Spring 2018 – Systems Biology of Reproduction
Lecture Outline – Fertilization & Implantation Systems
Michael K. Skinner – Biol 475/575
CUE 418, 10:35-11:50 am, Tuesday & Thursday
April 10, 2018
Week 14

Fertilization & Implantation Systems

Fertilization –
- Sperm and female reproductive tract
- Attraction, hyperactivation, binding, acrosome reaction
- Penetration, sperm-egg fusion
- PLC and calcium mobilization
- Fertilization and embryo induction

Implantation –
- Embryo development and fallopian tube
- Endocrine induction of uterine development
- Uterine cell biology, vascularization and maturation
- Proliferative and secretory stage
- Blastula and endometrium interactions
- Implantation apposition, adhesion, invasion and system biology

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Spring 2018 – Systems Biology of Reproduction
Discussion Outline – Fertilization & Implantation Systems
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April 12, 2018
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Fertilization & Implantation Systems

Primary Papers:

1. Teperek, et al. (2016) Genome Research 26:1034
2. Brosens, et al. (2014) Scientific Reports 4:3894
3. Smith, et al. (2014) Nature 511:611-614

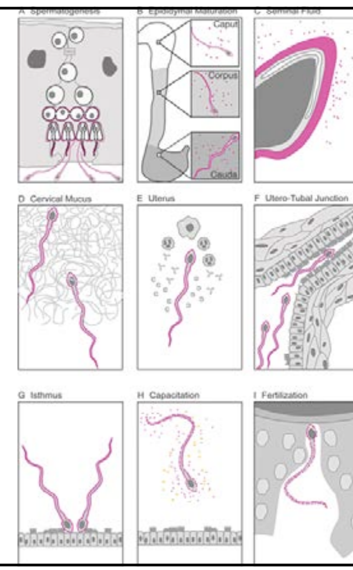
Discussion

Student 11: Reference 1 above
- What was the experimental design and objectives?
- What impact on the developing embryo was observed?
- Can sperm epigenetic alterations modify the embryo?

Student 12: Reference 2 above
- How do abnormal embryos influence the endometrial cells?
- What transcriptional influences were observed?
- How do component embryos promote a supportive uterine environment?

Student 14: Reference 3 above
- What was the experimental design and technology?
- Following fertilization what general changes occurred in the preimplantation embryo?
- What was the role of the paternal genome and suggested role of epigenetics?

Fertilization



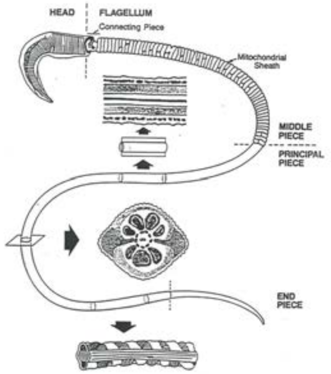


FIG. 1. General features of the mammalian sperm. The head of the spermatozoon is attached to the connecting piece of the flagellum. The other regions of the flagellum are the middle piece, the principal piece, and the end piece. The middle piece contains the mitochondrial sheath, while the principal piece contains the fibrous sheath. Longitudinal and cross-sectional views of the principal piece and a segment of fibrous sheath are indicated by arrows; the internal components of the flagellum are identified in Fig. 9.

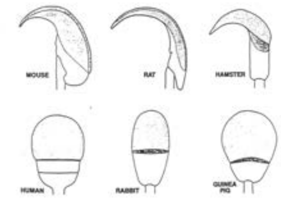


FIG. 3. Shape of the head of spermatozoa from different species. The falciform heads of mouse, rat, and hamster sperm are viewed laterally, whereas the spatulate heads of human, rabbit, and guinea-pig sperm are viewed dorsoventrally. (Adapted from ref. 184.)

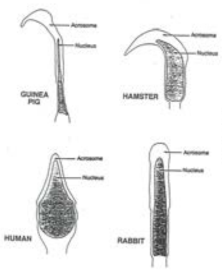


FIG. 4. Cross-sectional views of the heads of spermatozoa from different species. Guinea pig, rabbit, and human sperm heads are seen in the sagittal plane, whereas the hamster sperm head is seen in the coronal plane. The acrosome and nucleus of rabbit and human spermatozoa are symmetrical, but those of guinea pig and hamster are asymmetrical in these planes.

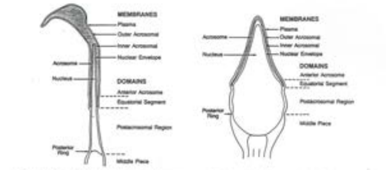


FIG. 6. Structure of the head of guinea-pig and human spermatozoa. The plasma membrane in the anterior acrosomal and equatorial segment domains overlies the outer acrosomal membrane. The inner acrosomal membrane, in turn, overlies the nuclear envelope. The acrosome is thinner in the equatorial segment region than in the anterior acrosome region. The posterior ring separates the postacrosomal domain of the head from the middle-piece domain of the flagellum.

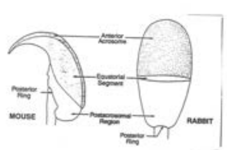


FIG. 5. Cytoskeleton of head of the hamster spermatozoon. The subacrosomal cytoskeleton (perforatorium) lies between the acrosome and the anterior part of the nucleus and extends to the tip of the falciform head. The para-acrosomal cytoskeleton lies between the plasma membrane and the acrosome on the concave margin of the sperm head. The postacrosomal cytoskeleton surrounds the posterior part of the nucleus, lying between the nuclear envelope and the plasma membrane of the postacrosomal domain.

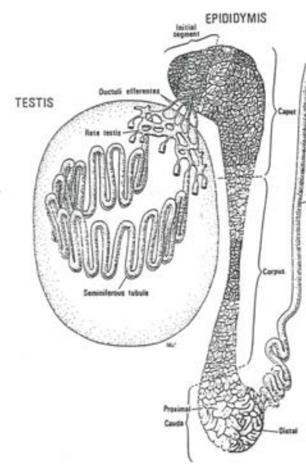


FIG. 1. Diagrammatic representation of the testis showing a seminiferous tubule and the rete testis, the ductuli efferentes, the epididymis, and vas deferens. The *shaded regions* indicate areas of the different segments of the epididymis, i.e., the initial segment, caput, corpus, and proximal and distal cauda, where data on the relative quantitative distribution of the major different epithelial cell types were obtained.

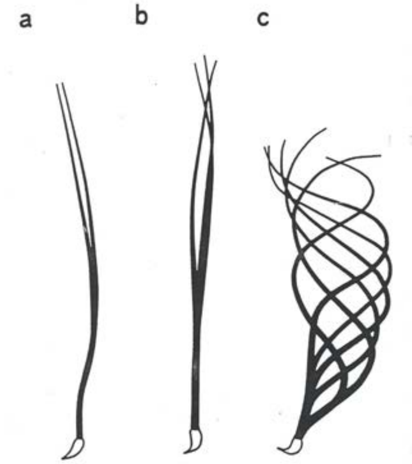


FIGURE 3. Changes in the beating pattern of golden hamster spermatozoa during the development of sperm motility: a, testicular; b, caput epididymal; and c, cauda epididymal spermatozoa. The time interval between successive images is 1.5 sec in a, 0.5 sec in b, and 1/60 sec in c. The scale bar = 30 µm.

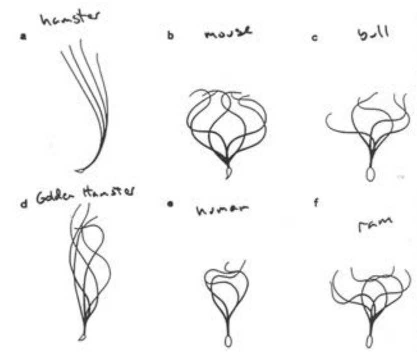
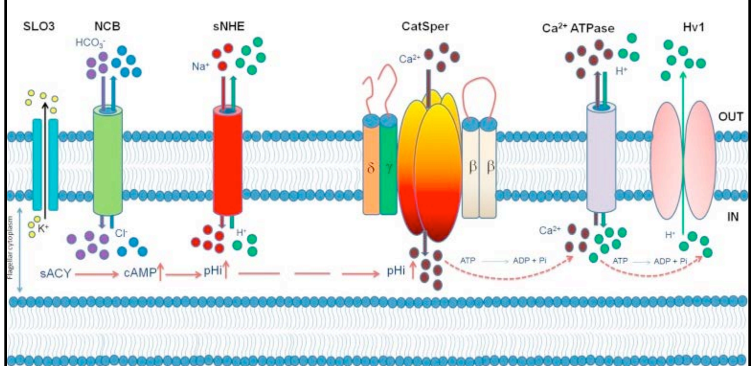
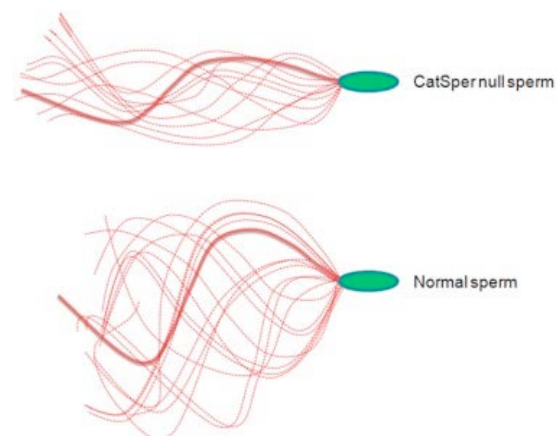


FIGURE 1. Tracings of flagellar waveform of intact mammalian spermatozoa. Each figure traced from published micrographs has been superimposed so that the head and the proximal part of the midpiece of each tracing is exactly aligned in order to easily distinguish the difference in the waveform: a, Chinese hamster; b, mouse; c, bull; d, golden hamster; e, human; f, ram. The time interval between successive images is 1/150 sec in a, 1/60 sec in b, d, e, and f, and 1/66 sec in c. The scale bar = 30 µm in both d (for a and d) and f (for b, c, e, and f). (a) Adapted from Phillips, D. M., *J. Cell Biol.*, 53, 561, 1972. With permission. (b) Redrawn from Wolf, D. E., Hagopian, S. S., and Ishijima, S., *J. Cell Biol.*, 102, 1372, 1986. With permission. (c) Adapted from Gray, J., *J. Exp. Biol.*, 35, 96, 1958. With permission. (d) Modified from Ishijima, S. and Mohri, H., *J. Exp. Biol.*, 114, 463, 1985. With permission. (e) Modified from Ishijima, S., Oshio, S., and Mohri, H., *Gamete Res.*, 13, 185, 1986. With permission. (f) Redrawn from Ishijima, S. and Witman, G. B., *Cell Motil. Cytoskeleton*, 8, 375, 1987. With permission.

CatSper channel, sperm function and male fertility.
Singh AP, Rajender S.
Reprod Biomed Online. 2015 Jan;30(1):28-38.

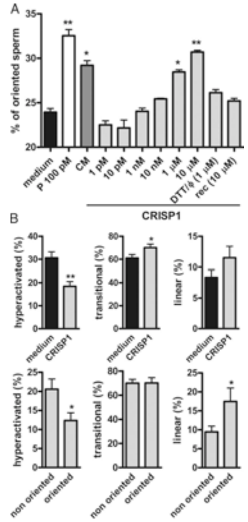




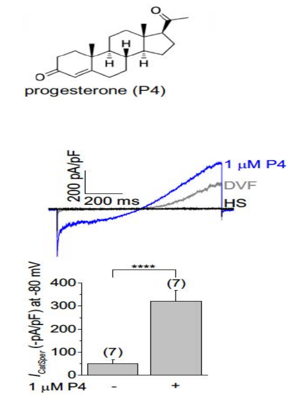
Hypermotility: normal sperm display vigorous and asymmetrical flagellar beating termed as hypermotility, which is essential for propagation through viscous ovi-ductal fluid. CatSper null sperm show only basal motility and are unable to propagate to destination and penetrate protective layers of the egg.

CRISP1 as a novel CatSper regulator that modulates sperm motility and orientation during fertilization.
Ernesto JI, Weigel Muñoz M, Battistone MA, et al.
J Cell Biol. 2015 Sep 28;210(7):1213-24.

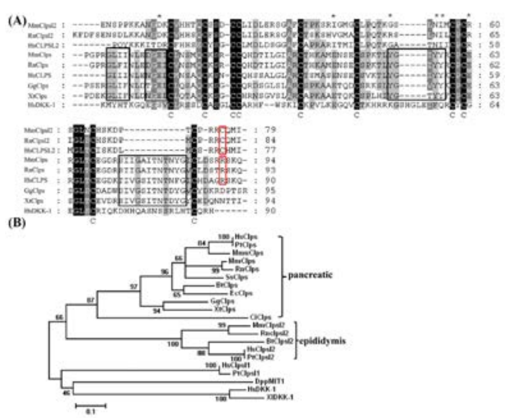
Sperm orientation and motility in the presence of CRISP1. (A) Capacitated sperm were placed in one well of a modified Zigmond chamber and CRISP1 (1 pM to 10 μM), DTT-treated and heat-denatured CRISP1 (1 μM; DTT/Φ), or recombinant CRISP1 (10 μM; rec) were loaded in the second well. Medium alone was used as negative control and both progesterone (100 pM; P) and cumulus-conditioned medium (CM) were used as positive controls. After 15 min, the percentage of oriented sperm toward the corresponding gradients was calculated by analyzing sperm trajectories. In all cases, results represent the mean ± SEM of at least three independent experiments in which >150 sperm trajectories per experiment were analyzed. *, P < 0.05; **, P < 0.005 vs. medium. (B) Percentages of hyperactivated (left), transitional (middle), or linear (right) patterns of motility for sperm exposed to either CRISP1 (1 μM) or medium (control; top) and for oriented and nonoriented cells within the CRISP1-exposed group (bottom). In all cases, results represent the mean ± SEM of seven independent experiments in which at least 100 sperm trajectories per experiment were analyzed. **, P < 0.005; *, P < 0.05.

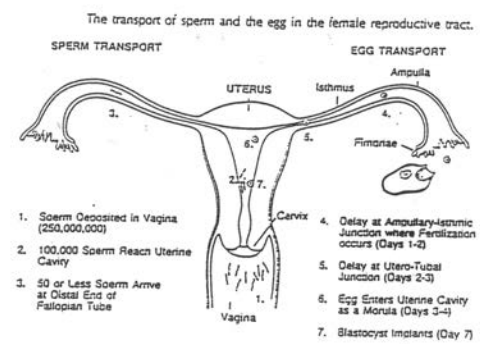


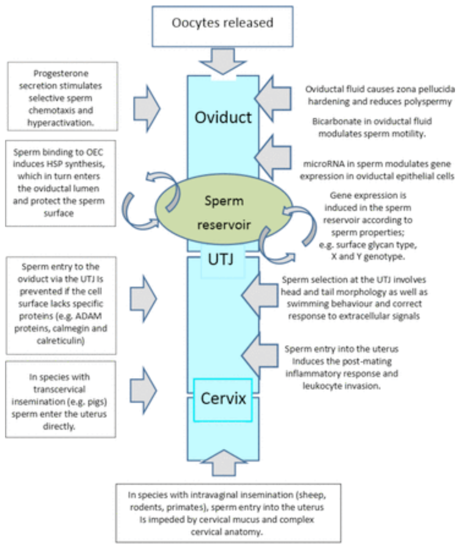
Regulation of the sperm calcium channel CatSper by endogenous steroids and plant triterpenoids.
Proc Natl Acad Sci U S A. 2017 May 30;114(22):5743-5748.
Mannowetz N, Miller MR, Lishko PV.



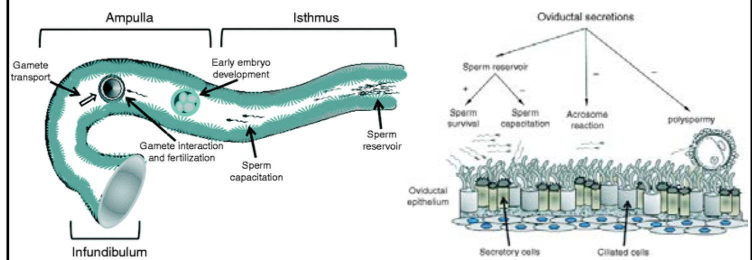
An epididymis-specific secretory protein Clpsl2 critically regulates sperm motility, acrosomal integrity, and male fertility.
J Cell Biochem. 2018 Jan 11. doi: 10.1002/jcb.26668. [Epub ahead of print]
Lu X, Ding F, Lian Z, Chen L, Cao Z, Guan Y, Chen R, Cai D, Yu Y.







Oviductal secretion and gamete interaction.
Ghersevich S, Massa E, Zumoffen C.
Reproduction. 2015 Jan;149(1):R1-R14.



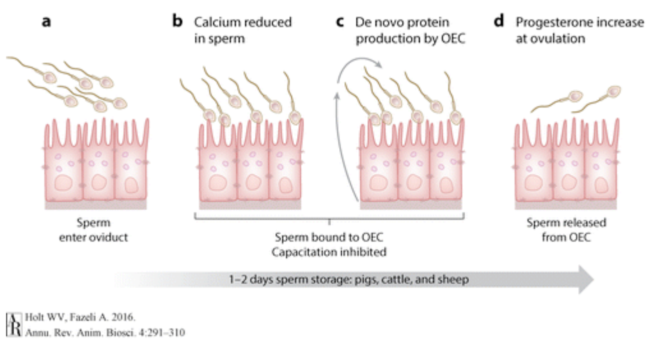
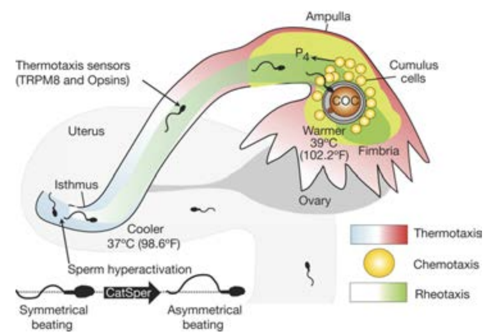


Diagram summarizing the main events that occur during oviductal sperm storage in pigs, cattle, and sheep. (a) Spermatozoa enter the oviductal isthmus via the utero-tubal junction. (b) Some spermatozoa bind to oviductal epithelial cell (OEC) surfaces, whereupon their motility and intracellular calcium concentrations are reduced; capacitation is also inhibited. (c) The direct contact between spermatozoa and epithelial cells induces de novo gene expression and protein synthesis. Multiple proteins, including heat shock proteins, are secreted into the oviductal lumen, where they protect sperm membranes and facilitate sperm storage. (d) Increased peri-ovulatory progesterone production induces spermatozoa to escape and resume their progress toward the oocyte(s).



Oviduct-guided fertilization. The oviduct regulates fertilization through sperm guidance and sperm hyperactivation. The sperm guidance is achieved through rheotaxis, thermotaxis and chemotaxis. Rheotaxis is created by tubal fluid, which generates a current flow from the ampulla toward the isthmus of the oviduct. Sperm swim against this current based on the physical rotation of the flagella upon CatSper (Cation channel of Sperm) activation. Thermotaxis is mediated through a Ca^{2+}-sensing transient receptor potential channel (TRPM8) and G protein-coupled receptor (opsins). This thermal sensibility of human sperm can detect a difference of 0.006° C (Bahat et al. 2012). Temperatures depicted (37° C vs 39° C) are from the finding in rabbits (Bahat et al. 2003). Chemotaxis is driven through progesterone (P4) released from the cumulus cells and through small cytokines found in the follicular fluid. Together, these processes provide guidance for sperm to swim toward the eggs and be competent for fertilization. COC, cumulus-oocyte complex.

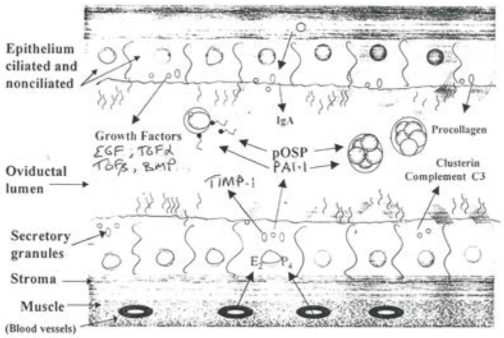
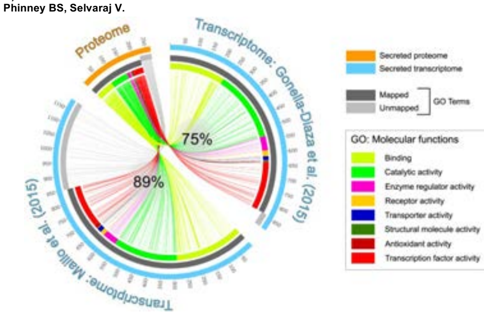


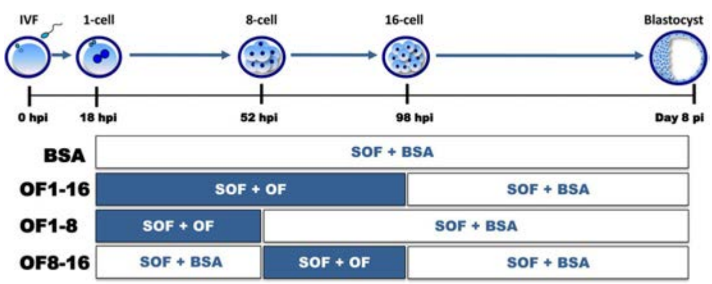
Fig. 9. Ciliated and secretory epithelium achieve maximum development, biosynthetic capacity and secretory activity during follicular development, ovulation and early cleavage-stage development. Secretory products are contributed as transudate and from active biosynthesis by secretory epithelium into the oviductal microenvironment. These molecules may operate in an autocrine and/or paracrine manner to regulate oviductal and embryonic growth and development.

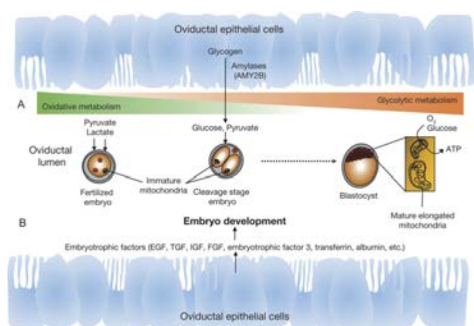
Profiling of proteins secreted in the bovine oviduct reveals diverse functions of this luminal microenvironment.
PLoS One. 2017, 12(11):e0188105.
Pillai VV, Weber DM, Phinney BS, Selvaraj V.



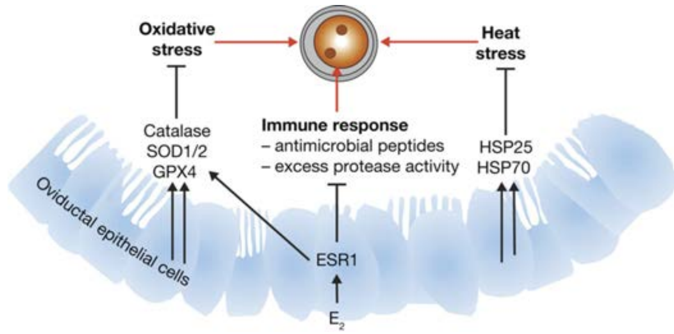
Comparison of oviductal cell secreted proteins to transcriptome of the bovine oviduct from two published datasets.
Of the 266 secreted proteins identified in oviductal cells, 236 (89%) and 200 (75%) of the proteins were detected as transcripts in the oviduct by Maillo et al. [35], and the Gonella-Diaza et al. [36] respectively. This comparison indicates that almost 90% of the proteins identified in this study are synthesized by the oviductal epithelium, with only 30 (11%) of proteins putatively derived by plasma protein transudation.

Embryo culture in presence of oviductal fluid induces DNA methylation changes in bovine blastocysts.
Reproduction. 2017 Jul;154(1):1-12.
Barrera AD, García EV, Hamdi M, Sánchez-Calabuig MJ, López-Cardona ÁP, Balvís NF, Rizos D, Gutiérrez-Adán A.

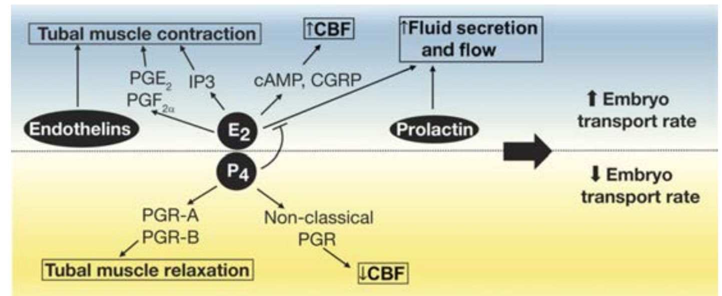




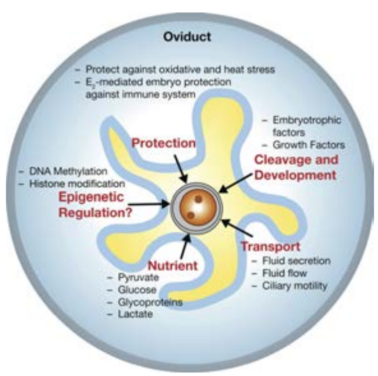
The influence of the oviduct on embryo development. (A) The main energy supply for the embryos is pyruvate and lactate. During the very early stage of embryo development, pyruvate and lactate are provided by the oviductal fluid as energy sources for oxidative metabolism. The oviduct can also supply the glycogen as an energy source for the embryos during the cleavage stage. Amylase (AMY2B) is produced within the oviductal epithelial cells and converts glycogen to sugar. At this stage, the mitochondria of the embryos are immature and do not function. During morula and blastocyst stages, the mitochondria are fully mature and can use oxygen and glucose to produce their own energy via glycolysis as they leave the oviduct. (B) At the same time, oviductal epithelial cells provide embryotrophic factors, such as growth factors, to promote cleavage and embryo development. EGF, epidermal growth factor; FGF, fibroblast growth factor; IGF, insulin-like growth factor; TGF, transforming growth factor.



Oviduct-mediated embryo protection against stress and immune responses. Oviductal epithelial cells produce heat shock protein family (HSP25 and HSP70) to handle heat stress. Oviductal fluid also contains catalase, superoxide dismutases (SOD1/2) and glutathione peroxidase (GPX4) to reduce stress of the embryos from reactive oxygen species. In addition to stress, the oviduct also protects the embryos against their own immune system, partly through the E_2/ESR1 signaling, by inhibiting the production of antimicrobial peptides and excess protease activity. ESR1, estrogen receptor α.

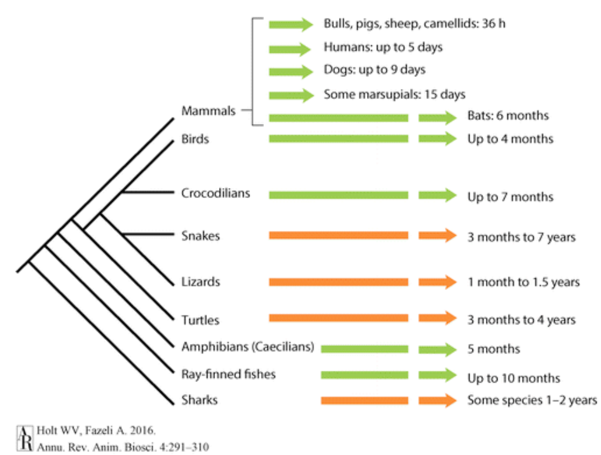


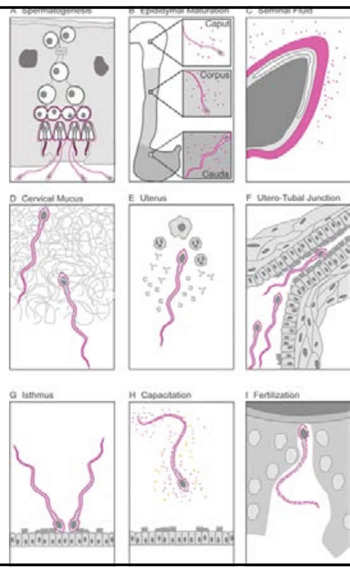
Roles of the oviduct during embryo transport. Embryo transport is composed of tubal muscle contraction and the motility of ciliated epithelial cells. Estrogen (E_2) generally increases the tubal muscle contraction, tubal fluid secretion, and ciliary beat frequency (CBF), which accelerate the embryo transport rate. Opposite to E_2, progesterone (P_4) causes muscle relaxation and decreases CBF to reduce the embryo transport rate. In addition, P_4 also inhibits E_2-induced tubal fluid production. Prostaglandins (PGs) can be produced in the oviductal epithelial cells or induced by E_2 treatment. PGE_2 and $PGF_{2\alpha}$ stimulate muscle contraction in both human and bovine oviducts. Endothelin 1 and 2 are expressed and contribute to the oviduct contraction. IP3, inositol triphosphate; PGE_2, prostaglandin E_2; $PGF_{2\alpha}$, prostaglandin F_2; PGR, progesterone receptor.

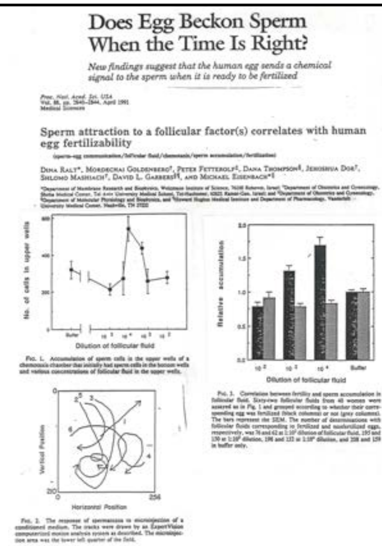


Essential roles of the oviduct in assisting embryo development. Schematic cross-section of the oviduct and the embryo with their interaction regulating embryo development. The interactions are divided into five domains: protection, cleavage and development, transport, nutrients and epigenetic regulation. E_2, estrogen.

Sperm Storage in the Female Reproductive Tract.
Holt WV, Fazeli A.
Annu Rev Anim Biosci. 2016 Feb 15;4:291-310.






Does Egg Beckon Sperm When the Time Is Right?

New findings suggest that the human egg sends a chemical signal to the sperm when it is ready to be fertilized

Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 2840–2844, April 1991
Medical Sciences

Sperm attraction to a follicular factor(s) correlates with human egg fertilizability

Dina Ralt*, Mordechai Goldenberg†, Peter Fetterolf‡, Dana Thompson§, Jehoshua Dor†, Shlomo Mashiach†, David L. Garbers§¶, and Michael Eisenbach*‖

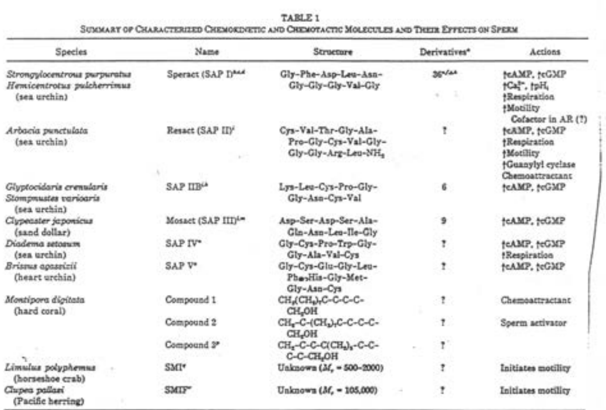
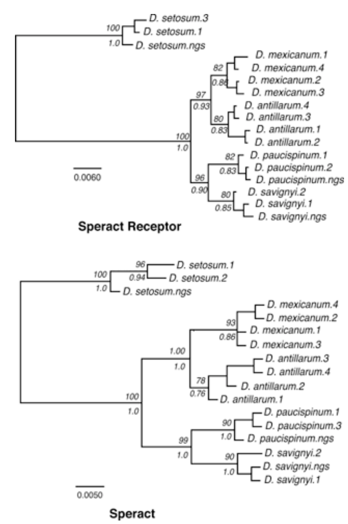


TABLE 1

SUMMARY OF CHARACTERIZED CHEMOKINETIC AND CHEMOTACTIC MOLECULES AND THEIR EFFECTS ON SPERM

Species	Name	Structure	Derivatives*	Actions
Strongylocentrous purpuratus *Hemicentrotus pulcherrimus* (sea urchin)	Speract (SAP I)	Gly-Phe-Asp-Leu-Asn-Gly-Gly-Gly-Val-Gly	36	↑cAMP, ↑cGMP ↑Ca_i^{2+}, ↑pH_i ↑Respiration ↑Motility Cofactor in AR (?)
Arbacia punctulata (sea urchin)	Resact (SAP II)	Cys-Val-Thr-Gly-Ala-Pro-Gly-Cys-Val-Gly-Gly-Gly-Arg-Leu-NH_2	?	↑cAMP, ↑cGMP ↑Respiration ↑Motility ↑Guanylyl cyclase Chemoattractant
Glyptocidaris crenularis *Stompnustes varioaris* (sea urchin)	SAP IIB	Lys-Leu-Cys-Pro-Gly-Gly-Asn-Cys-Val	6	↑cAMP, ↑cGMP
Clypeaster japonicus (sand dollar)	Mosact (SAP III)	Asp-Ser-Asp-Ser-Ala-Gln-Asn-Leu-Ile-Gly	9	↑cAMP, ↑cGMP
Diadema setosum (sea urchin)	SAP IV	Gly-Cys-Pro-Trp-Gly-Gly-Ala-Val-Cys	?	↑cAMP, ↑cGMP ↑Respiration
Brissus agassizii (heart urchin)	SAP V	Gly-Cys-Glu-Gly-Leu-Phe-His-Gly-Met-Gly-Asn-Cys	?	↑cAMP, ↑cGMP
Montipora digitata (hard coral)	Compound 1	$CH_3(CH_2)_7C$-C-C-C-CH_2OH	?	Chemoattractant
	Compound 2	CH_3-C-$(CH_2)_7C$-C-C-C-CH_2OH	?	Sperm activator
	Compound 3*	CH_3-C-C-$C(CH_2)_5$-C-C-C-C-CH_2OH	?	
Limulus polyphemus (horseshoe crab)	SMI	Unknown (M_r = 500–2000)	?	Initiates motility
Clupea pallasi (Pacific herring)	SMIF	Unknown (M_r = 105,000)	?	Initiates motility



Progesterone at the picomolar range is a chemoattractant for mammalian spermatozoa

By means of a videomicroscopy system and a computer image analysis, we performed chemotaxis assays to detect true chemotaxis in human spermatozoa, in parallel to immunohistochemistry detection of progesterone inside the cumulus cells. Progesterone indeed chemotactically guides mammalian spermatozoa at very low hormone concentrations, and the cumulus oophorus could be a potential place for sperm chemotaxis mediated by progesterone in vivo. (Fertil Steril® 2006;86:745–9. ©2006 by American Society for Reproductive Medicine.)

Xenopus tropicalis allurin: Expression, purification, and characterization of a sperm chemoattractant that exhibits cross-species activity

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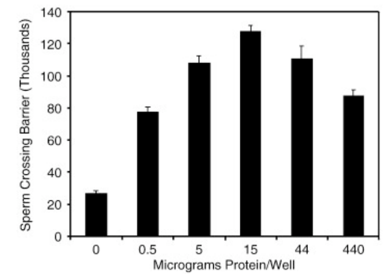
Received 19 December 2007; revised 30 January 2008; accepted 31 January 2008. Available online 15 February 2008.



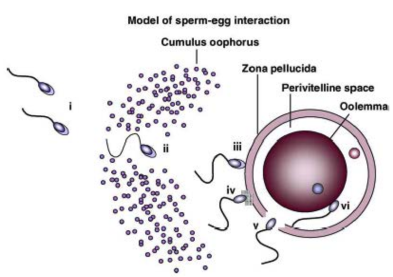


Fig. 1. Schematic diagram of the fertilization process. Within the female reproductive tract (i), sperm undergo a series of surface and intracellular transformations, collectively termed capacitation, which enables them to penetrate the cumulus oophorus (ii), bind to the zona pellucida (ZP) (iii), and undergo the acrosome reaction (iv). The release of hydrolytic enzymes from the acrosome facilitates sperm passage through the ZP (v), and fusion with the oolemma (vi).

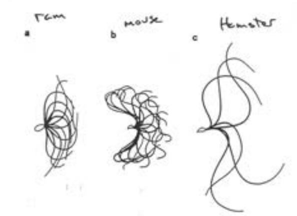
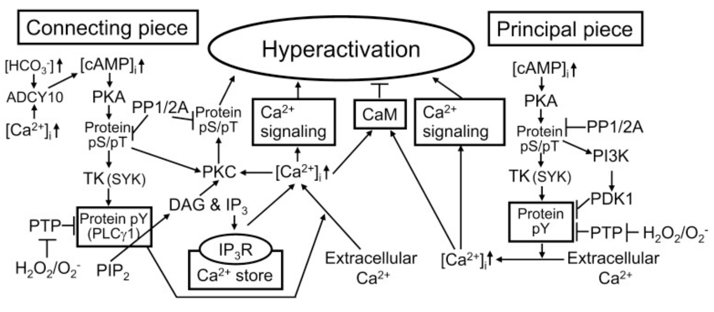


FIGURE 4. Tracings of the beating patterns of hyperactivated mammalian spermatozoa: a, rat; b, mouse; c, golden hamster. The time interval between successive images is 1/30 sec in a and 1/60 sec in b and c. (a) Redrawn from Cummins, J. M., *Gamete Res.*, 6, 53, 1982. With permission. (b) Redrawn from Wolf, D. E., Hagopian, S. S., and Ishijima, S., *J. Cell Biol.*, 102, 1372, 1986. With permission. (c) Reproduced from Ishijima, S., unpublished data, 1989.

TABLE 4. *The ability of acrosome-reacted guinea-pig spermatozoa to fertilize zona-intact and zona-free eggs**

Age (hours) of acrosome-reacted sperm at insemination	% Acrosome-reacted sperm (in entire population) which are		% Eggs fertilized	
	Motile	Hyperactivated	Zona-intact	Zona-free
1	100	95	100	—
2	96	66	98	—
3	92	39	33	—
4	90	6	0	100
6	57	0	0	—
8	—	—	—	94
10	0	0	—	0

*From Flemming and Yanagimachi (159). Guinea-pig spermatozoa were induced to undergo a synchronous acrosome reaction. A population of 100% acrosome-reacted spermatozoa was isolated and incubated for up to 10 hr before they were mixed with zona-intact or zona-free guinea-pig eggs. Note that (a) there is a close correlation between hyperactivated motility of spermatozoa and the ability of spermatozoa to fertilize zona-intact eggs (to cross the zona) and (b) spermatozoa retain their ability to fuse with zona-free eggs for many hours after losing their ability to cross the zona.



Possible segment-specific cAMP signal transductions regulating transition of the flagellar movement pattern to hyperactivation in boar spermatozoa. ADCY10, adenylyl cyclase 10; cAMP, cyclic adenosine 3´,5´-monophosphate; PKA, protein kinase A (cAMP-dependent protein kinase); pS/pT, serine/threonine phosphorylation; PP, protein phosphatase; TK, tyrosine kinase; SYK, spleen tyrosine kinase; PTP, protein tyrosine phosphatase; pY, tyrosine phosphorylation; PLC, phospholipase C; PIP2, phosphatidylinositol 4,5-bisphosphate; DAG, 1,2-diacylglycerol; IP3, inositol 1,4,5-trisphosphate; IP3R, IP3 receptor; PKC, protein kinase C; PI3K, phosphatidylinositol-3 kinase; PDK1, phosphoinositide-dependent protein kinase-1; CaM, calmodulin.

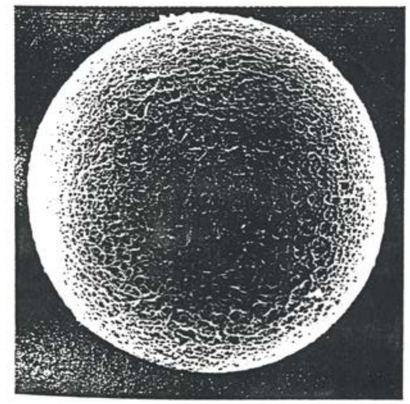


Figure 1–3. Hamster zona pellucida. The surface of the zona pellucida exhibits a fenestrated, multilayered appearance. ×1500. *(Reproduced, with permission, from Phillips, DM, et al.* J Exp Zool. *213:1, 1980.)*

Current Biology Vol 14 No 17
R692

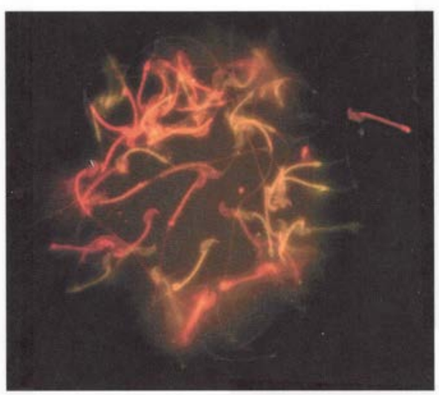
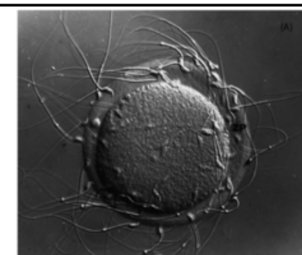


Figure 1. Mouse sperm labeled with two fluorescent dyes bound to the egg coat.



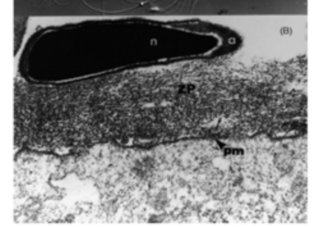


Fig. 1. Binding of free-swimming mouse sperm to the ZP of ovulated mouse eggs. (A) Photomicrograph (Nomarski differential interference contrast) of sperm bound to the ZP of an ovulated egg. (B) Transmission electron micrograph of a sperm head bound to the ZP of an ovulated egg. Zona pellucida (ZP), nucleus (n), acrosome (a), plasma membrane (PM).

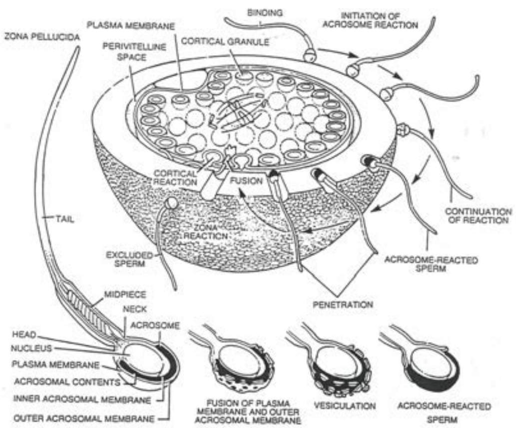
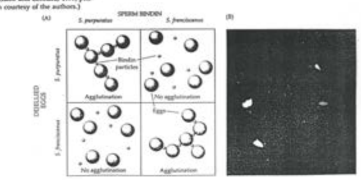


Figure 1–5. Fertilization pathway. After the spermatozoa binds to the zona pellucida, the acrosome reaction takes place (see detail at the bottom). The outer membrane of the acrosome fuses at several points with the plasma membrane surrounding the sperm head. Those fused membranes form vesicles that are eventually sloughed from the head, exposing the proteolytic enzymes of the acrosomal granule. The enzymes digest a pathway through the zona pellucida, enabling the sperm to advance to the egg surface. Eventually, the sperm fuses with the egg membrane, completing the fertilization process. This fusion triggers the cortical and zona reactions. The zona as a result of enzyme modification becomes impermeable to further sperm penetration and polyspermy. (Reproduced, with permission, from Wassarman PM. Sci Am. *259: 1988.*)

FIGURE 13
Species-specific agglutination of dejellied eggs by bindin. (A) Agglutination was promoted by adding 212 µg bindin to a plastic well containing 0.25 ml of a 2 percent (volume:volume) suspension of eggs. After 2–5 minutes of gentle shaking, the wells were photographed. (The interpretive diagram is based on photographs of Glabe and Vacquier, 1977.) (B) Fluorescence photomicrograph of *S. purpuratus* eggs bound together by fluorescein-labeled *S. purpuratus* bindin particles. Bindin particles were invariably present at the places where two eggs came together. (From Glabe and Lennarz, 1979; photograph courtesy of the authors.)

FIGURE 12
Contact of a sea urchin sperm acrosomal process with an egg microvillus. (From Epel, 1977; photograph courtesy of F. D. Collins and D. Epel.)



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Tecle E, Gagneux P.
Mol Reprod Dev. 2015 Sep;82(9):635-50.

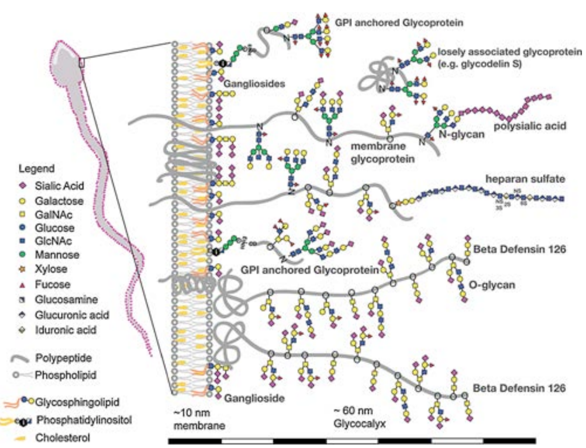
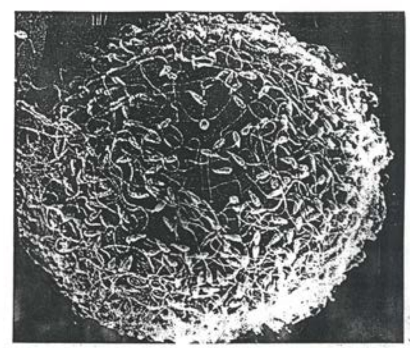
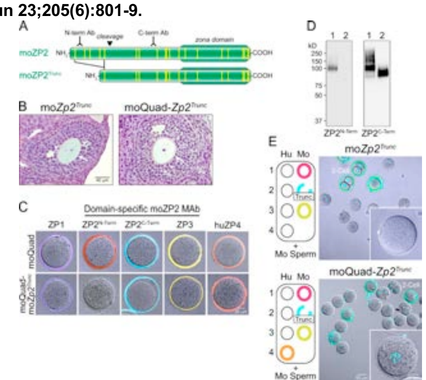


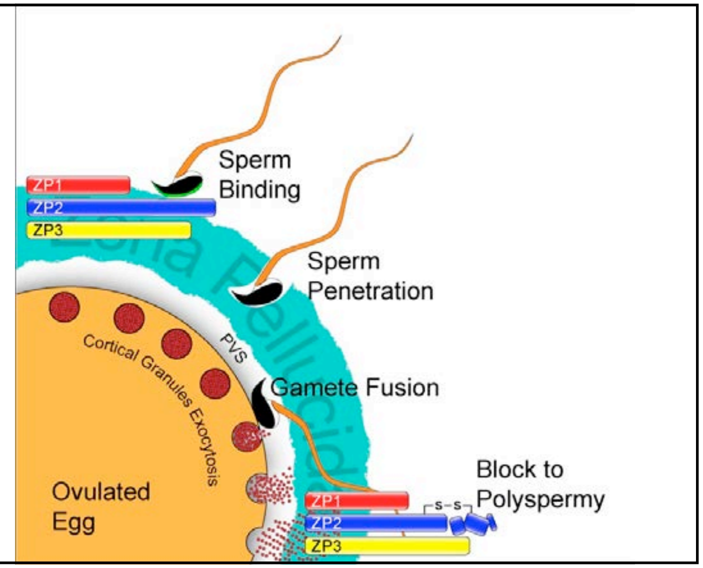
FIGURE 15
Scanning electron micrograph of sea urchin sperm bound to the vitelline envelope of an egg. (Photograph courtesy of C. Glabe, L. Perez, and W. J. Lennarz.)

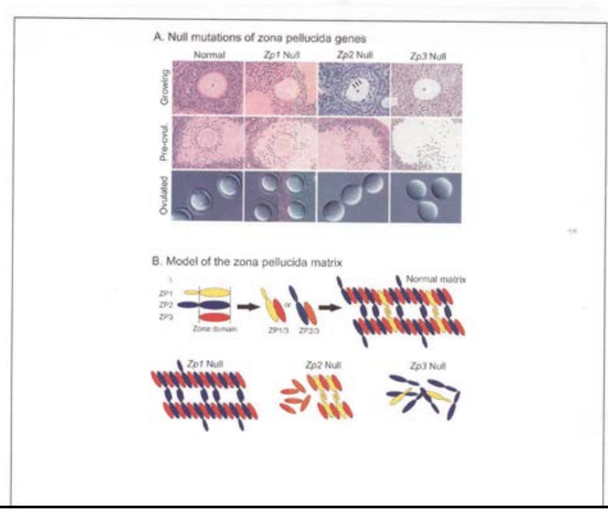


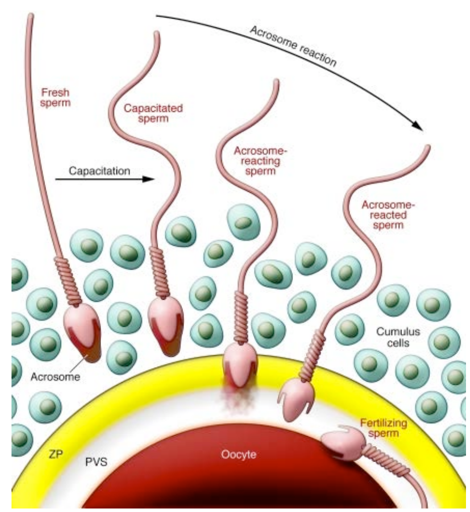
A single domain of the ZP2 zona pellucida protein mediates gamete recognition in mice and humans.
Avella MA, Baibakov B, Dean J.
J Cell Biol. 2014 Jun 23;205(6):801-9.



Truncated ZP2 does not support sperm binding, and female mice are sterile. (A) Representation of secreted ectodomains of normal mouse ZP235–633 and truncated ZP2 lacking ZP251–149. Cysteine residues, yellow. Monoclonal antibodies that bind N and C terminal to the postfertilization cleavage site (arrowhead) and zona domains are indicated above. (B) Ovarian histology of moZp2Trunc and moQuad-Zp2Trunc transgenic mice in Zp2Null background as in Fig. 1 C. (C) moQuad(huZP4) and moQuad-Zp2Trunc eggs stained with domain-specific monoclonal antibodies as in Fig. 1 D. (D) Immunoblot of eggs (15) from moQuad(huZP4) (1) and moQuad-Zp2Trunc (2) mice stained with domain-specific monoclonal antibodies. Molecular masses are indicated on the left. (E) Mouse sperm binding to Zp2Trunc and moQuad-Zp2Trunc eggs as in Fig. 1 E.







Mechanism of sperm-egg interaction.
Over the nucleus of each mammalian sperm is a membranous sac known as the acrosome, which is filled with many kinds of hydrolytic enzymes. In the female reproductive tract or in an IVF medium, sperm undergo capacitation, which permits the acrosome reaction. Near the eggs, probably stimulated by the cumulus cells and the ZP, sperm release their acrosomal contents by exocytosis and penetrate the ZP. Only acrosome-reacted sperm fuse with eggs, but their competency for fusion does not last long. Cumulus cells are packed together by hyaluronic acid at ovulation and become diffuse during fertilization. PVS, perivitelline space.

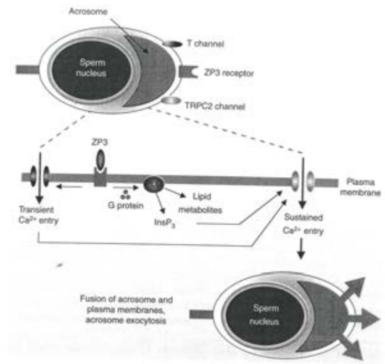


Figure 2 **Triggering of the acrosome reaction.** A model of the events involved in ZP3 signal transduction is shown. In the sperm head, TRPC2–ZP3 receptor activation during adhesion to the zona pellucida results in calcium entry through T-type channels, causing a transient elevation of cytosolic calcium concentration and activation of PLC through a G_i and/or G_q protein-mediated pathway, resulting in the production of $InsP_3$ and diacylglycerol. PLC and the transient calcium elevation function in concert to produce persistent calcium entry through a TRPC2 channel that directly drives the acrosome reaction, triggering fusion of the outer acrosome membrane with the plasma membrane and releasing acrosomal contents. See text for details.

TABLE 2
SUMMARY OF CHARACTERIZED ACROSOME REACTION-INDUCING MOLECULES AND THEIR EFFECTS ON SPERM

Species	Name	Structure	Actions
Sea urchin	FSG[a]	Fucose sulfate glycoconjugate	↑Ca_i^{2+}, ↑Na_i^+ ↑H^+; K^+ release ↑pH_i ↑Adenylyl cyclase ↑cAMP ↑Protein kinase A ↑IP_3 ↑Phospholipase D ↑Phosphatidate
Starfish	ARIS[b]	Fucose sulfate glycoconjugate	↑Ca_i^{2+}, ↑Na_i^+ ↑H^+, K^+ release ↑pH_i; ↑cAMP (only in presence of CoARIS)
	CoARIS[b]	Sulfated steroidal saponins	Cofactor for ARIS
Mouse	ZP3[c]	Glycoprotein	G_i activation ↑Ca_i^{2+} ↑pH_i ↑cAMP

[a] SeGall and Lennarz, 1979, 1981; Garbers and Kopf, 1980; Garbers *et al.*, 1983; Trimmer and Vacquier, 1986.
[b] Ikadai and Hoshi, 1981a,b; Matsui *et al.*, 1986a,b; Nishiyama *et al.*, 1987a; Hoshi *et al.*, 1990.
[c] Wassarman, 1988, 1990; Kopf and Gerton, 1990; Florman and Babcock, 1990.

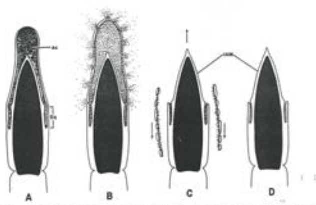


FIG. 9. Diagrams showing the progression of a typical acrosome reaction. (Ac) Acrosomal cap; (Eq) equatorial segment of the acrosome; (IAM) inner acrosomal membrane. (From ref. 530, slightly modified.)

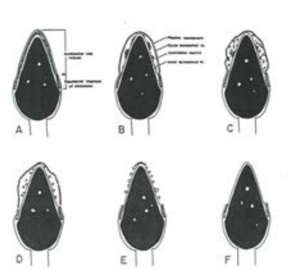


FIG. 10. A possible process of the acrosome reaction in human spermatozoa. (From ref. 348.)

TABLE 2. ***Enzymes reported to be of acrosomal origin***

First reported before 1980	First reported after 1980 (references)
Hyaluronidase	β-*N*-Acetylhexosaminidase (454)
Acrosin	β-Galactosidase (454)
Proacrosin	β-Glucuronidase (454)
Acid proteinase	α-L-Fucosidase (454)
Esterase	Phospholipase C (453)
Neuraminidase	Cathepsin D (456)
Phosphatase	Peptidyl peptidase (471b)
Phospholipase A	Ornithin decarboxylase (400)
β-*N*-acetylglucosaminidase	
Arylsulfatase	
Arylamidase	
Collagenase	

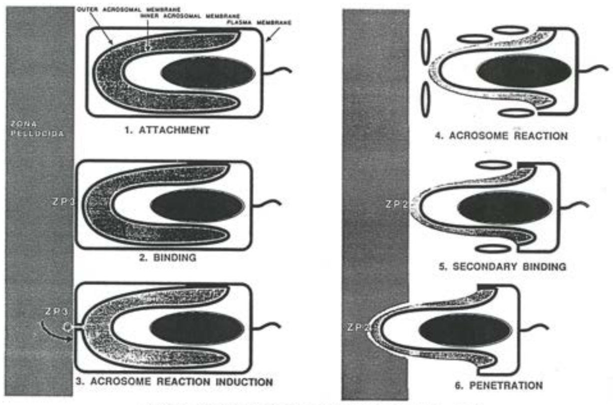


FIGURE 1. Sequence of interactions between the sperm head and the egg's zona pellucida.

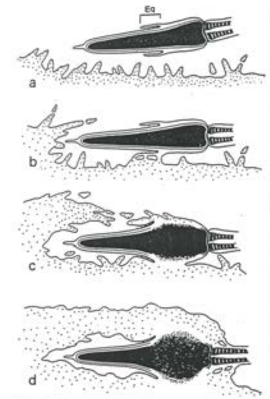
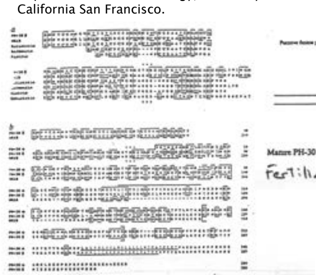


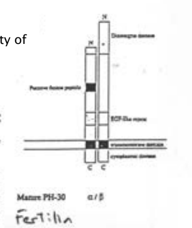
FIG. 14. Diagrams of the sequence of events through which the fertilizing spermatozoon fuses and is believed to be incorporated by the vitellus. (Eq) Equatorial segment of the acrosome. (From ref. 50, with an added label.)

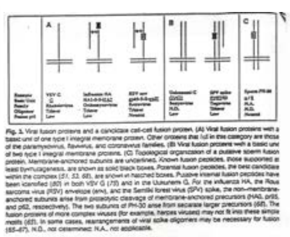
A POTENTIAL FUSION PEPTIDE AND AN INTEGRIN LIGAND DOMAIN IN A PROTEIN ACTIVE IN SPERM-EGG FUSION.

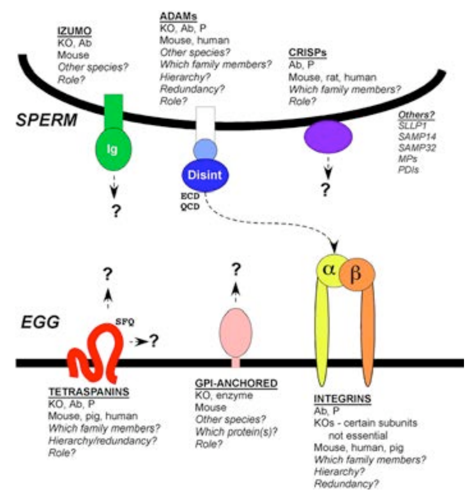
Blobel CP, Wolfsberg TG, Turck CW, Myles DG, Primakoff P, White JM.

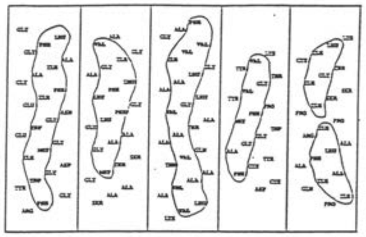
Department of Pharmacology, University of California San Francisco.











Protein	Influenza HA2	HIV gp41	SV5 F1	SFV E1	PH-30 α
Fusion pH	low	neutral	neutral	low	neutral
Location	amino terminal	amino terminal	amino terminal	internal	internal
Residues	23	18	26	16	21
Average H.I.	0.5	0.7	0.7	0.6	0.5
H.I. hydrophobic face	1.1	0.9	1.0	0.9	1.2

Fig. 4. Characteristics of the fusion peptides of several viral fusion proteins and a potential fusion peptide from a candidate sperm fusion protein. The sequences analyzed encompass those from the first to the last residue of the hydrophobic face (encircled residues) of the displayed helices. Bulky hydrophobic residues (H.I. ≥0.64: Ile, Phe, Val, Leu, Trp, Met) are in bold. Hydrophobicity indices (H.I.) were calculated with the normalized consensus scale of Eisenberg (53). Helices were plotted by using the program HELO from R. Stroud.

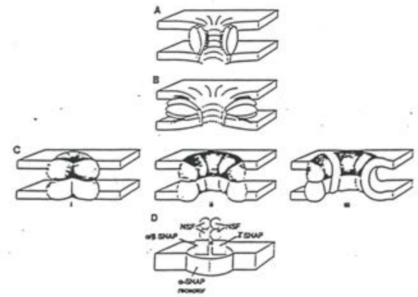


Fig. 2. Models of fusion pores and a fusion machine. (A) A model for an HA fusion pore lined with several upright HA trimers. The exposed fusion peptides projecting into the pore are thought to promote lipid mixing (21, 51, 52). (B) A model for an HA fusion pore lined with several tilted HA trimers. The exposed fusion peptides are thought to bind to both the viral and target membranes, bringing them into close apposition (11). (C) A model for the exocytic fusion pore formed by paired integral membrane multimeric proteins in the vesicle and plasma membranes (49, 59). (i) The pore is closed. (ii) The pore opens. (iii) The pore dilates. (D) Minimal components of the NSF-containing fusion machine (32, 45, 46). It is not yet known whether γ-SNAP binds to the α-SNAP receptor or to a different molecule.

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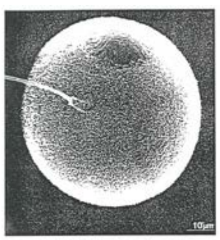


FIG. 15. Scanning electron micrograph of a golden hamster spermatozoon fusing with the vitellus. (From ref. 530.)

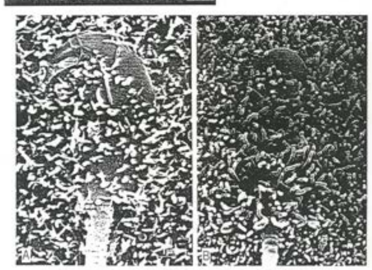
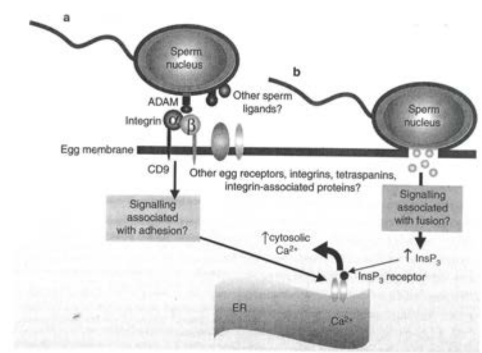
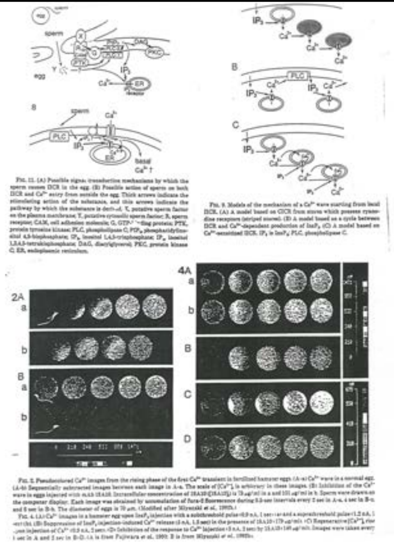


FIG. 16. Scanning electron micrographs of hamster spermatozoa fusing with eggs. (From ref. 530.)





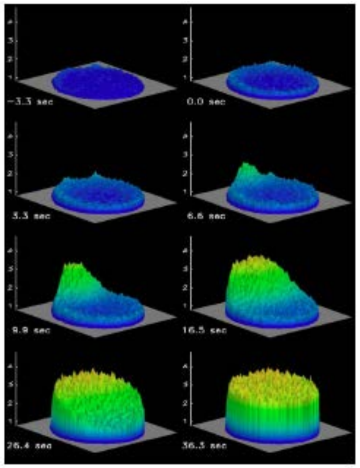
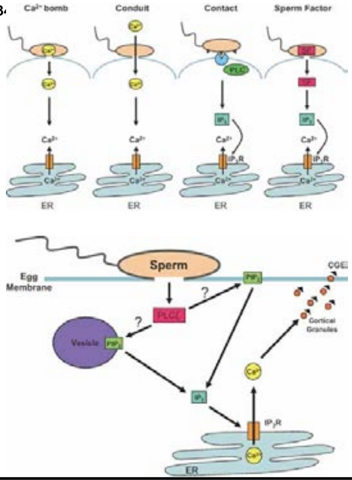


FIG 1. The fertilization calcium wave in a sea urchin (*lytechinus pictus)* egg. The calcium wave initiates at the point of sperm entry and crossed the egg as a tsunami-like wave, traversing the egg in ~20 s. Calcium concentrations were visualized using the calcium indicator calcium green dextran and confocal microscopy. Calcium levels are represented by warm colors and height in this topographical plot. A pseudoratio image is generated by pixelwise division of each image by an image of resting dye distribution acquired before fertilization. [Adapted from McDougall et al. (360).

Starting a new life: sperm PLC-zeta mobilizes the Ca2+ signal that induces egg activation and embryo development: an essential phospholipase C with implications for male infertility.

Nomikos M, Swann K, Lai FA.

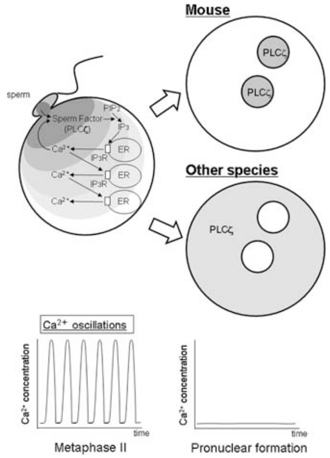
Bioessays. 2012 Feb;34(2):126-3

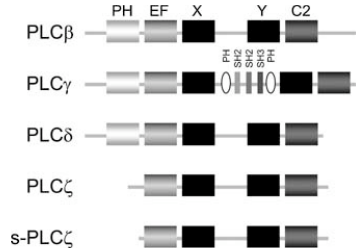


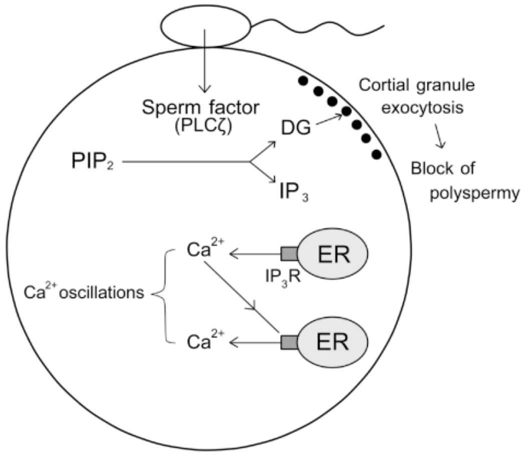
Mol Reprod Dev. 2011 Oct-Nov;78(10-11):846-53. doi: 10.1002/mrd.21359. Epub 2011 Aug 5.

PLCζ and its role as a trigger of development in vertebrates.

Ito J, Parrington J, Fissore RA.

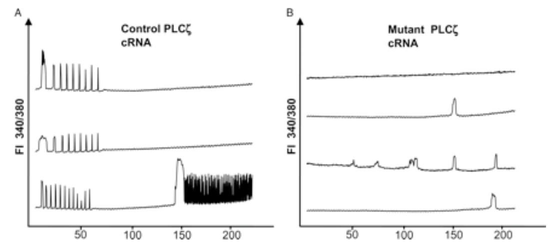




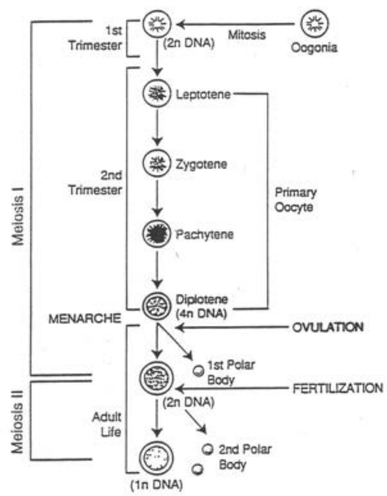


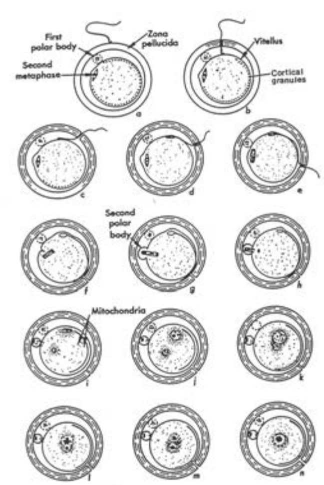
Model of oocyte activation induced by phospholipase C zeta (PLCζ). PLCζ was released from the sperm into ooplasm. PLCζ hydrolyzes phosphatidylinostitol (4,5)-bisphosphate (PIP2) into IP3 and diacyl glycerol (DG) and the IP3 leads to the release of Ca2+ from the endoplasmic reticulum (ER). Ca2+ induces amplitude of the Ca2+ release from ER, resulting in the induction of Ca2+ oscillations. Alternatively, Ca2+ oscillations depend upon Ca2+ induced IP3 production via PLCζ.

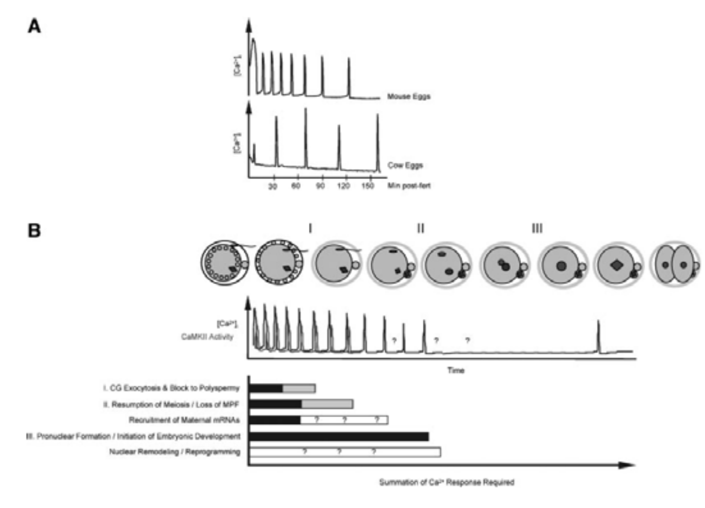
Reduced amounts and abnormal forms of phospholipase C zeta (PLCzeta) in spermatozoa from infertile men.
Heytens E, et al.
Hum Reprod. 2009 Oct;24(10):2417-28.



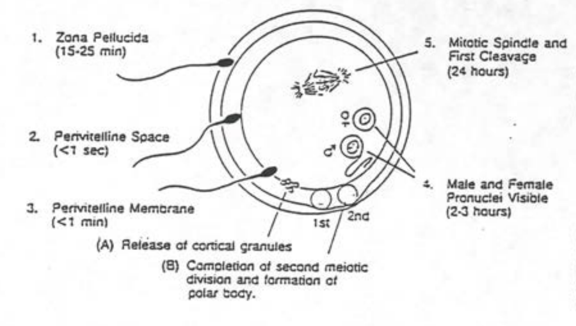
Microinjection of wild type control (A) and mutated (B) PLC ζ into mouse oocytes and analysis of resultant intracellular calcium release.







The process of fertilization of a human egg. (Adapted after R Blandau.)



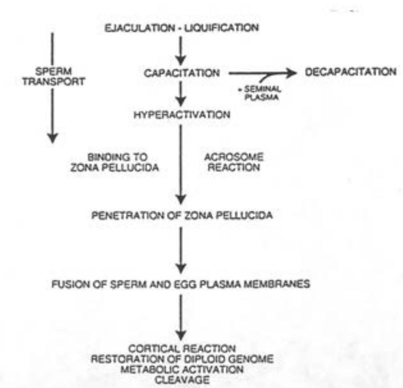
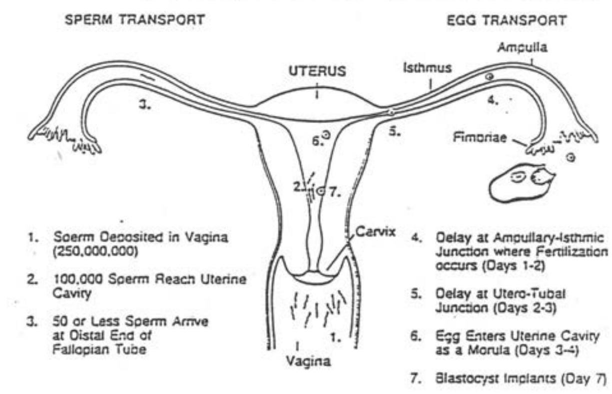


Figure 1–2. Sequence of events in the maturation of spermatozoa and the subsequent fertilization of an oocyte.

The transport of sperm and the egg in the female reproductive tract.



Preimplantation embryo

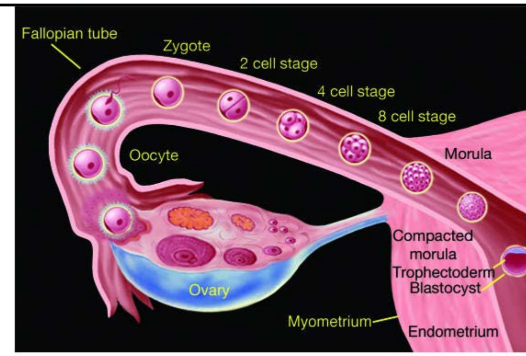
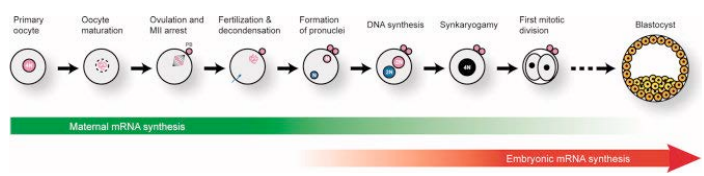
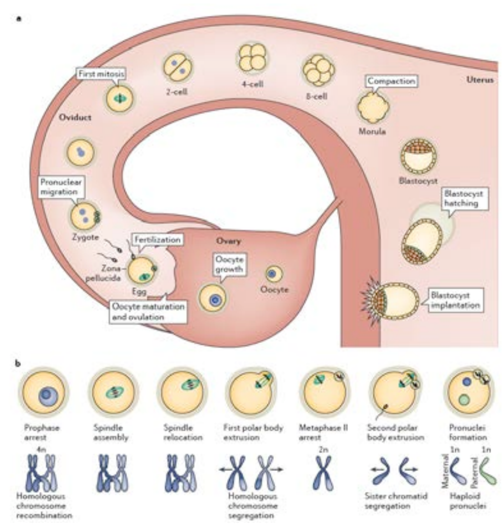
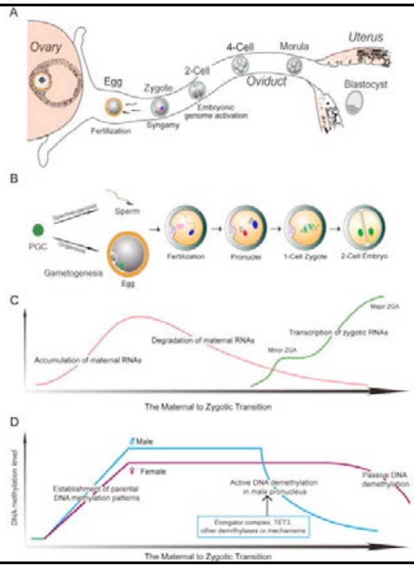


Figure 1.
The early stages of human development from fertilization to blastocyst formation. Fertilization occurs in the fallopian tube within 24 to 48 hours of ovulation. The initial stages of development, from fertilized ovum (zygote) to a solid mass of cells (morula), occur as the embryo passes through the fallopian tube encased within a nonadhesive protective shell (the zona pellucida). The morula enters the uterine cavity approximately two to three days after fertilization. The appearance of a fluid-filled inner cavity marks the transition from morula to blastocyst and is accompanied by cellular differentiation: the surface cells become the trophoblast (and give rise to extraembryonic structures, including the placenta) and the inner cell mass gives rise to the embryo. Within 72 hours of entering the uterine cavity, the embryo hatches from the zona, thereby exposing its outer covering of trophectoderm. Figure kindly provided by S.S. Gambhir and J. Strommer, Stanford University (Stanford, California, USA).

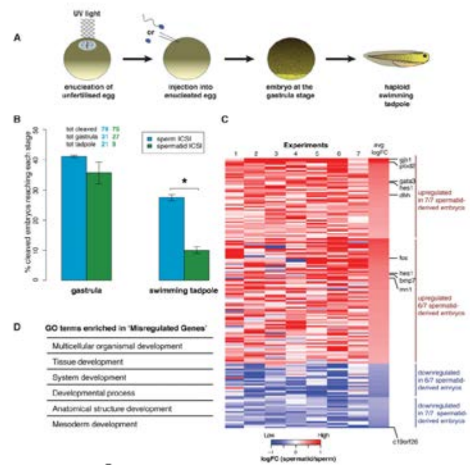


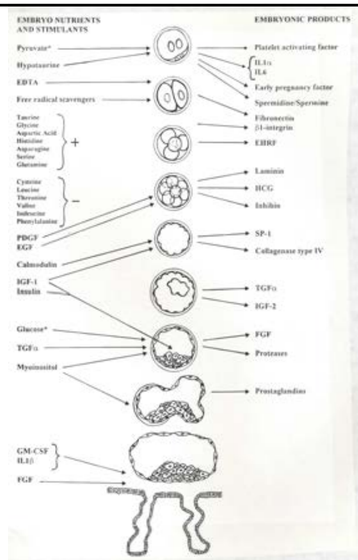
Summary of events in mammalian preimplantation development. Top: immature oogonia undergo DNA replication and pause in prophase of meiosis I as 4N primary oocytes. Completion of meiosis I results in extrusion of the first polar body (PB) and formation of a diploid secondary oocyte, which is released from the follicle upon ovulation. Thereafter, the second meiotic division is initiated and the secondary oocyte arrests in metaphase II (MII) until fertilization. Fertilization induces completion of meiosis II, producing the second polar body and a two-pronucleus zygote. The haploid pronuclei (paternal, blue; maternal, pink) migrate towards the center of the zygote and replicate their DNA content. Diploid pronuclei fuse during synkaryogamy and completion of the first mitotic division produces a two-cell zygote, which undergoes further cleavage divisions (not shown) to produce the blastocyst, which is comprised of the trophectoderm (orange) and the inner cell mass (yellow). Bottom: zygotic genome activation (represented in red) initiates during the two-pronucleus stage and is fully underway by the two-cell stage (see text). Maternal transcripts (represented in green) are gradually degraded and represent less than 10% of the total cellular transcripts by the two-cell stage.

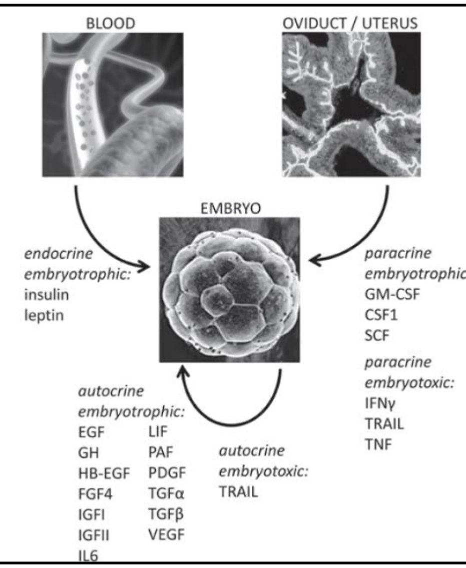




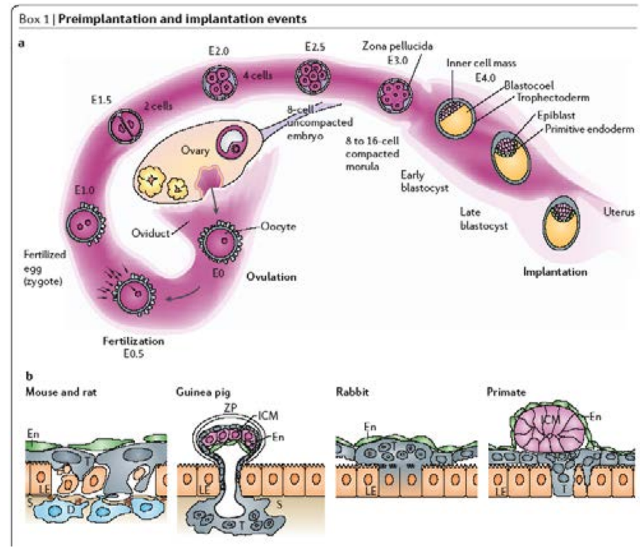
Sperm is epigenetically programmed to regulate gene transcription in embryos
Genome Res. (2016) 26(8):1034-46.
Teperek M, Simeone A, Gaggioli V, et al.



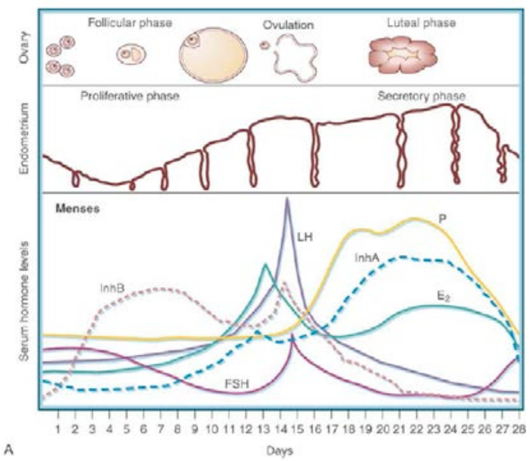




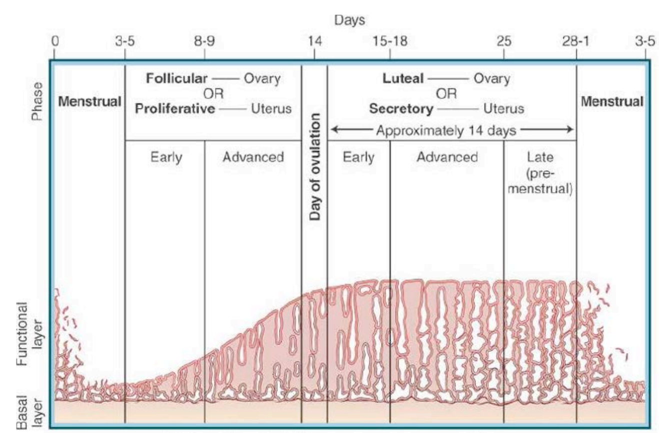
Implantation



Endocrinology of Menstrual Cycle



Functionalis shed at each menstruation



(From Cunningham FG, MacDonald PC, Gant NF, et al: The endometrium and decidua: menstruation and pregnancy. In Williams Obstetrics, 19th ed. Stamford, CT: Appleton & Lange, 1993:81-109.)

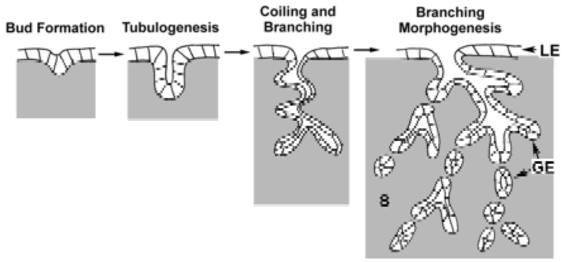


Figure 1. General illustration of the process of endometrial gland development. Uterine glands originate as shallow gland buds from the lumenal epithelium (LE) before undergoing invagination to form tubules. As the tubules progress through the stroma (S) toward the myometrium, they begin to coil and branch. The final stage of endometrial glandular epithelial (GE) differentiation is the process of branching morphogenesis, which does not occur in rodents. This process is similar to that occurring in epitheliomesenchymal organs, such as the lung, salivary gland, prostate, and mammary gland.

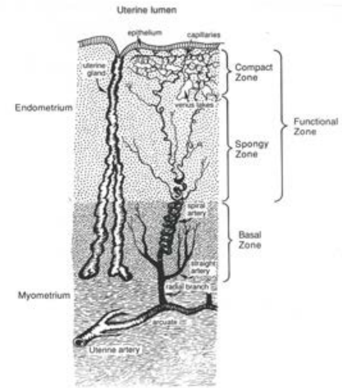


Figure 9–2 ■ Diagram of the histologic organization of the secretory phase human endometrium. (Modified from Blandau RJ. Weiss-Greep Histology, 4th ed. New York, McGraw-Hill, 1977, p 911. © by the Williams & Wilkins Co., Baltimore.)

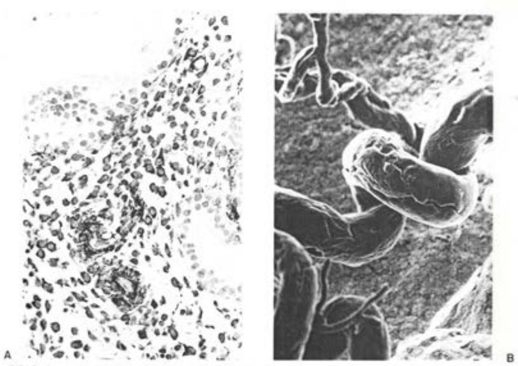
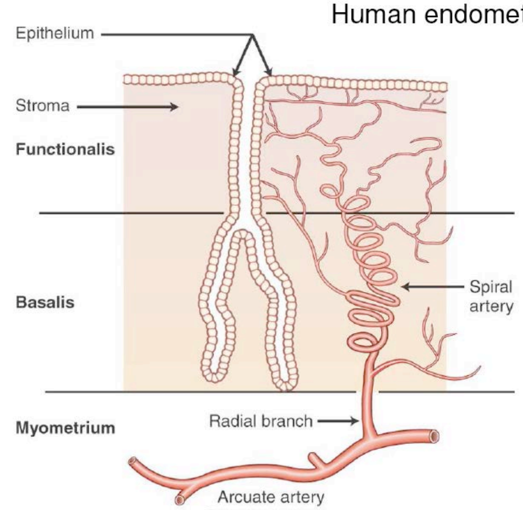


FIG. 8. Secretory endometrium, cycle day 24. **A:** Vascular endothelium of capillary system is highlighted by factor VIII antibody immunostaining (H&E ×350). **B:** Scanning electron microscopy of tortuous endometrial vessel with collateral branching *(lower right)* (×10,000).

Human endometrium

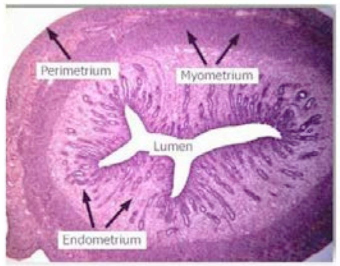


Female Reproductive Anatomy

Uterus

Prominent organ of the female reproductive tract, organ of pregnancy

1. serosa – perimetrium
2. muscularis – myometrium
3. mucosa – endometrium



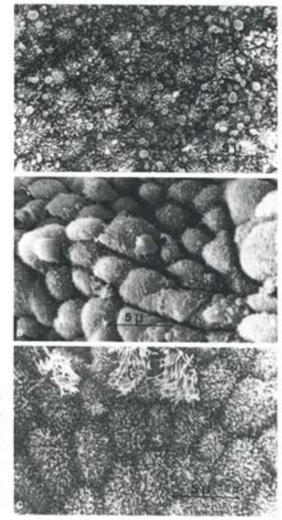
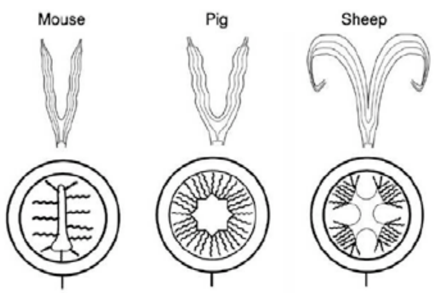
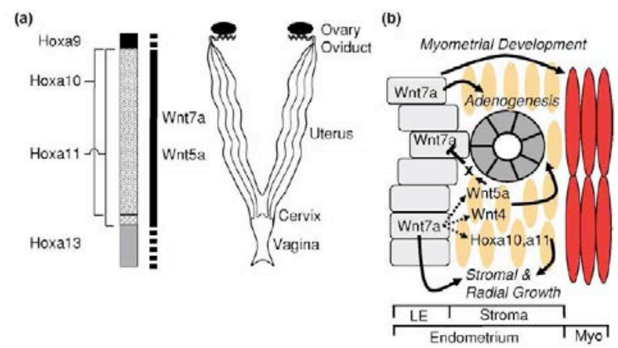


Figure 9-13 • Scanning electron microscopy of the uterine lumen.
A. Luminal epithelium, 2 days after ovulation during spontaneous menstrual cycle.
B. Luminal epithelium on day 6 after ovulation during spontaneous menstrual cycle.
C. Luminal epithelium on day 9 after ovulation during spontaneous menstrual cycle.
(From Martel D, et al. In Yoshinaga K (ed). Blastocyst Implantation. Boston, Adams Publishing Group Ltd. 1989, p 178.)



Curved lines - tubular, coiled, and branched glands that extend from the uterine lumen to the inner layer of myometrium
rodent uterus - a few endometrial glands
sheep uterus contains a large number of glands in the intercaruncular areas of the endometrium
pig uterus contains large numbers of glands throughout the endometrium

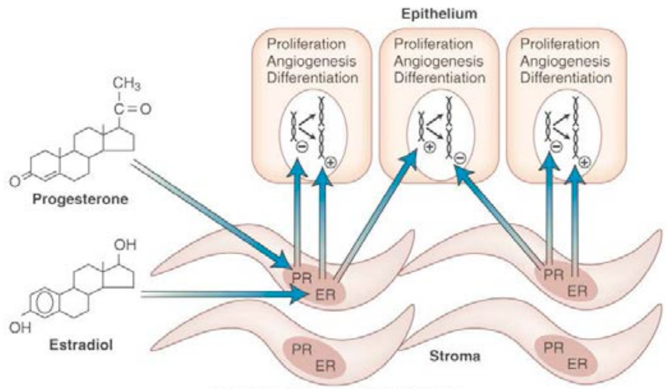
Spencer et al Curr Top Dev Biol 2005; 68:85



Female reproductive tract organogenesis in the mouse.

During fetal development – no region specific expression

Birth - Hoxa gene expression start to regionalize along the anteroposterior axis



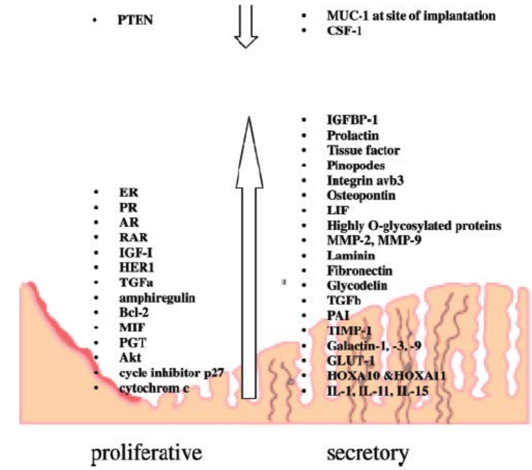
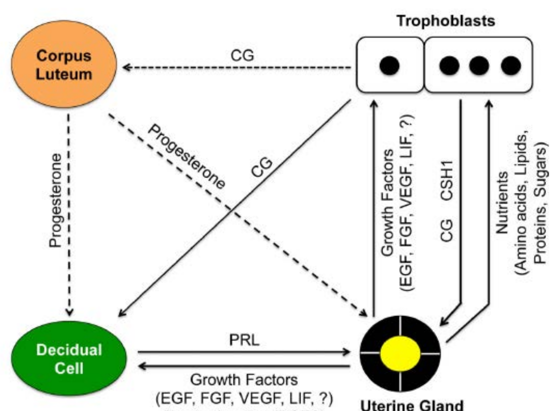
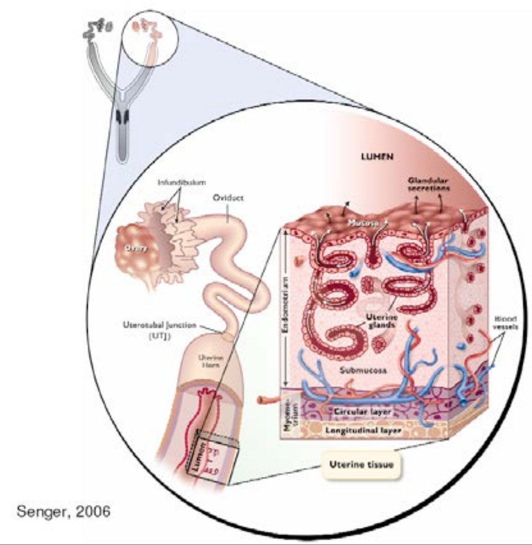


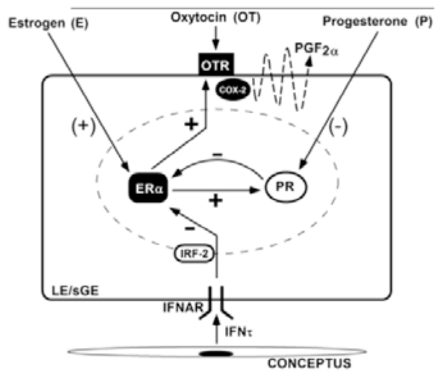
Figure 1. Up- and down-regulated factors of the proliferative and secretory phase.





Senger, 2006

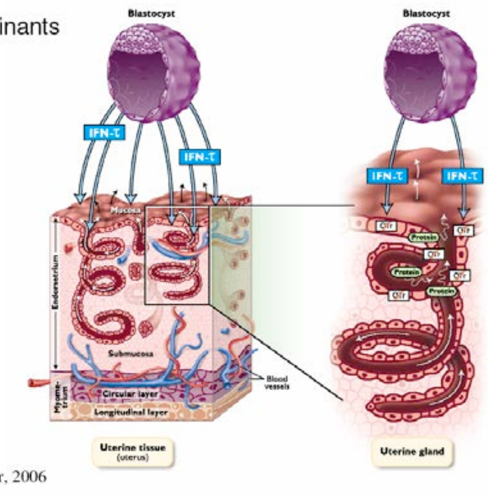
Ruminant endometrial cell



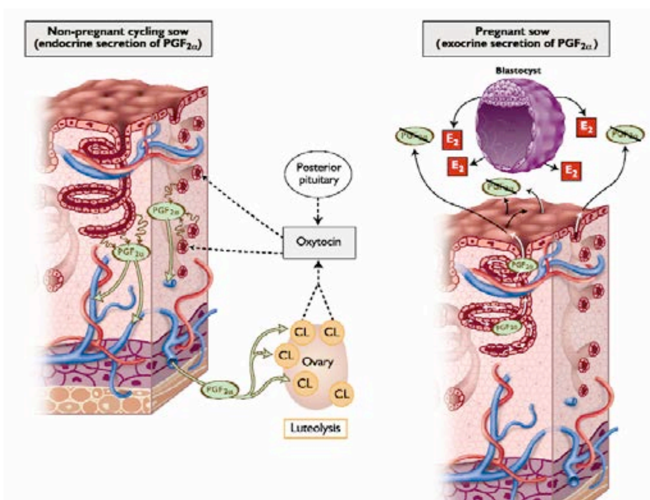
INFτ is critical day 15-16 bovine pregnancy, day 13-14 sheep

Spencer et al, BIOLOGY OF REPRODUCTION **71**, 2–10 (2004)

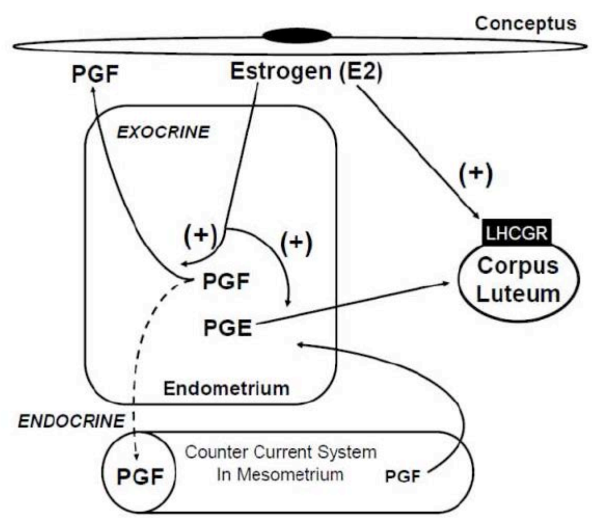
Ruminants

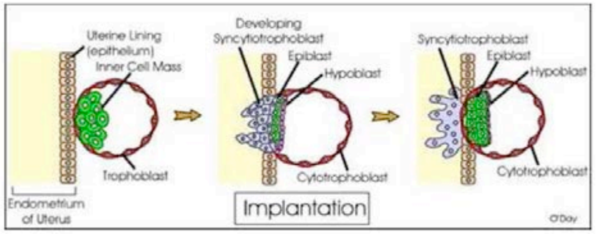


Senger, 2006



Senger, 2006

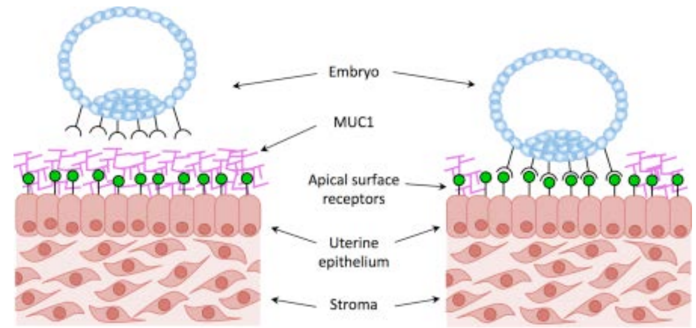




Apposition

Adherence

Formation of Syncytiotrophoblast: Fusion of cytotrophoblast cells results in giant multinucleate cell that will surround complete embryo



MUC1 as an anti-adhesion molecule acting as a barrier to embryo attachment to the apical surface of the uterine epithelium. MUC1 clearance allows access to the apical cell surface receptors for implantation.

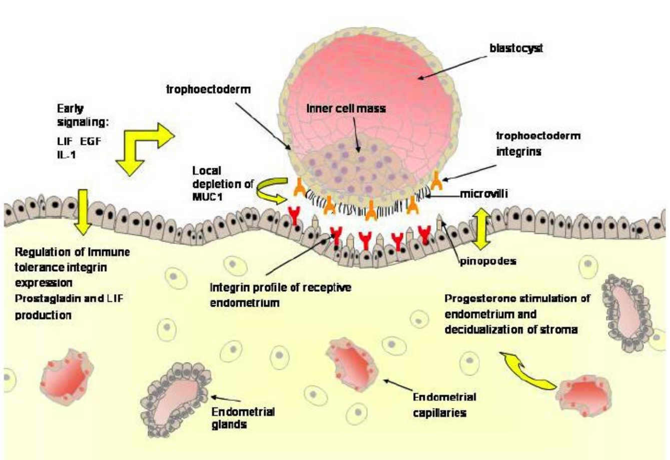


Figure 1
A schematic representation of a blastocyst approaching the receptive endometrium, defined by the integrin profile and appearance of pinopodes. Early signaling between the blastocyst and the endometrium precedes the attachment.

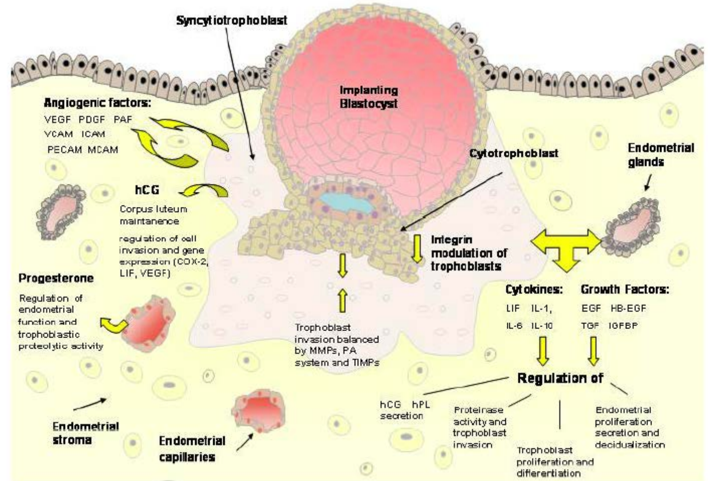
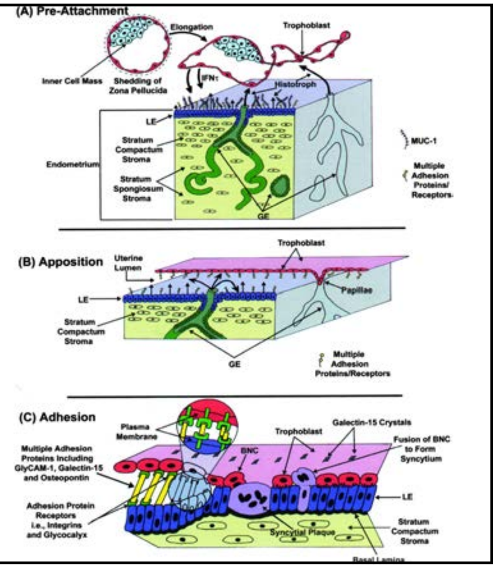


Figure 2
A schematic representation of an implanting blastocyst, highlighting interactions between trophoblastic and endometrial cells, including integrins, growth factors, cytokines, hormones and proteases.

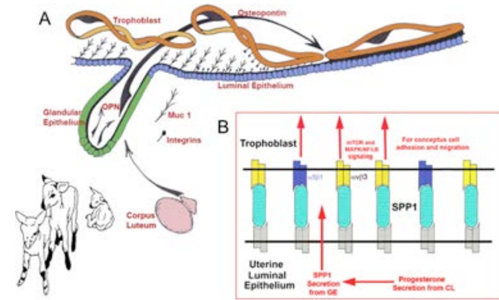
Figure 2 Apposition and adhesion phases of blastocyst implantation in sheep. (A) Preattachment involving shedding of the zona pellucida (phase 1) and precontact and blastocyst orientation (phase 2). The first phase of implantation is the shedding of the zona pellucida on day 8 that exposes the trophoblast. The second phase of implantation is before contact and involves the blastocyst orientation which occurs on days 9–11 as the blastocyst grows from a spherical to a tubular conceptus and migrates to the middle region of the uterine horn ipsilateral to the corpus luteum. The antiadhesive mucin MUC-1 is present on the endometrial LE, thereby preventing contact of the trophoblast with adhesive receptors such as integrins. Histotroph, secreted from the endometrial LE and GE, nourishes the developing blastocyst. (B) Apposition and transient attachment (phase 3). After day 11, the tubular blastocyst elongates to form a filamentous conceptus. During this period, expression of MUC-1 declines on the LE, which exposes constitutively expressed integrins on the LE as well as trophoblast. Apposition occurs between the trophoblast and endometrial LE and between the trophoblast papillae and GE ducts. Elongation of the blastocyst probably requires apposition and transient attachment to the endometrial LE. (C) Adhesion (phase 4). Firm adhesion of the mononuclear cells of the trophoblast to the LE occurs between days 15 and 16. Available evidence indicates that several molecules (GlyCAM-1, galectin-15 and osteopontin) interact with receptors (integrins and glycoconjugates) on the apical surfaces of the trophoblast and LE to facilitate adhesion. The binucleate cells (BNC) differentiate from the mononuclear trophoblast and then migrate to and fuse with the LE to form a multinucleated syncytial plaque. Although the BNC are inherently invasive, they do not cross the basal lamina that supports the LE.



Osteopontin: a leading candidate adhesion molecule for implantation in pigs and sheep.

Johnson GA, Burghardt RC, Bazer FW.

J Anim Sci Biotechnol. 2014 Dec 17;5(1):56.



Expression, regulation and proposed function of OPN produced by the uterine GE of pregnant sheep. A) As the lifespan of the CL is extended as the result of the actions of interferon tau secretion from elongating ovine conceptuses (Trophoblast) they secrete progesterone. Progesterone then induces the synthesis and secretion of OPN (Osteopontin) from the uterine GE (Glandular Epithelium)[51]. The implantation cascade is initiated with down-regulation Muc 1 (the regulatory mechanism remains to be identified) on the LE surface to expose integrins on the LE and trophoblast surfaces for interaction with OPN to mediate adhesion of trophoblast to LE for implantation[29, 51, 52, 66]. B) In vitro experiments have identified the αvβ3 integrin receptor on trophoblast as a binding partner for OPN[66]. OPN then likely acts as a bridging ligand between αvβ3 on trophoblast and as yet unidentified integrin receptor(s) expressed on the opposing uterine LE. Note that the α5 integrin subunit was immunoprecipitated from membrane extracts of biotinylated oTr1 cells that were eluted from an OPN-Sepharose column, but the β1 integrin subunit, the only known binding partner for α5, could not be immunoprecipitated. Therefore, while we cannot definitively state that OPN binds α5β1 integrin on oTr1, we are reticent to exclude this possibility.

Cytokines critical for implantation

LIF – uterine gland expression and by stromal cells that surround the blastocyst during attachment

1. Uterine preparation
2. Attachment

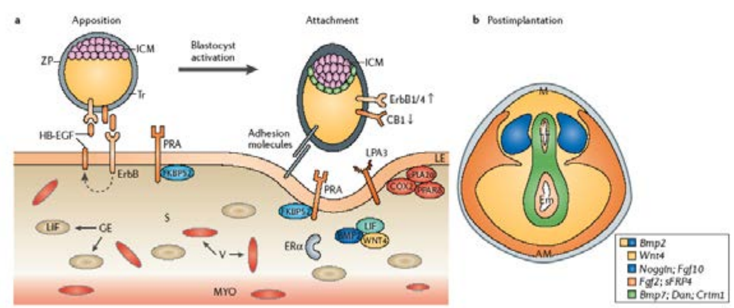
Lif -/- mice: blastocyts remain dormant, do not implant

Molecular mechanisms unclear

Gp130 – mutate the STAT binding site results in implantation failure

LIF – high expression in human uterine tissue

Homeobox proteins – Hoxa10, Hoxa11



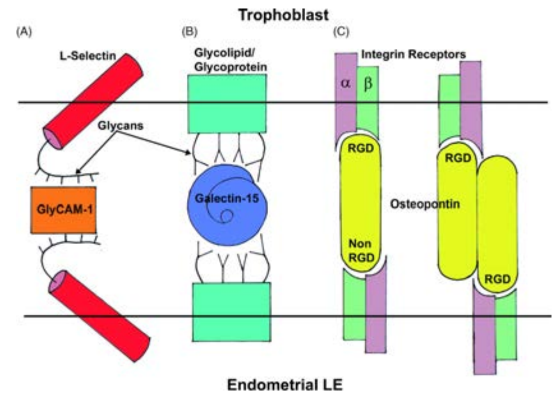
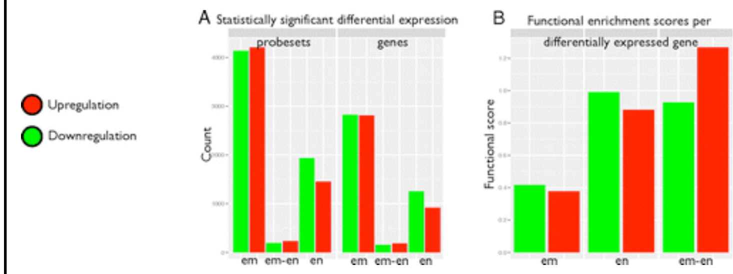
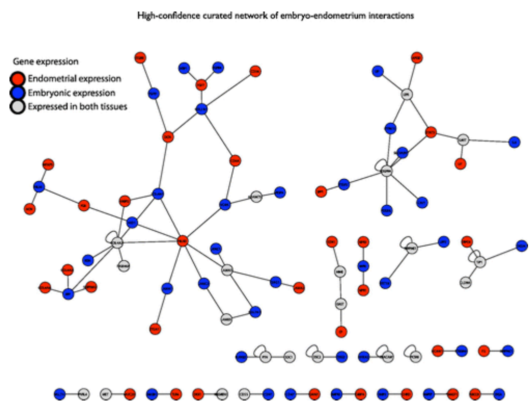


Figure 3 Possible interactions between trophoblast and endometrial epithelial cells regulating adhesion during implantation. Evidence for these interactions are from *in vivo* and *in vitro* studies in sheep, mice and humans. (A) Homotypic binding of GlyCAM-1 by L-selectin. GlyCAM-1 functions as a carbohydrate ligand for the lectin domain of L-selectin. (B) Homotypic and heterotypic binding of glycans on proteins and/or lipids via the multifunctional, secreted bridging ligand galectin-15. There is evidence that galectin-15 can bind to a large number of proteins and lipids, including mucins and integrins, which contain β-galactosides, using a carbohydrate recognition domain. (C) Homotypic and heterotypic integrin-mediated adhesion via the bifunctional, secreted bridging ligand OPN. There is evidence that OPN can homodimerize and bind integrins in a RGD-dependent and RGD-independent manner.

Research resource: interactome of human embryo implantation: identification of gene expression pathways, regulation, and integrated regulatory networks.
Altmäe S, et al.
Mol Endocrinol. 2012 Jan;26(1):203-17.



Transcriptional profiling of the embryo-endometrium interface. A, Number of Affymetrix probe sets (left) and corresponding HUGO Gene Nomenclature Committee gene symbols (right) detected in microarray analysis. em, Embryo; en, endometrium; em-en, coregulated in embryo and endometrium; red, up-regulation; green, down-regulation. B, Functional scores of known genes in embryonic and endometrial gene lists from GO and pathway enrichment analysis.



High-confidence embryo-endometrium interaction network from protein-protein interaction data and literature curation. Node color represents tissue-specific differential gene expression. blue, Expressed in embryo; red, expressed in endometrium; gray, expressed in both tissues.

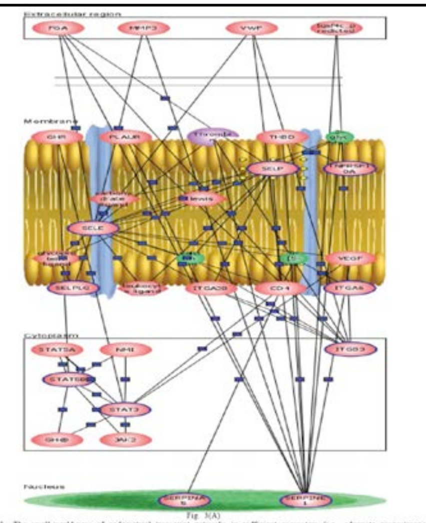
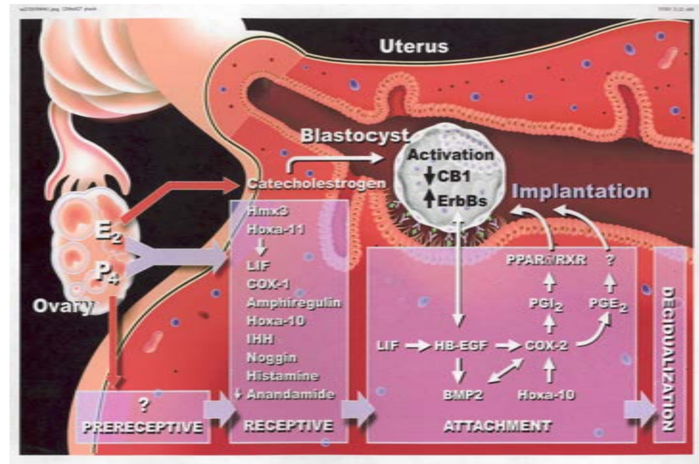


Fig. 3: The small-world-ness of endometrial transcript networks in sufficient ecosystem (i.e., adequate progesterone and viable preimplantation stage embryo) on day 6 after ovulation (A), and its entropization by administration of low dose high affinity anti-progestin (mifepristone, 2 mg/kg body weight) (B) is seen. The probable physiological significance of observations as shown in (A) and (B) has been discussed in the essay.

Genes expressed in the glandular epithelia of the mouse uterus and effects of mutation on pregnancy outcomes

Symbol	Name	Expression[1]	Null/Conditional Phenotype	Reference
Cdh1	E-cadherin	LE and GE (GD1-4), stroma (GD5-8)	Embryonic lethal, Implantation defect (conditional)	101,102
Clca3	chloride channel calcium activated 3	LE and GE (peaks on GD1)	Viable and fertile	103,104
Cxcl15	chemokine (C-X-C motif) ligand 15	GE, LE	Viable and fertile	105,106
Fnbp1	formin binding protein 1	GE (GD4-5)	N/A	44
Foxa2	forkhead box A2	GE (neonatal and adult)	Embryonic lethal, Implantation defect (conditional)	35,107
Gulo	gulonolactone (L-) oxidase	GE>>LE (GD4-5)	Viable and fertile	44,108
Ihh	Indian Hedgehog	LE and GE (peaks on GD3-4)	Embryonic lethal, Implantation defect (conditional)	109
Il6st	interleukin 6 signal transducer	GE (GD3-5) Decidua (GD7)	Viable and fertile	110,111
Klf5	Kruppel-like factor 5	LE and GE (GD1-5) Decidua (GD5-8)	Embryonic lethal, Implantation defect (conditional)	112
Lgr4	leucine-rich repeat-containing G protein-coupled receptor 4	GE, LE	Implantation defect	41
Lif	leukemia inhibitory factor	GE>>Stroma (GD4)	Implantation defect	34
Ltf	lactotransferrin	LE and GE (GD1-2)	Viable and fertile	113,114
Lyz2	lysozyme 2	Stroma, GE (GD3-5)	Viable and fertile (knock-in)	44,115
Msx1	homeobox, msh-like 1	LE and GE (peaks on GD4 and declines)	Embryonic lethal, Subfertile (conditional)	116,117
Msx2	homeobox, msh-like 2	LE and GE (peaks on GD4)	Viable and fertile, Infertile (double conditional)	116,117
Prss28	protease, serine, 28	GE (GD5-8)	N/A	118
Prss29	protease, serine, 29	GE (GD5-9)	N/A	119
Ptgs1	Prostaglandin-endoperoxide synthase 1	LE and GE (peaks on GD4)	Viable, delayed parturition	120,121
Sh3tc2	SH3 domain and tetratricopeptide repeats 2	GE (GD4-5)	Viable and fertile	44,122
Slc23a2	solute carrier family 23 (nucleobase transporters), member 2	GE	Postnatal lethal	44,123
Spink3	serine peptidase inhibitor, Kazal type 3	GE (onset GD4)	Postnatal lethal	54,124
Sult1d1	sulfotransferase family 1D, member 1	GE>>LE (GD3-4)	N/A	44
Tro	Trophinin	LE and GE (peaks between GD4 and 6)	Viable and fertile	125
Ttr	transthyretin	GE only (peaks on GD4)	Viable and fertile	126,127

[1] GD, gestational day; GE, glandular epithelium; LE, luminal epithelium



"Systems Biology of Reproduction"

Spring 2018 (Even Years) - Course Syllabus
BIOL 475/575 Level Undergraduate/Graduate (3 Credit)
SLN: (475) - 06206, (575) - 06207
Time - Tuesday and Thursday 10:35 am-11:50 am
(Course Lectures on Blackboard/Panopto and Discussion Sessions on WSU Blackboard/Collaborate for all campuses)
Room – CUE 418
Course Director - Michael Skinner, Abelson Hall 507, 335-1524, skinner@wsu.edu
Learning Objective -
Current literature based course on the Systems Biology of Reproduction. Learning Systems approaches to the biology of reproduction from a molecular to physiological level of understanding.
Schedule/Lecture Outline -

January	9 & 11	Week 1	Systems Biology Introduction
	16 & 18	Week 2	Molecular/ Cellular/ Reproduction Systems
	23 & 25	Week 3	Sex Determination Systems
February	30 & 1	Week 4	Male Reproductive Tract Development & Function
	6 & 8	Week 5	Female Reproductive Tract Development & Functio
	13 & 15	Week 6	Gonadal Developmental Systems Biology
	20 & 22	Week 7	Testis Systems Biology
March	27 & 1	Week 8	Ovary Systems Biology
	6 & 8	Week 9	Epigenetics and Transgenerational Gonadal Disease
	12 - 16	**Week 10**	**Spring Break**
	20 & 22	Week 11	Gametogenesis/ Stem Cells/ Cloning
	27 & 29	Week 12	Hypothalamus-Pituitary Development & Function
April	3 & 5	Week 13	Reproductive Endocrinology Systems
	10 & 12	Week 14	Fertilization & Implantation Systems
	17 & 19	Week 15	Fetal Development & Birth Systems
	24 & 26	Week 16	Assisted Reproduction/Contraception
May	1 & 3	Week 17	Exam or Grant Review