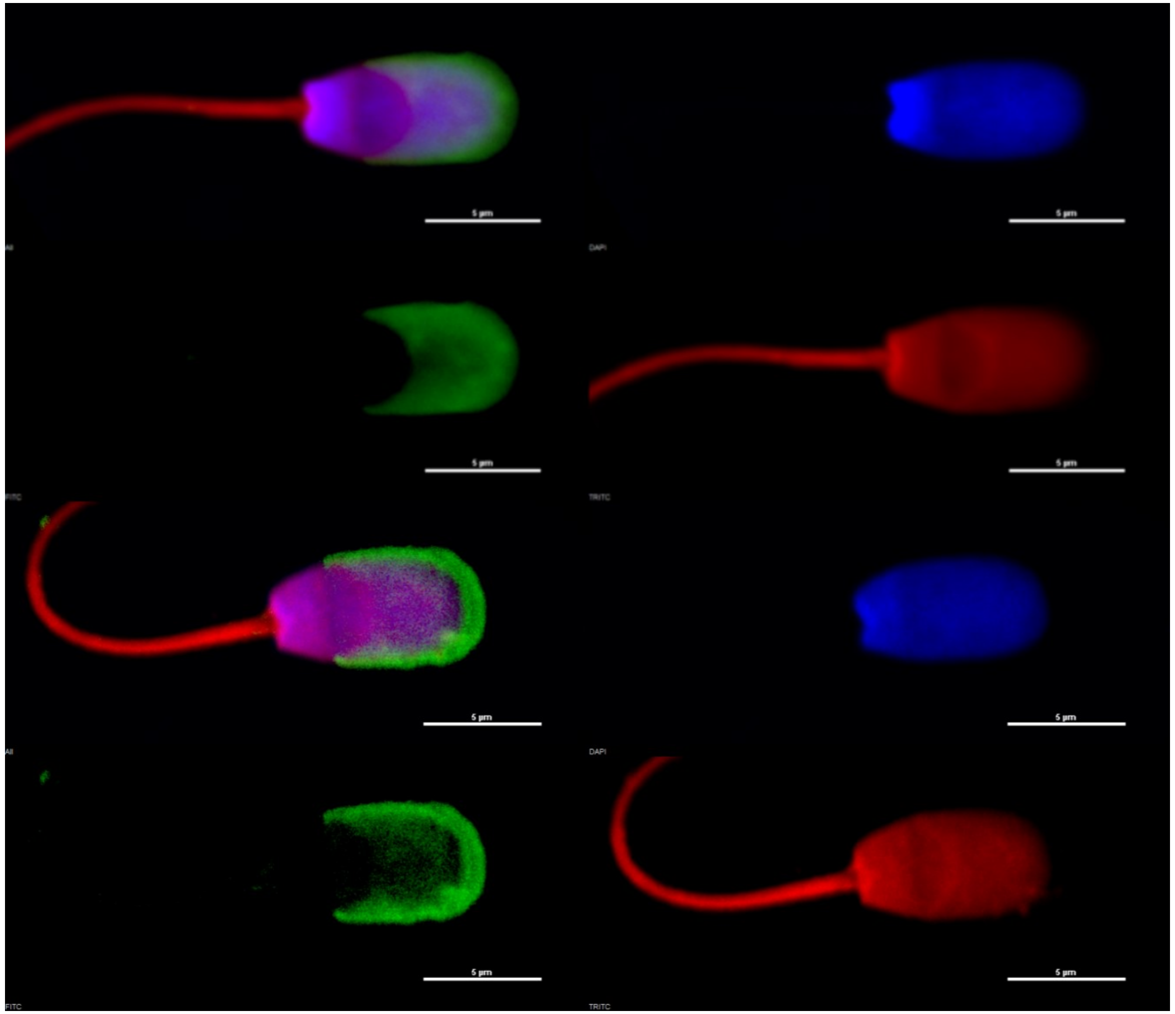


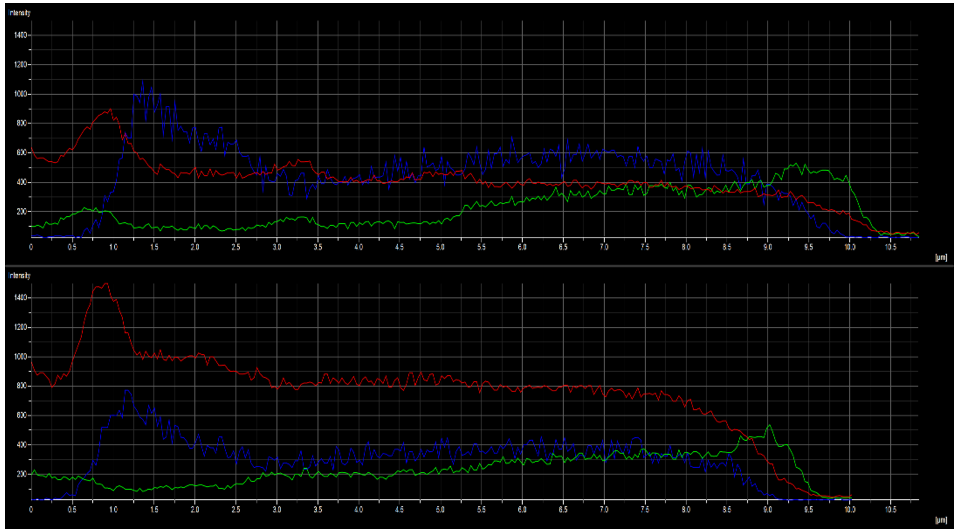


Leahy and Gadella, Reproduction (2011) 142 759–778.

Bernabò et al., OMICS: A Journal of Integrative Biology Vol. 19, No. 11 2015

Cytosckeleton reorganization





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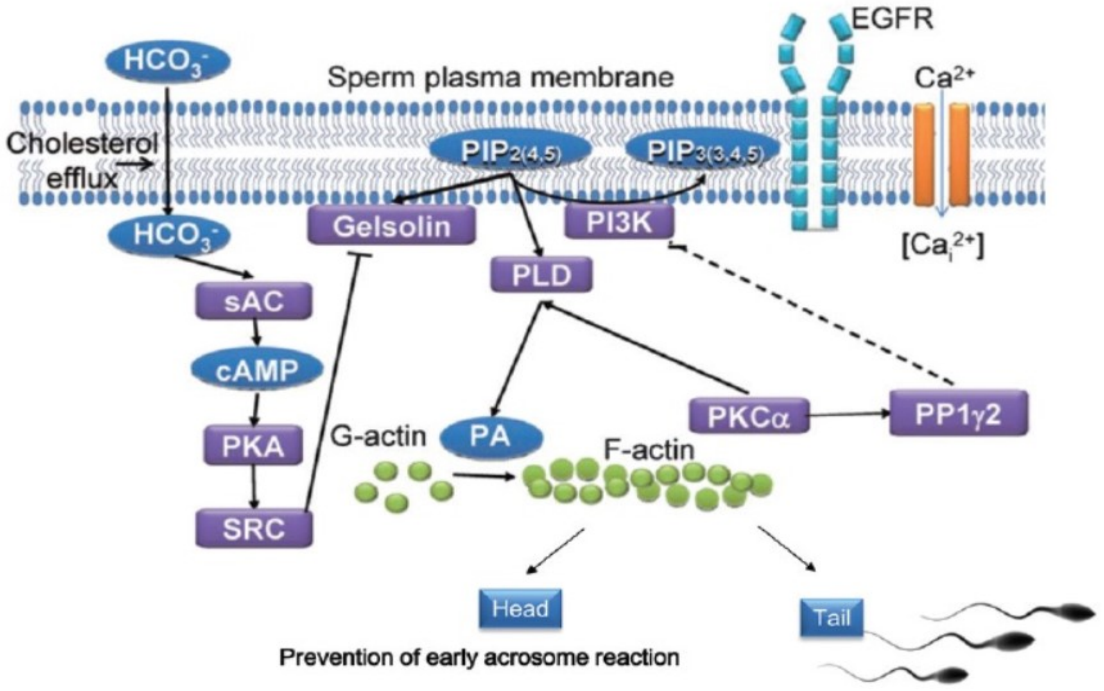
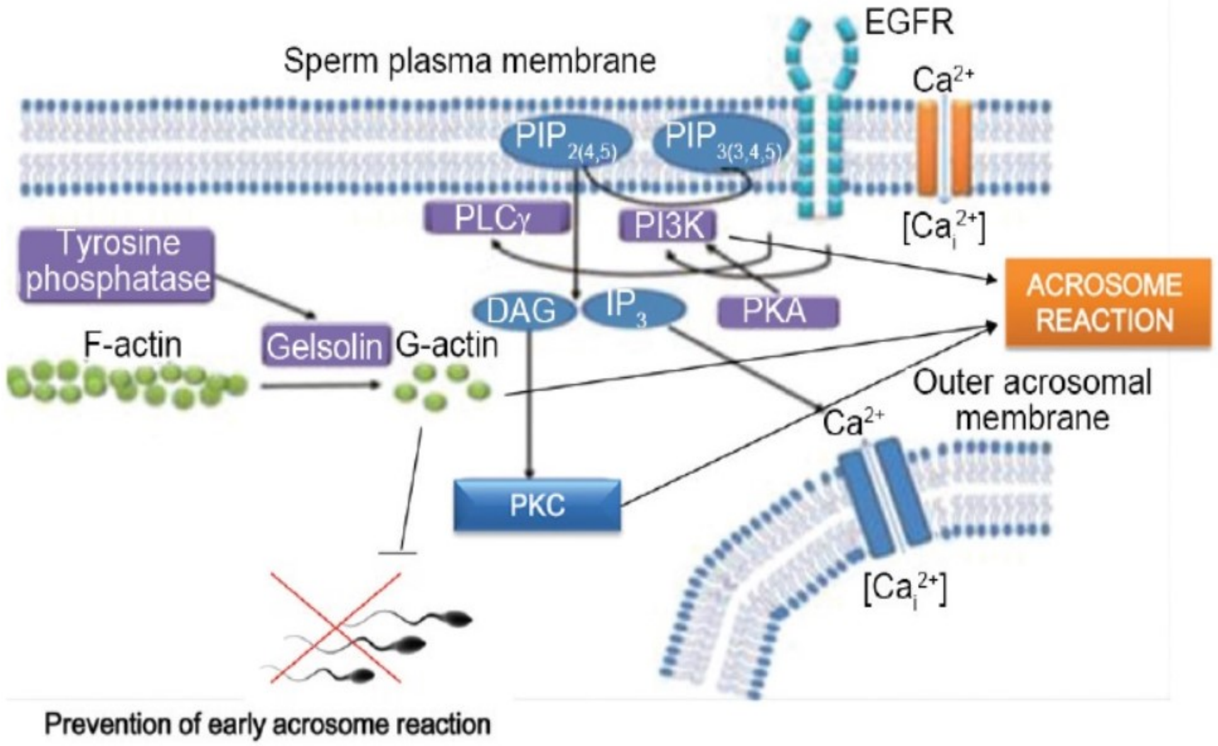
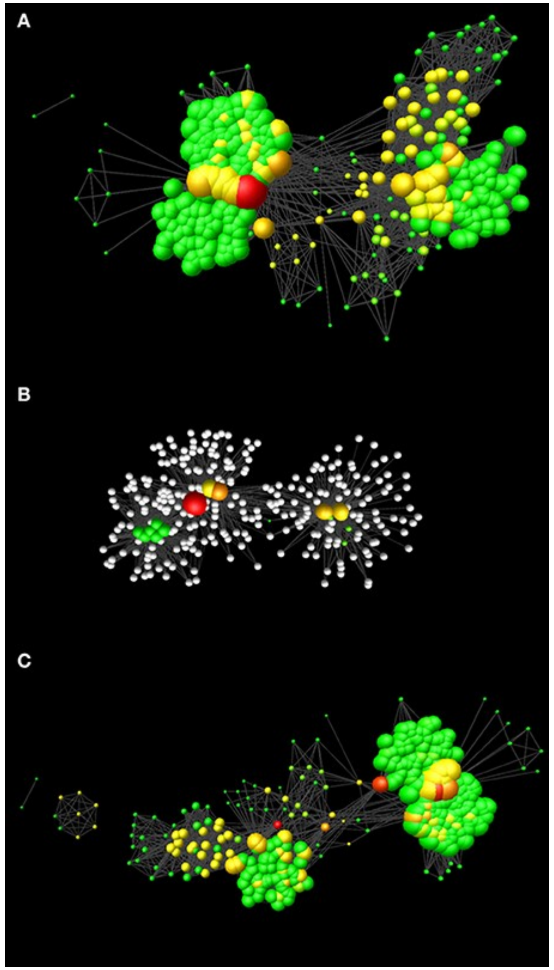
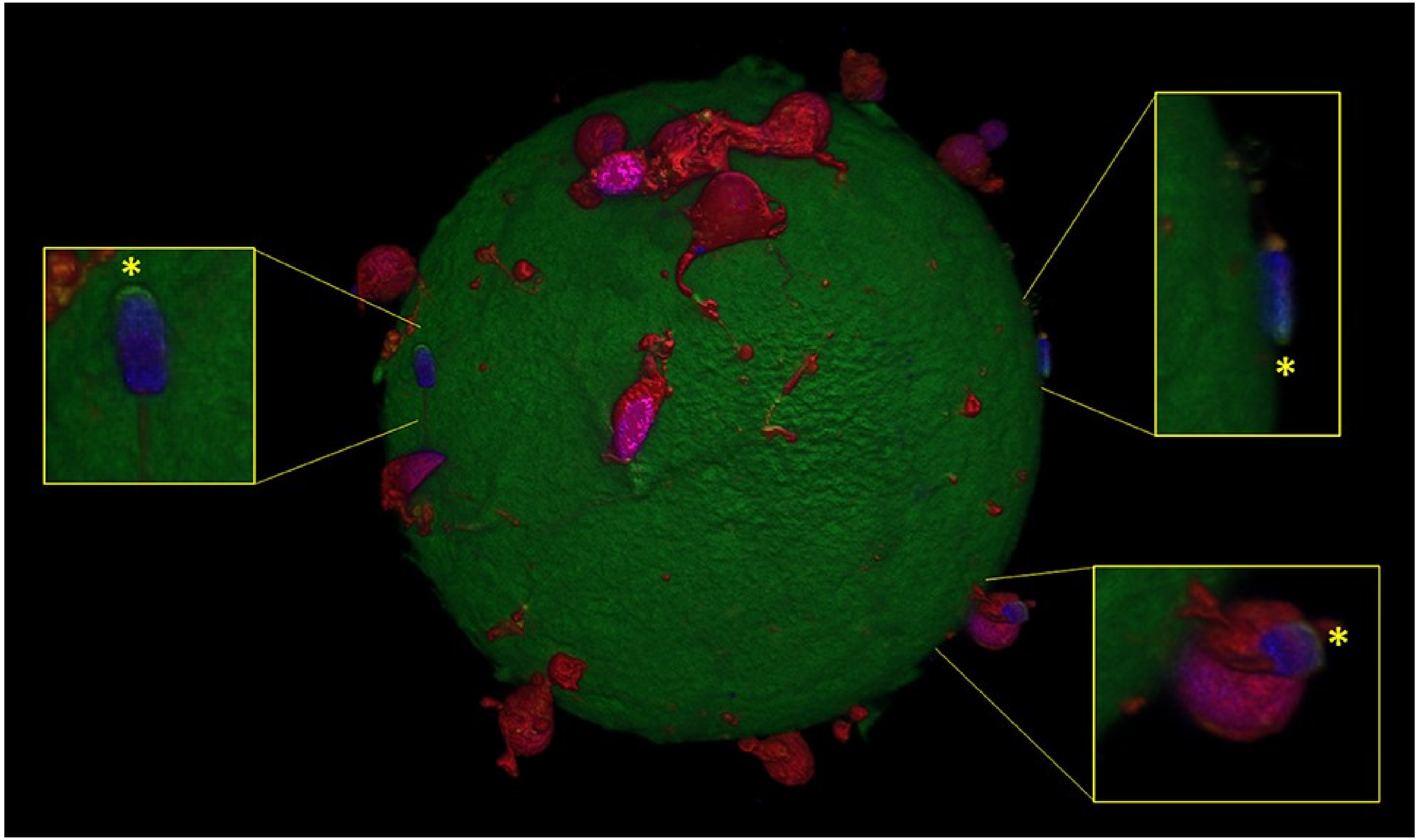




Breitbart H, Finkelstein M. Asian J Androl 2015;17:597-600

A new model





Bernabò et al., Front. Physiol. (2018) 8:1097.

Intracellular signalling

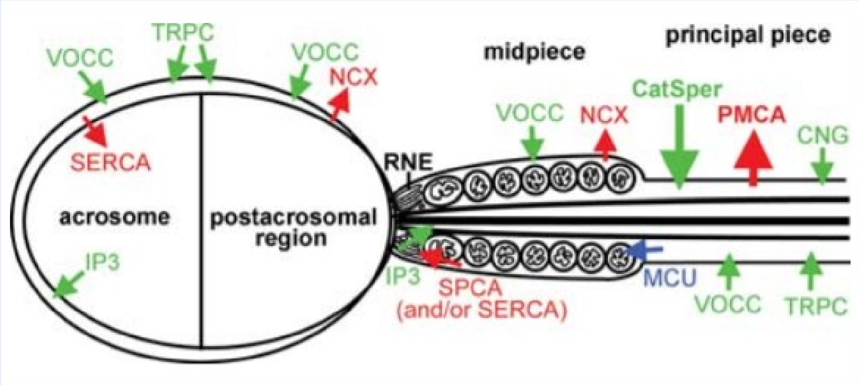
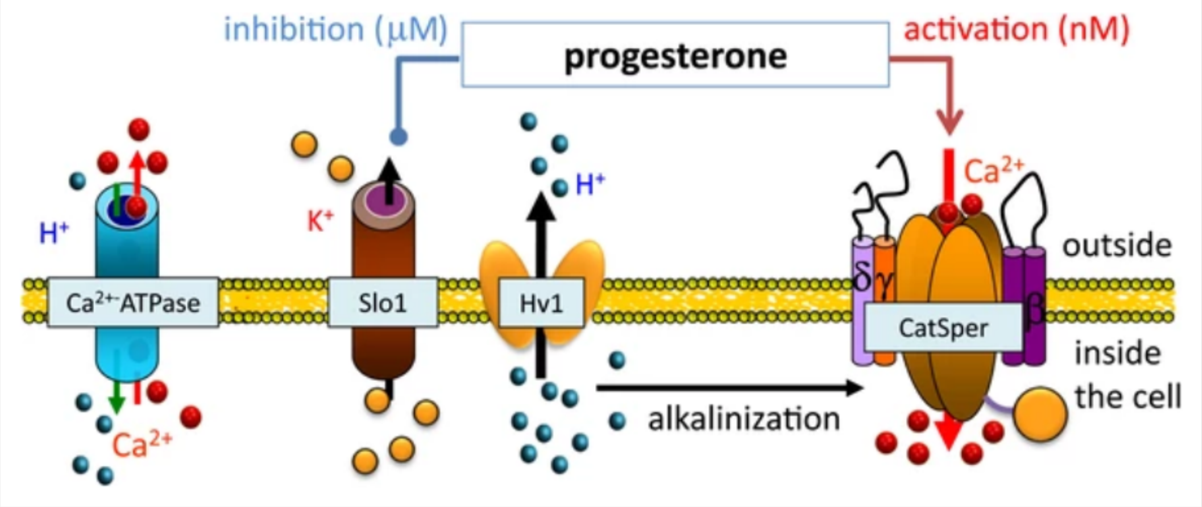


Figure 1 Ca^{2+} channels and pumps that have been immunolocalized in mammalian sperm. Arrows indicate the most common direction of Ca^{2+} movement caused by these entities in most cell types. The chief channels and pumps involved in hyperactivation are CatSper channels and PMCA, which are indicated by large arrows. Others that have been identified include the following: sarcoplasmic/endoplasmic reticular Ca^{2+} ATPase (SERCA), IP_3-gated channels (IP3); voltage-operated Ca^{2+}channels (VOCC), TRPC Ca^{2+} channels, secretory pathway Ca^{2+} ATPase (SPCA), NCX, mitochondrial uniporter (MCU) and CNG Ca^{2+} channels.

Olson et al., Molecular Human Reproduction, Vol.17, No.8 pp. 500–510, 2011

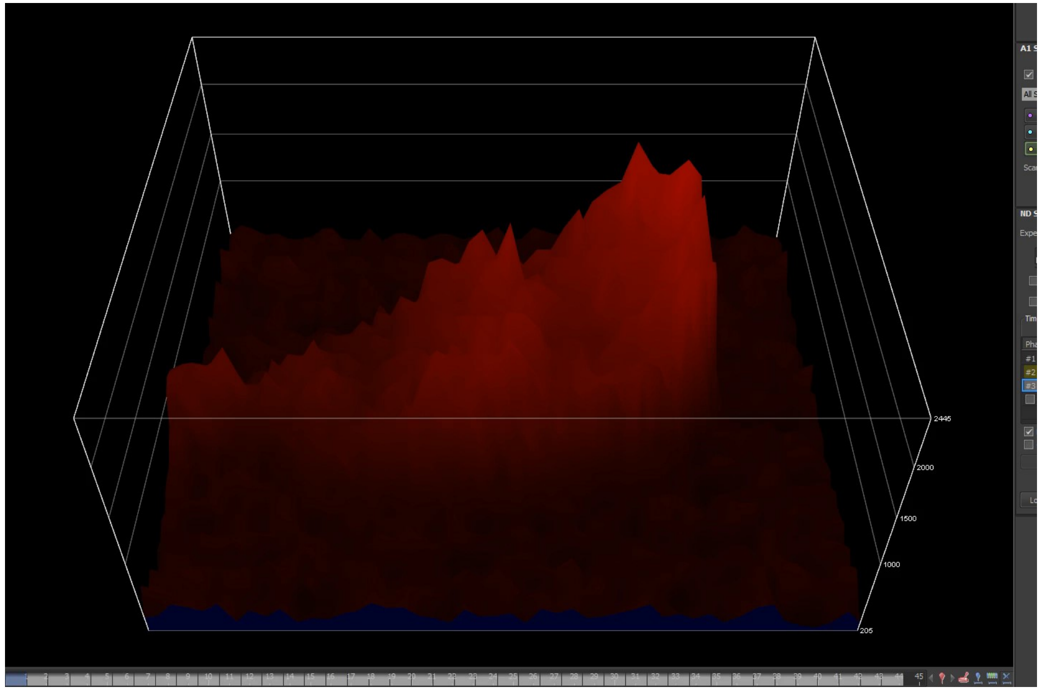


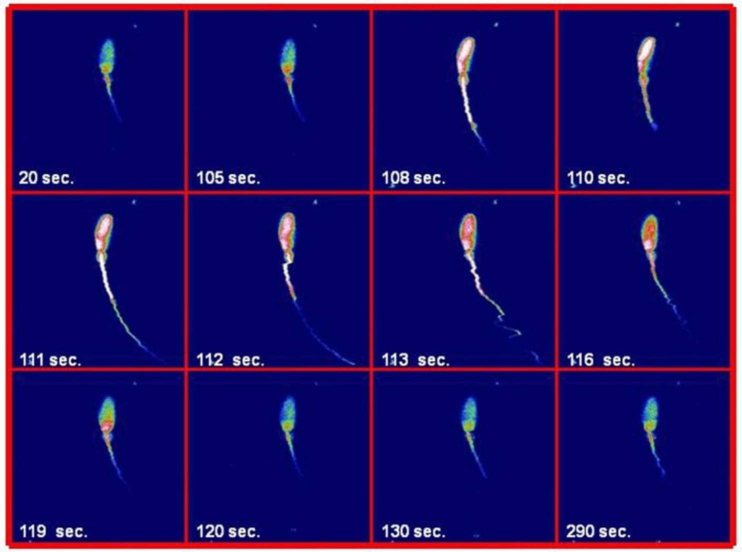
Ion channels work together to ensure that sperm cells are hyperactivated.

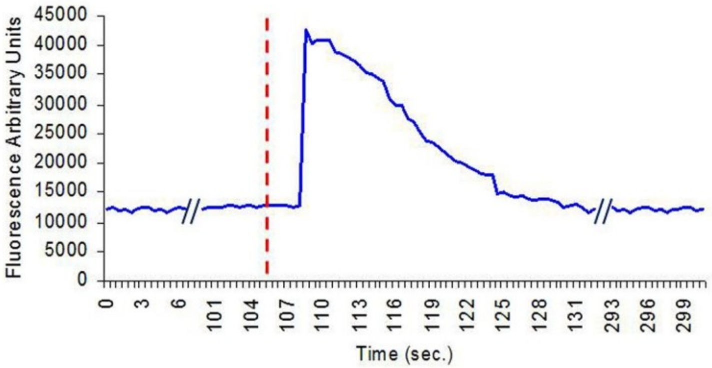
Sperm cells contain a variety of ion channels that control the movement of ions and protons (H^+) into and out of the cell (Mannowetz et al., 2013). As a sperm cell moves up the fallopian tube, the CatSper ion channel (right), which controls the movement of calcium ions (Ca^{2+}), is partially activated as a result of alkalinization inside the cell (caused by protons leaving through the Hv1 ion channel) and low levels of progesterone outside the cell. As the sperm gets closer to the egg, the increased levels of progesterone inhibit the Slo1 ion channel, causing potassium ions (K^+) to leave the cell. This hyperpolarizes the cell membrane and leads to full activation of the CatSper ion channel. The resulting influx of large numbers of calcium ions leads to hyperactivation of the sperm—the vigorous tail thrashing motion that is a prerequisite of fertilization. Protons and calcium ion can also move through the Ca2+ ATPase transporter (left).

https://elifesciences.org/articles/01469/figures

Acrosome reaction

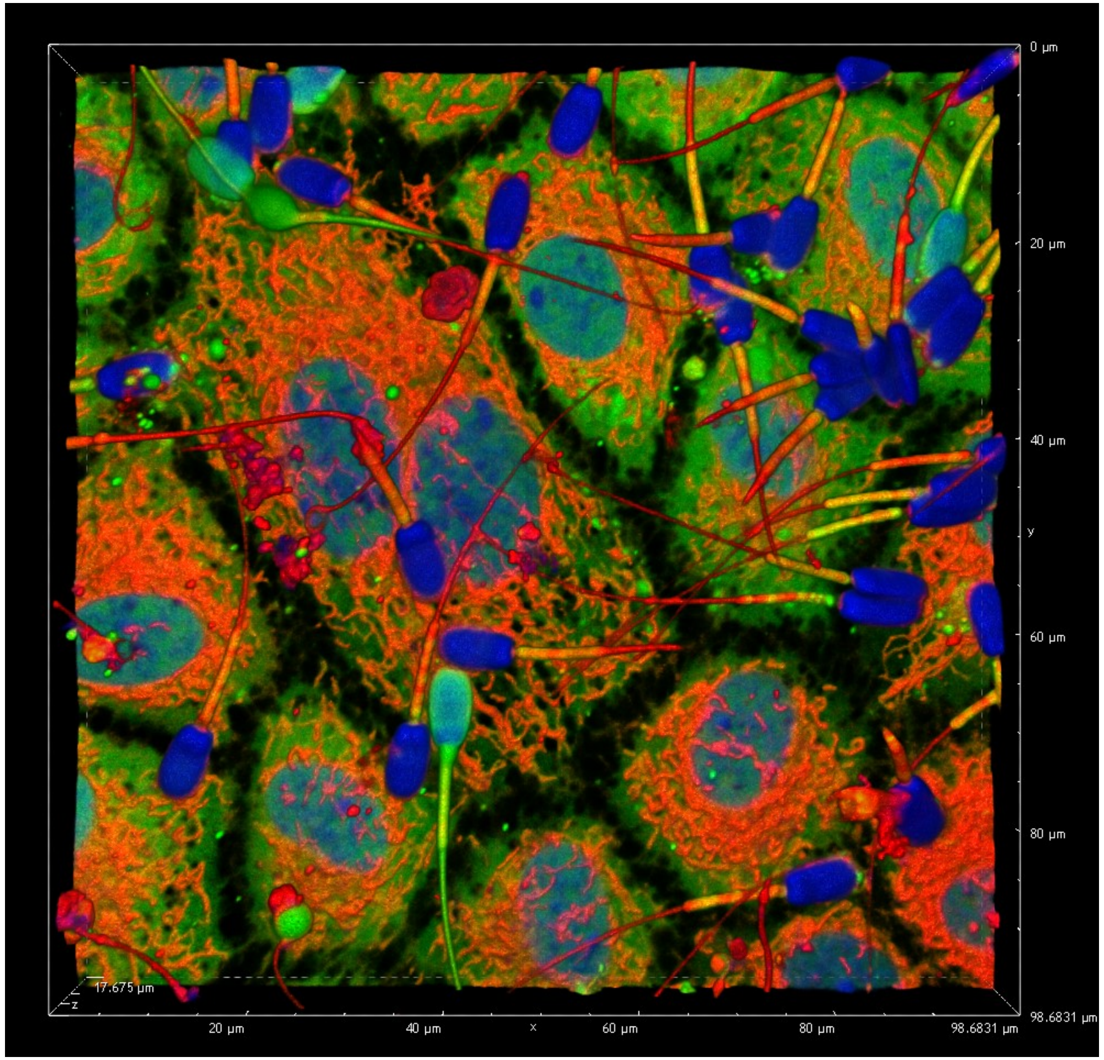


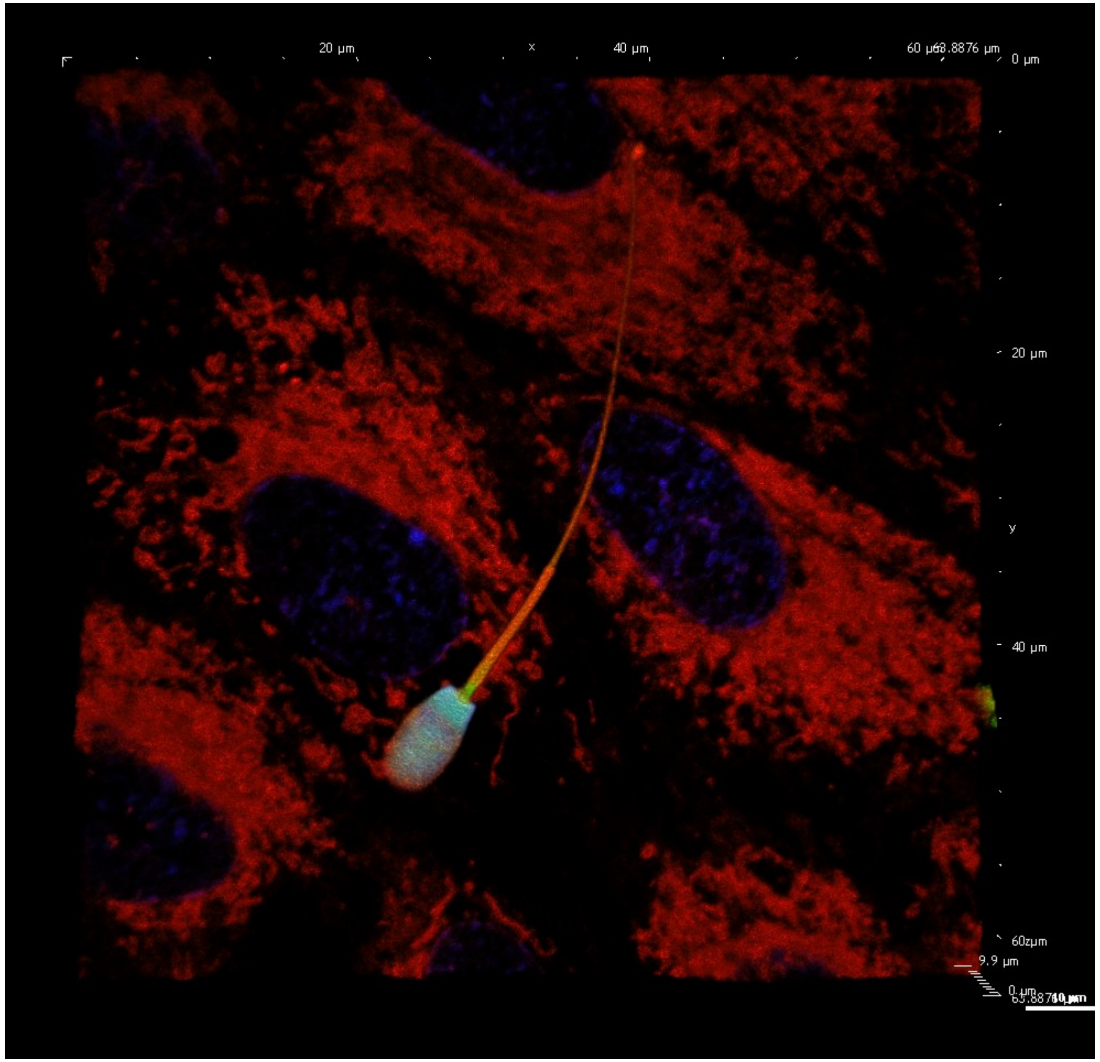




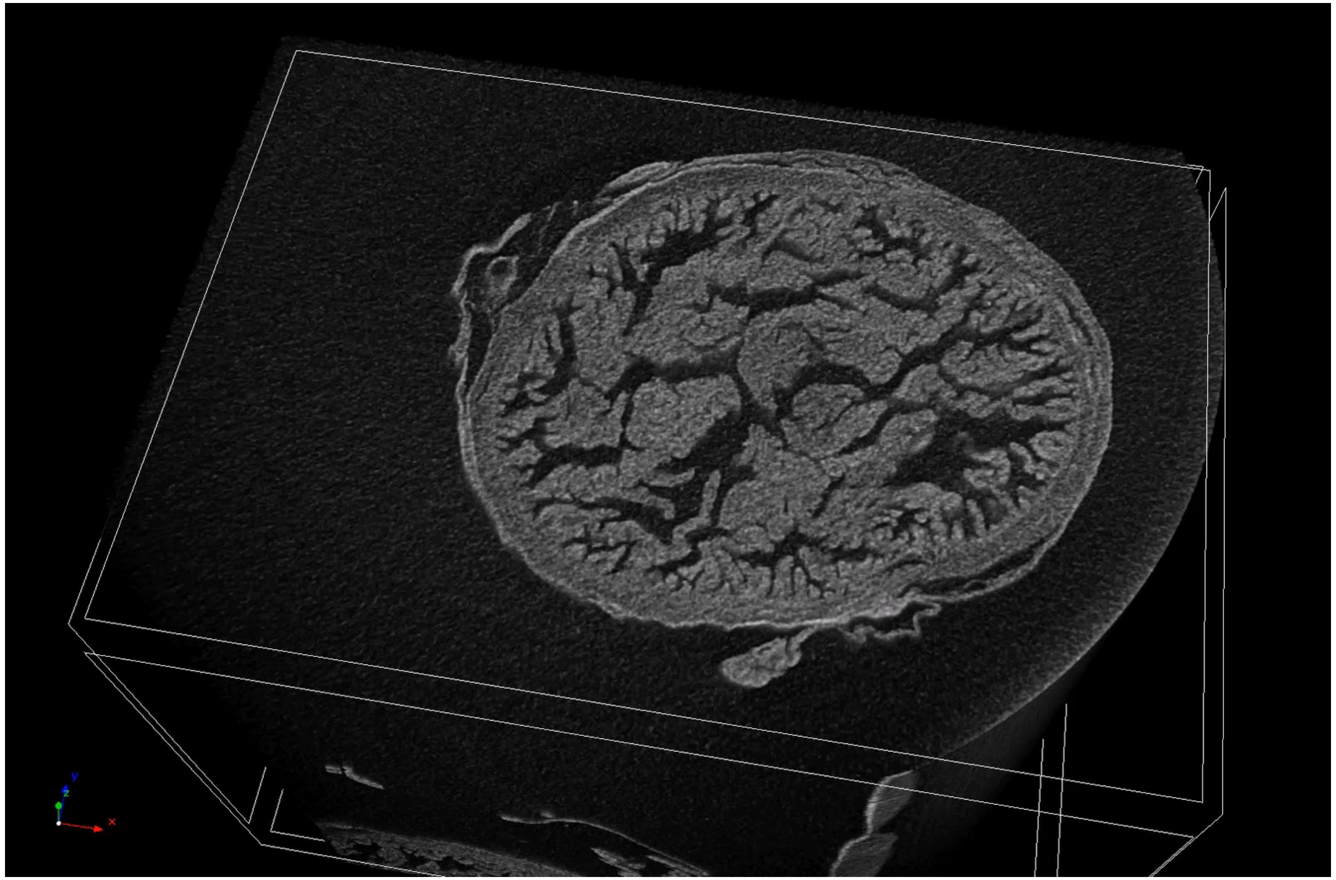
*Bernabò et al., BMC Systems Biology*20115:47

IVF on Oviductal Cells Monolayers





IVF on 3D scaffolds

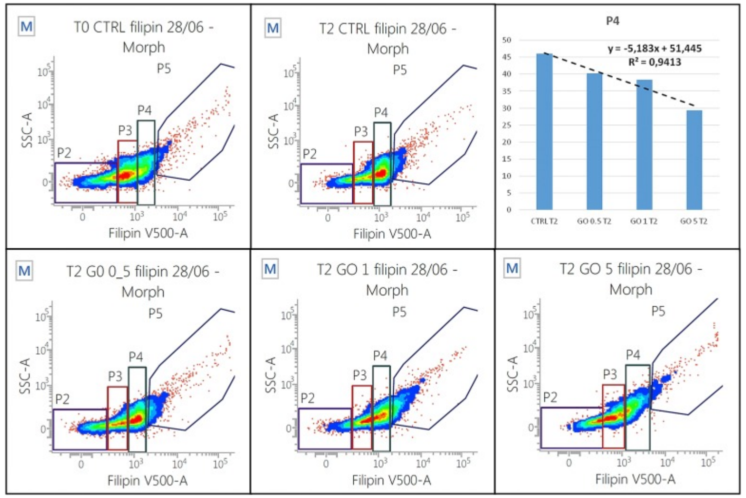


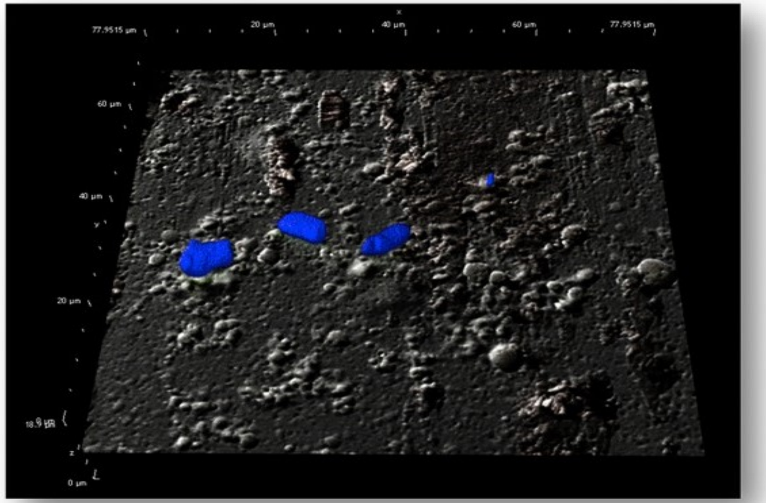
Biomaterials: Graphene Oxide

Table 2. Effect of different GO concentration on IVF outcome.

	CTRL	GO 0.5 µg/mL	GO 1 µg/mL	GO 5 µg/mL
Fertilized oocytes (%)	56.6 ± 4.5[a]	72.2 ± 3.7[b]	87.9 ± 13.7[c]	28.3 ± 15.6[d]
Polyspermic oocytes (% on fertilized oocytes)	64.3 ± 13.6	72.4 ± 6.8	60.1 ± 5.3	75.9 ± 22.1
N° of spermatozoa per polyspermic oocyte	4.1 ± 0.0	3.5 ± 0.4	3.5 ± 0.5	3.3 ± 0.3

Different superscript denote statistically different groups of data (p<.05).





Bernabò et al., Carbon Volume 129, April 2018, Pages 428-437.

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Thank You!