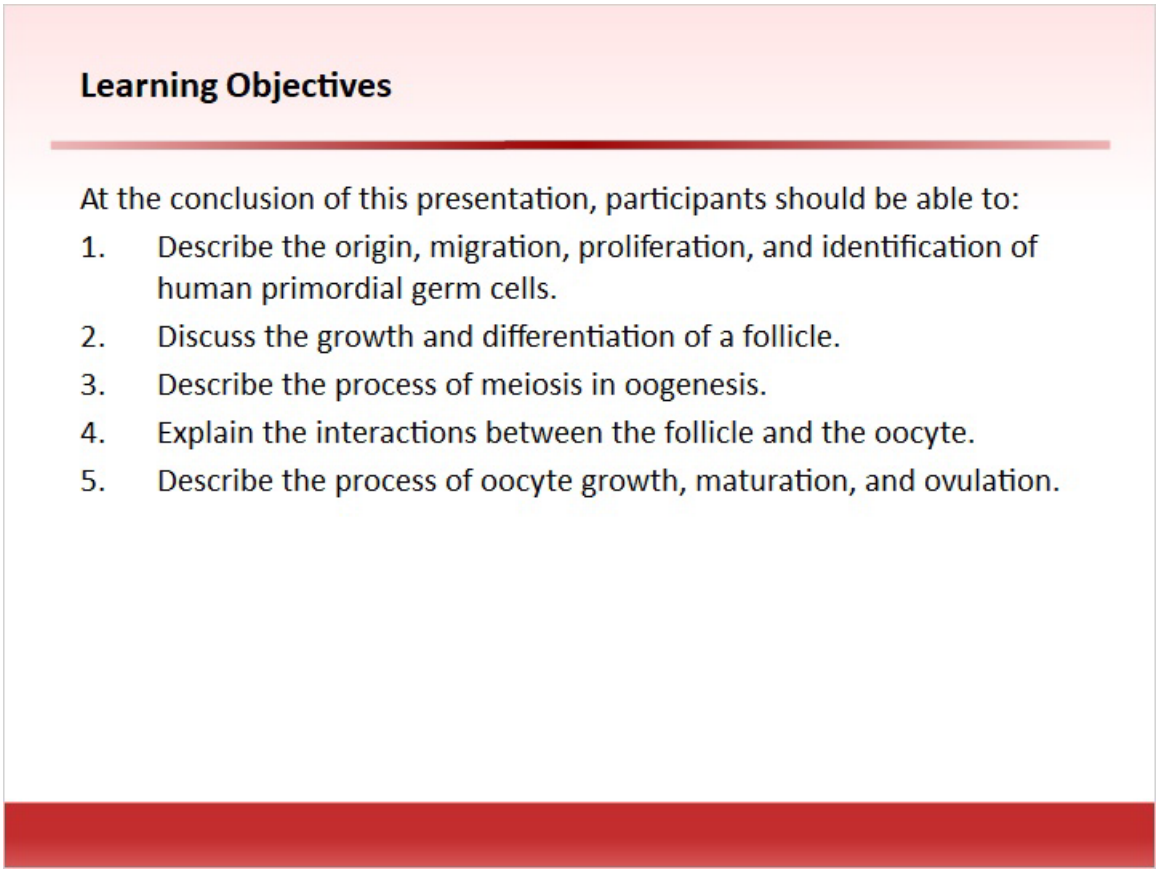
LABCC100 Lesson 3

1.1 Primordial Germ Cells and Oogenesis

Notes:

Welcome to the American Society for Reproductive Medicine's eLearning modules. The subject of this presentation is Primordial Germ Cells and Oogenesis.

1.2 Learning Objectives

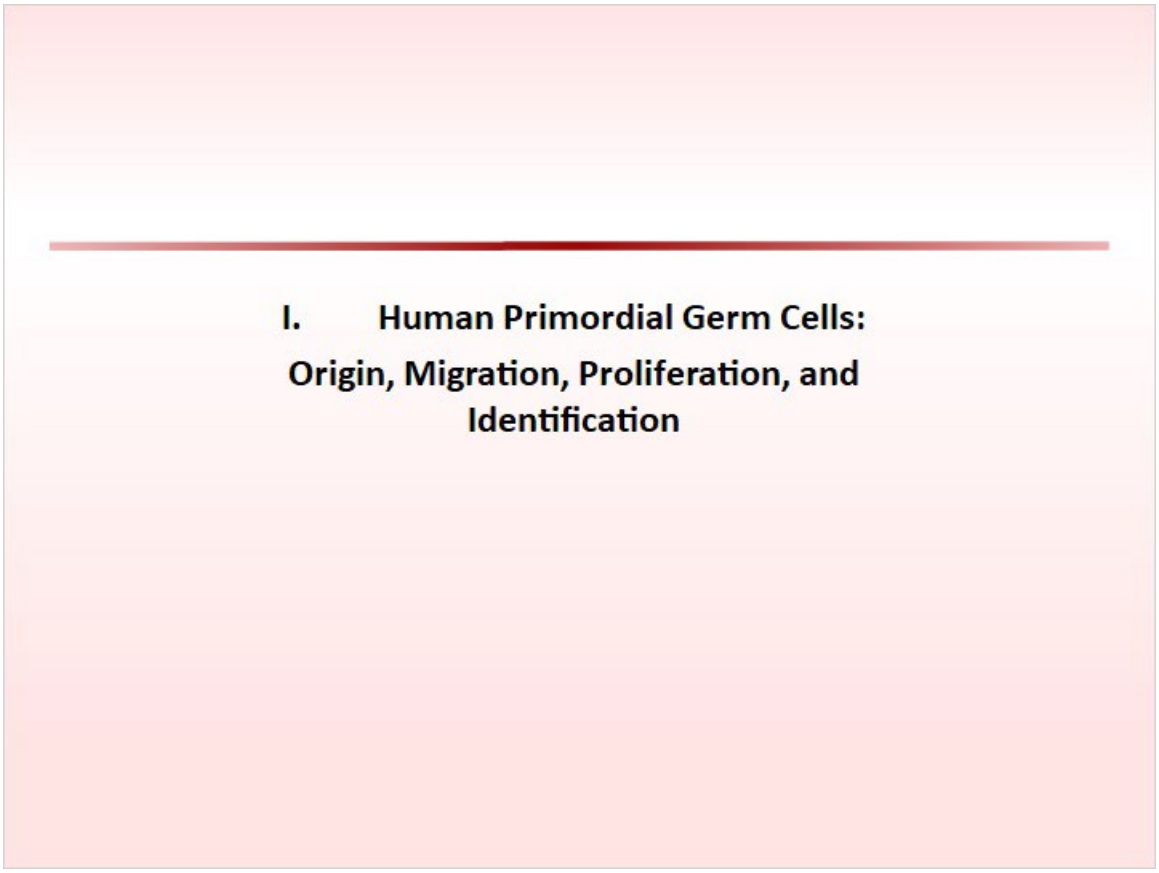


Notes:

At the conclusion of this presentation, participants should be able to:

1. Describe the origin, migration, proliferation, and identification of human primordial germ cells.
2. Discuss the growth and differentiation of a follicle.
3. Describe the process of meiosis in oogenesis.
4. Explain the interactions between the follicle and the oocyte.
5. Describe the process of oocyte growth, maturation, and ovulation.

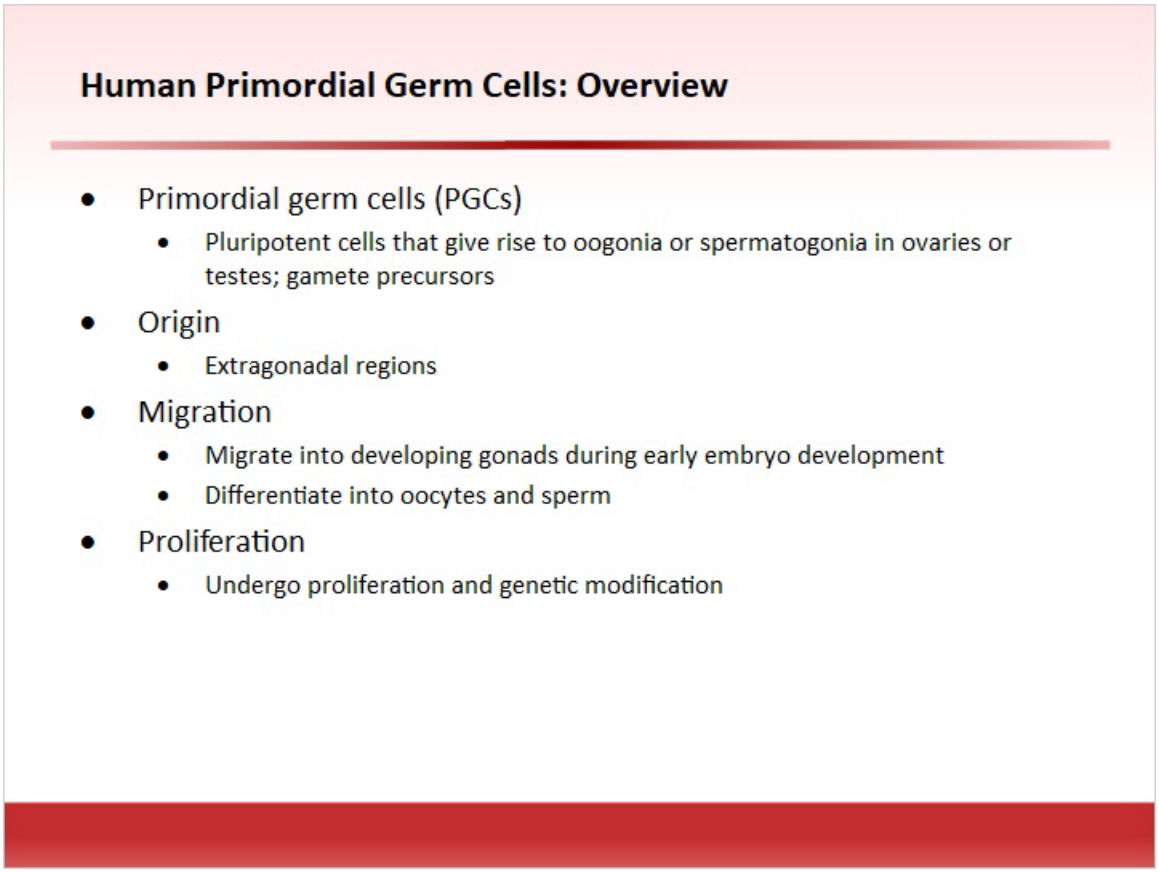
1.3 Untitled Slide



Notes:

Part 1 will focus on human primordial germ cells, their origin, migration, and proliferation during formation of the embryo and fetus, and how to identify these cells.

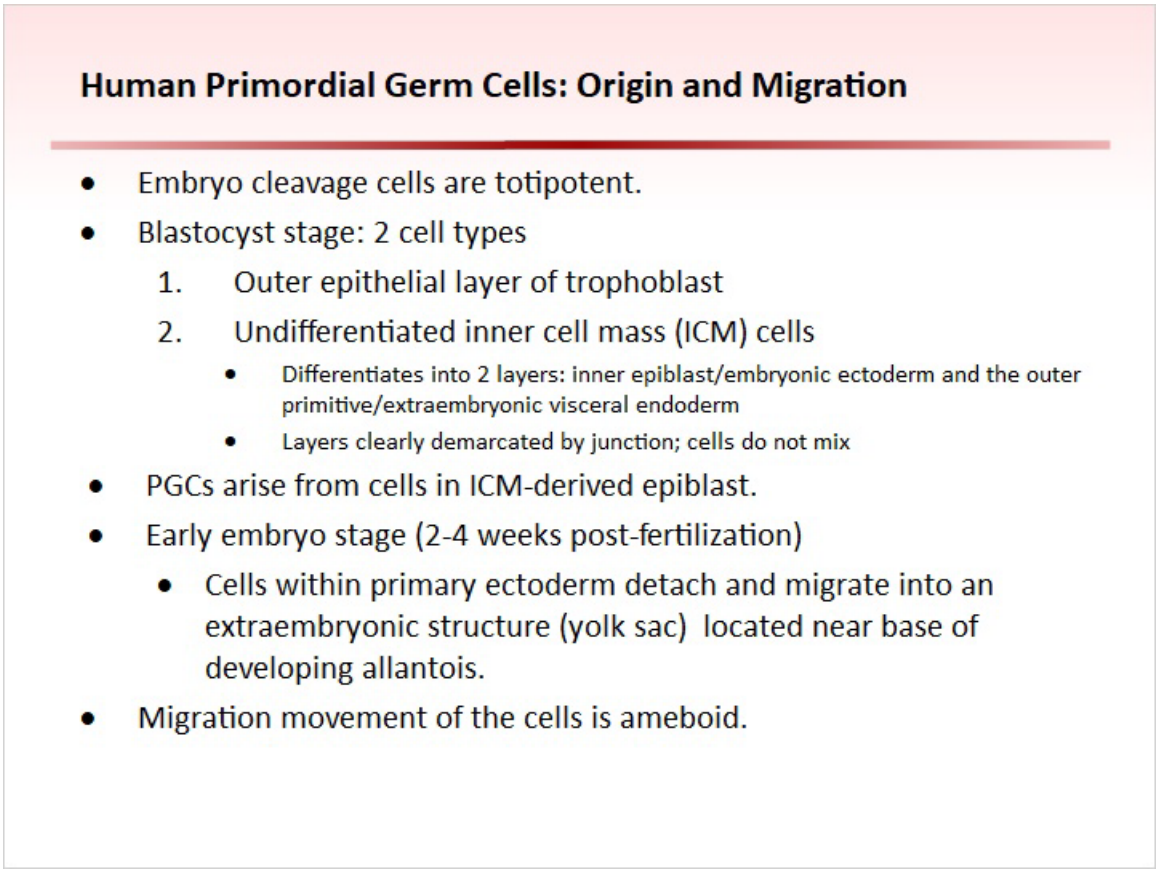
1.4 Human Primordial Germ Cells: Overview



Notes:

Primordial germ cells are a group of pluripotent cells that give rise to oogonia or spermatogonia. Their origin is extragonadal and they migrate into developing gonads during early embryo development where they differentiate into oocytes and sperm. Primordial germ cells proliferate during the journey and undergo genetic modification.

1.5 Human Primordial Germ Cells: Origin and Migration



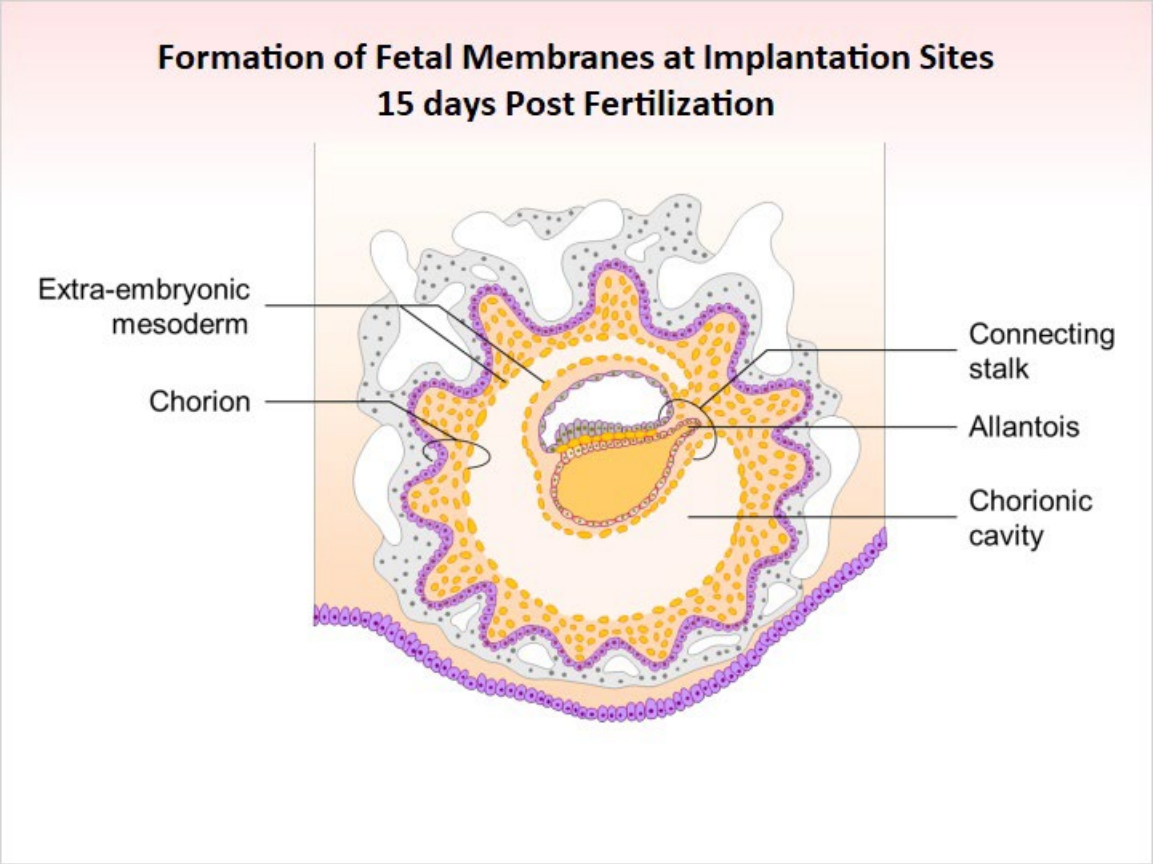
Notes:

At fertilization, an oocyte unites with sperm to become a zygote and it begins dividing, called cleavage. Cells produced by the first few cleavages are all totipotent, which means they can give rise to any type of cell in the body.

When the embryo reaches blastocyst stage, it differentiates and consists of 2 cell types: the outer epithelial layer of trophoblast and the undifferentiated inner cell mass. Later, the inner cell mass develops into 2 layers: the inner epiblast or embryonic ectoderm and the outer primitive endoderm. These two layers are defined by a junction and cells do not mix.

Primordial germ cells arise from cells in the inner cell mass-derived epiblast. At 2 to 4 weeks post-fertilization, a group of cells inside the primary ectoderm detach from the ectoderm and migrate into an extraembryonic structure called the yolk sac, which is located near the developing allantois. This movement is ameboid style.

1.6 Formation of Fetal Membranes at Implantation Sites



Notes:

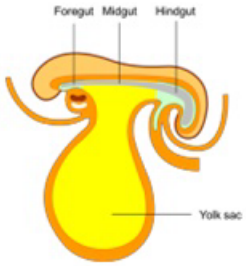
Formation of fetal membranes at implantation sites at approximately 15 days is shown here.

1.7 Migration of Primordial Germ Cells

Migration of Primordial Germ Cells

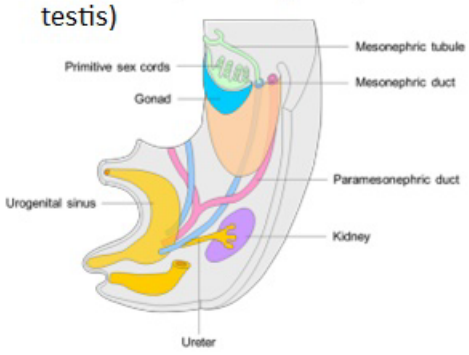
5-6 weeks of fetal development

- PGCs migrate to adjacent yolk sac, pass the hindgut tube to the wall of the gut tube, and from there via the mesentery to dorsal body wall
- When PGCs pass the mesentery, they split into 2 populations to either the right or the left side of the dorsal wall



6-12 weeks of fetal development

- PGCs arrive in the presumptive gonad region-final destination.
- Induce the formation of the genital ridge: primordial gonads
- After sex differentiation, PGCs differentiate into oogonia (in ovary) or spermatogonia (in testis)



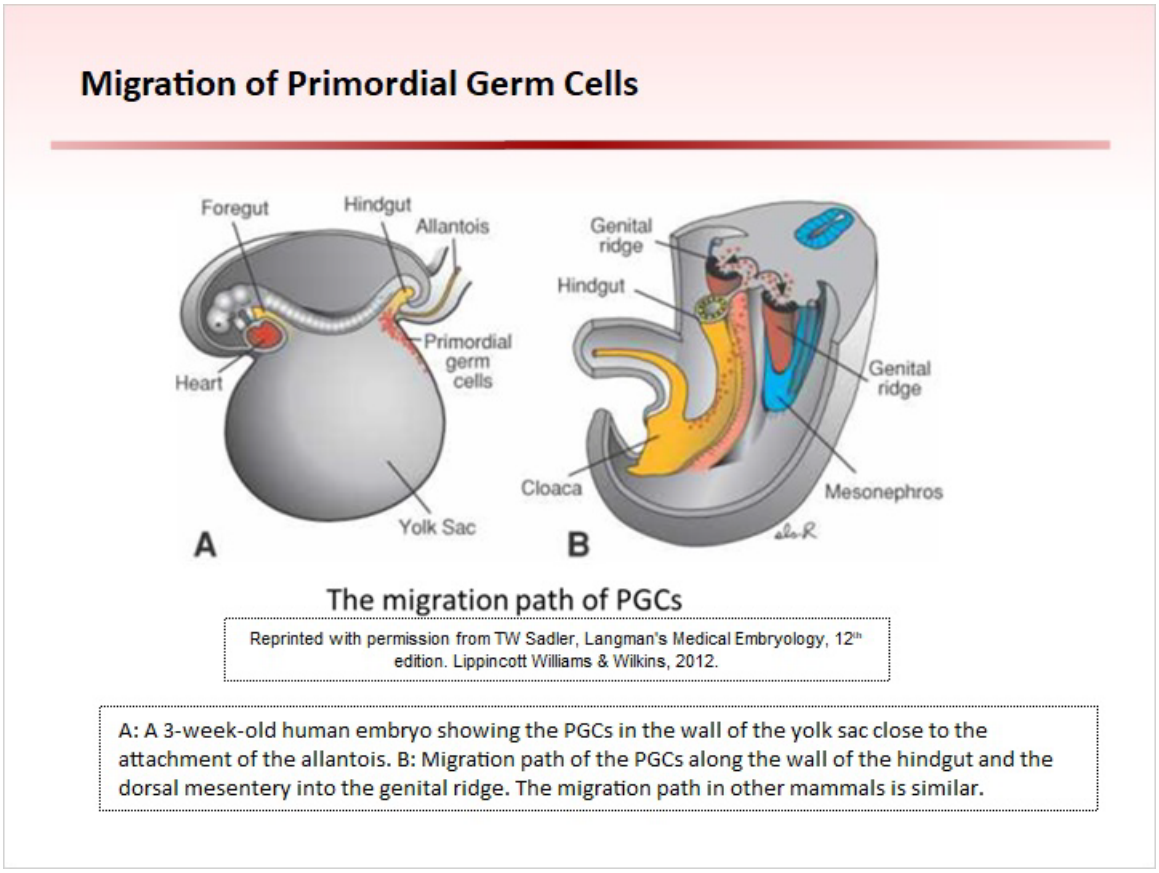
Notes:

At approximately 5-6 weeks of human fetal development, primordial germ cells migrate to the adjacent yolk sac, pass the hindgut tube to the wall of the gut tube and then via the mesentery to the dorsal body wall.

When primordial germ cells pass the mesentery, they split into 2 populations to either the right or the left side of the dorsal wall.

From 6 to 12 weeks, primordial germ cells arrive in the region called the presumptive gonad; this is the final destination. At the presumptive gonad region, primordial germ cells induce the formation of the genital ridge, the primordial gonad. After sex differentiation, primordial germ cells differentiate into oogonia in the ovary or spermatogonia in testis.

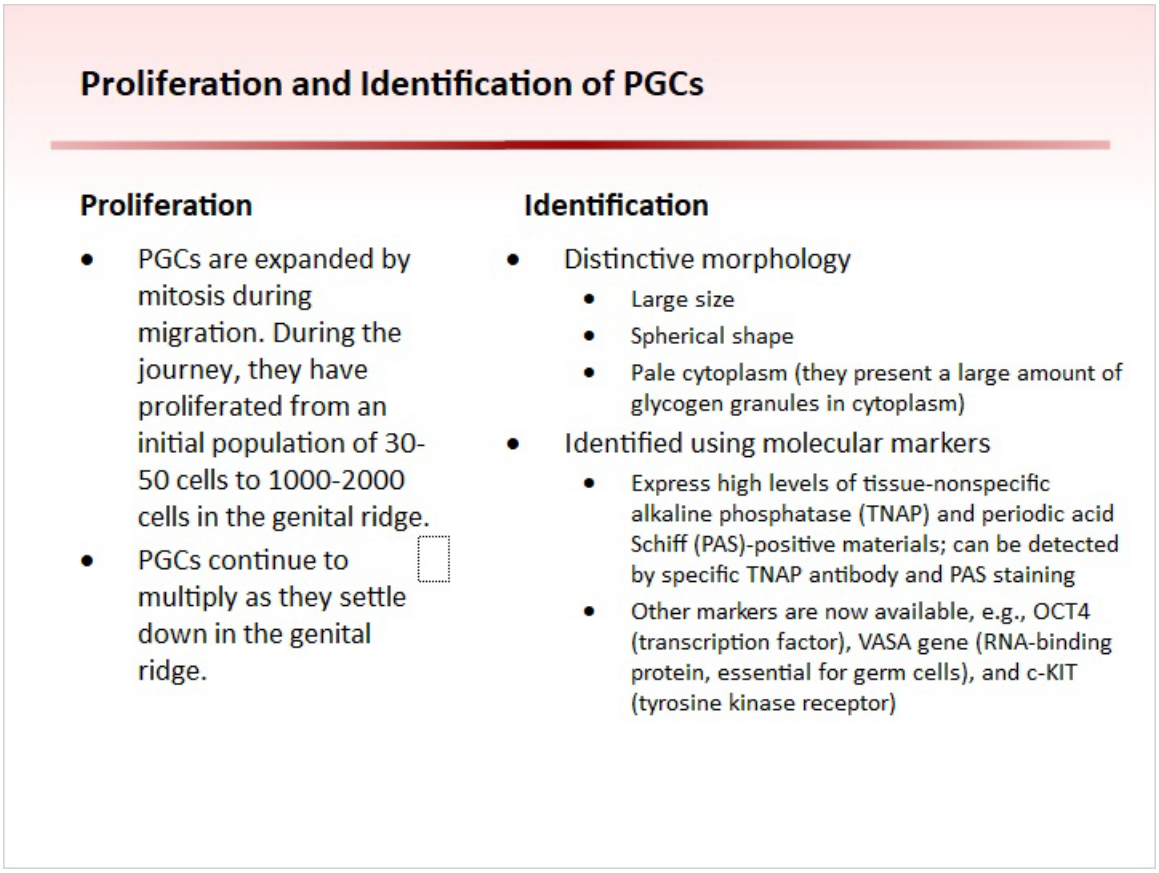
1.8 Migration of Primordial Germ Cells



Notes:

Figure A shows the primordial germ cells of a 3-week-old human embryo in the wall of the yolk sac close to the attachment of the allantois. In figure B is the migration path of the primordial germ cells along the wall of the hindgut and the dorsal mesentery into the genital ridge. When these cells pass the mesentery, they split into 2 populations to either the right or the left side, and then they arrive in the genital ridges.

1.9 Proliferation and Identification of PGCs

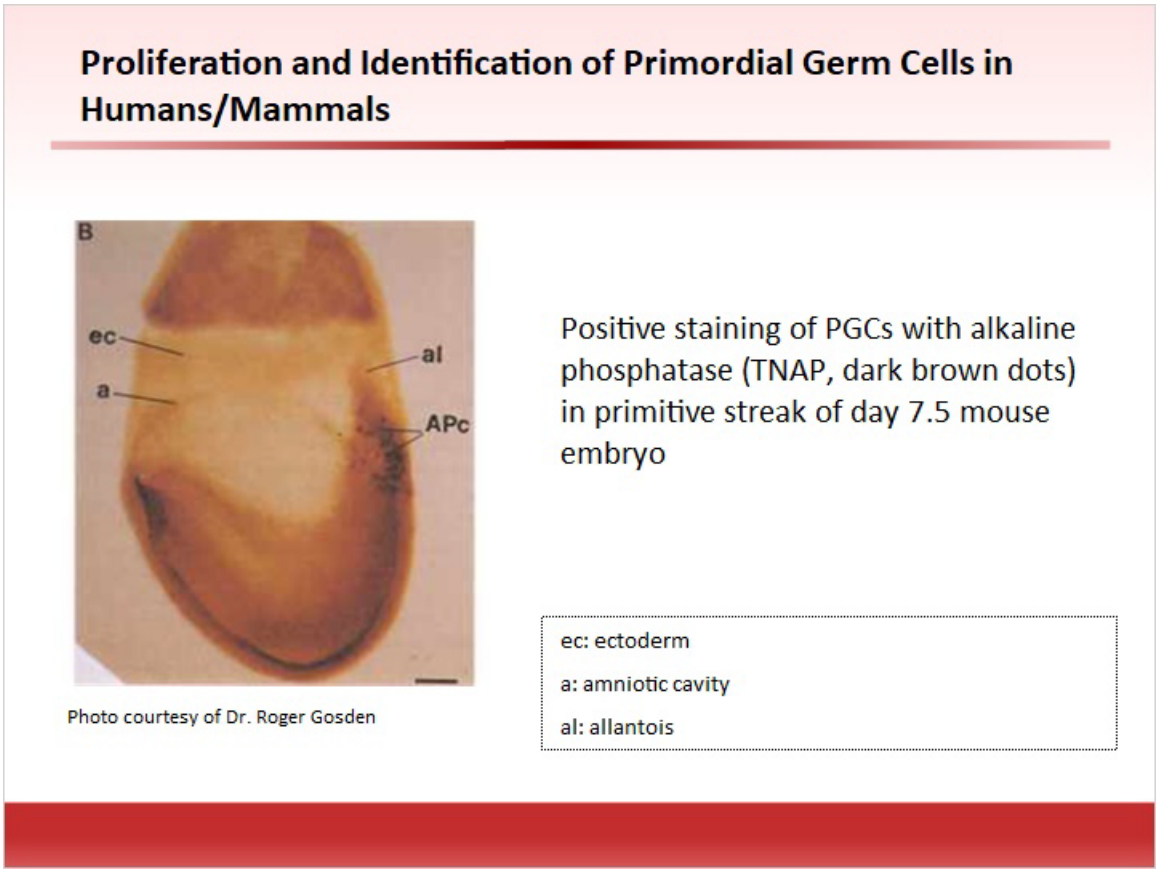


Notes:

As with other somatic cells, primordial germ cells multiply by mitosis during migration. During the journey, the number of the cells increases from an initial population of 30-50 cells to 1000-2000 cells in the genital ridge. Primordial germ cells continue to multiply as they settle down in developing gonads.

Primordial germ cells can be recognized by their morphology: they are large and spherical with pale cytoplasm. They can also be identified using molecular markers: they express high levels of tissue-nonspecific alkaline phosphatase (TNAP) and periodic acid Schiff-positive materials, which can be detected by specific TNAP antibody (this was the first marker to identify germ cells) and PAS staining. Other antibodies are now available, for example: OCT4, a transcription factor; VASA gene, an RNA-binding protein, essential for germ cells; and c-KIT, a tyrosine kinase receptor.

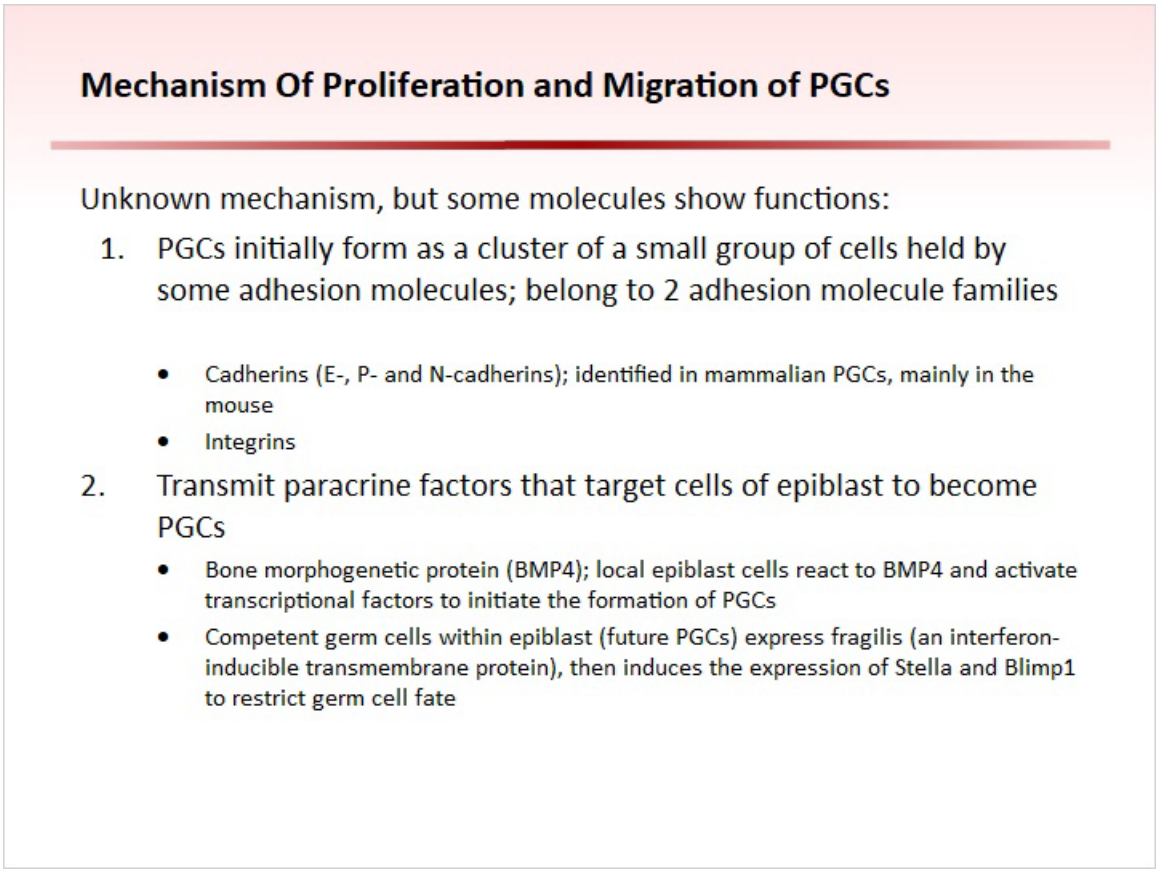
1.10 Proliferation and Identification of Primordial Germ Cells in Humans/Mammals



Notes:

This figure shows the positive staining of primordial germ cells with alkaline phosphatase. They are shown as dark brown dots in the primitive streak of this day 7.5 mouse embryo.

1.11 Mechanism Of Proliferation and Migration of PGCs



Notes:

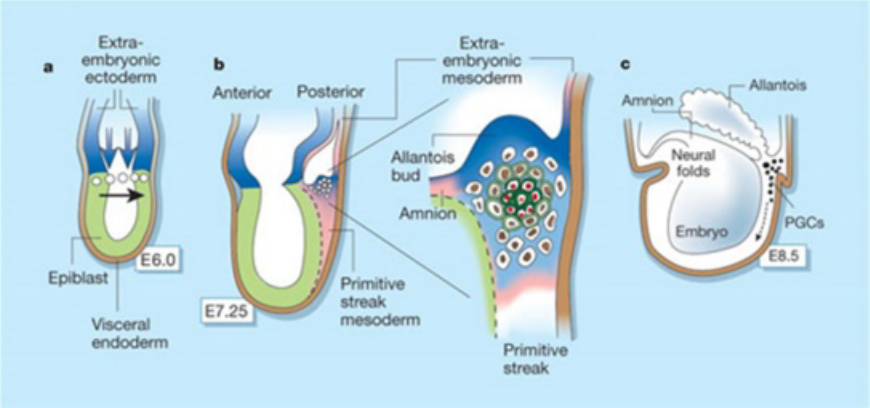
The mechanism of proliferation and migration of PGCs is still unknown, especially in humans; however, some molecules show important functions for proliferation and migration of these cells.

Adhesion molecules may play important roles. PGCs initially form as a cluster of a small group of cells held together by some adhesion molecules. These molecules belong to 2 adhesion molecule families: cadherins and integrins. Cadherins are identified in mammalian PGCs, mainly in the mouse.

Transmitted paracrine factors target cells of the epiblast to form primordial germ cells. With bone morphogenetic protein (BMP4), the local epiblast cells react to BMP4 and activate transcriptional factors to initiate the formation of primordial germ cells. The competent germ cells within the epiblast express fragilis, which is an interferon-inducible transmembrane protein. It then induces the expression of Stella and Blimp1 from approximately 20 cells in the center of this cluster to restrict germ cell fate. Stella and Blimp1 are two important determinants for onset and specification of development of primordial germ cells.

1.12 Mechanism Of Proliferation and Migration of PGCs

Mechanism Of Proliferation and Migration of PGCs



A. In mouse embryo, BMP signals (blue arrows) from the extraembryonic ectoderm induce neighboring epiblast cells (white circles) to become PGCs.

B. On embryonic day 7, these cells emerge from the posterior primitive streak, in the center of the cell cluster are PGC precursors.

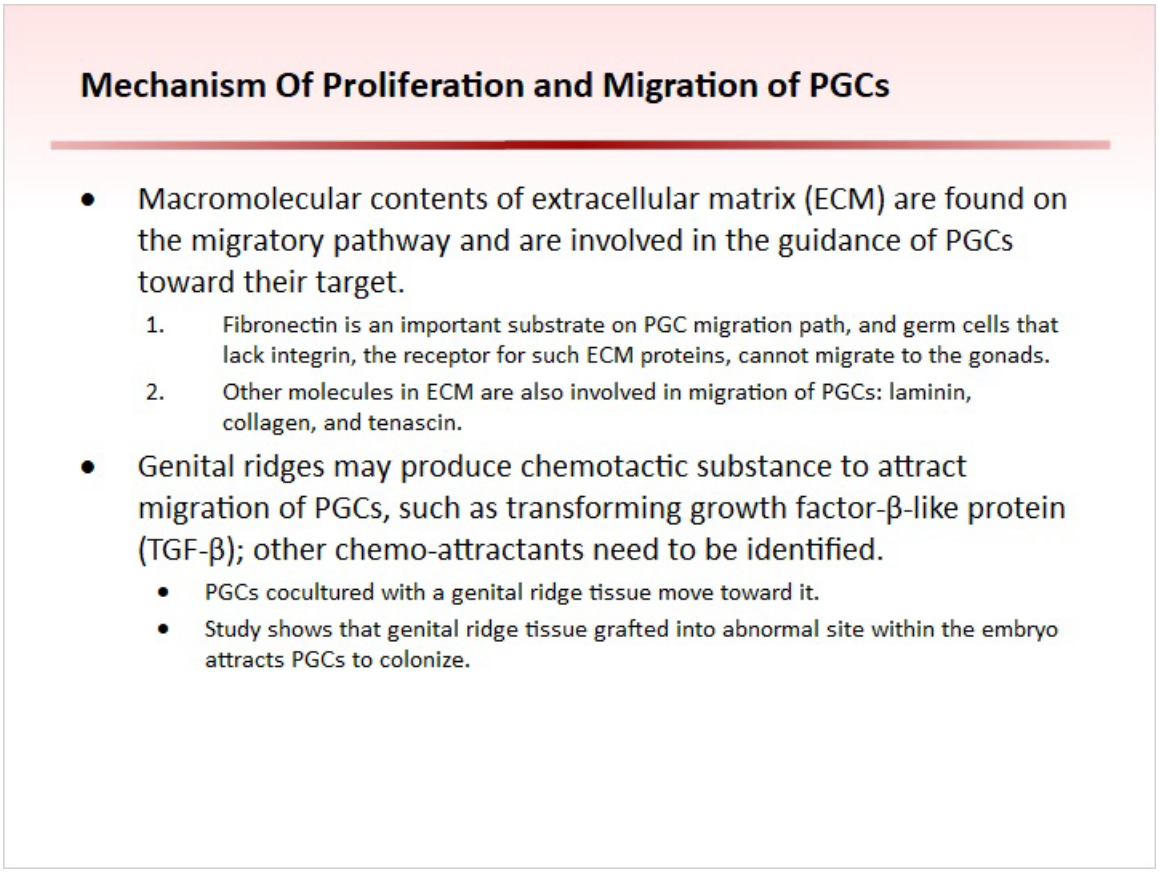
C. PGCs migrate to eventual gonads (dashed arrow)

BMP4 absent from the developing embryo would completely lack both allantois and PGCs.

Notes:

Panel A shows how in the mouse embryo BMP signals (in the blue arrows) from the extraembryonic ectoderm induce neighboring epiblast cells (in white circles) to become primordial germ cells. In Panel B, on embryonic day 7 (E7.25) in the mouse, these cells emerge from the posterior primitive streak; in the center of the cell cluster are primordial germ cell precursors. Panel C shows the migration path of the PGCs to the eventual gonads (dashed arrow). Studies shows that absence of BMP4 from the developing embryo would result in complete lack of growth of both the allantois and primordial germ cells.

1.13 Mechanism Of Proliferation and Migration of PGCs

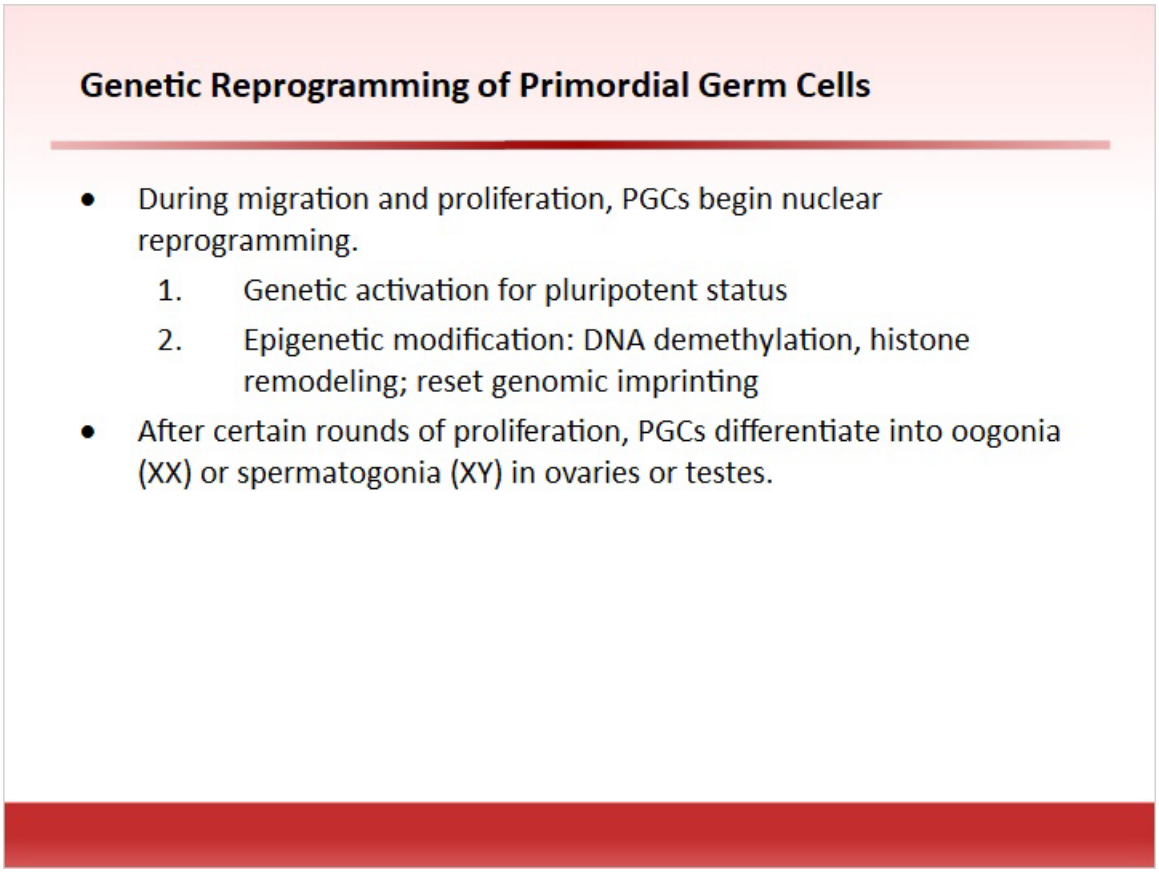


Notes:

In extracellular matrix, the macromolecular contents are found on the migratory pathway; they control and direct the primordial germ cells toward their right destination. Fibronectin is one of these molecules; its receptor integrin is found on germ cells. If germ cells lack integrin, they cannot migrate to the gonads. Other molecules found in extracellular matrix are laminin, collagen, and tenascin. These are also involved in control of migration of primordial germ cells.

Genital ridges may produce chemotactic substances to attract the primordial germ cells, such as transforming growth factor-β like protein. Experiments show that in coculture of primordial germ cells with genital ridge tissue, the cells move toward and settle around the tissue. Other research has found that genital ridge tissue grafted into an abnormal site within the embryo attracts primordial germ cells to colonize. Other chemo-attractants need to be identified in future studies.

1.14 Genetic Reprogramming of Primordial Germ Cells



Notes:

During migration and proliferation, primordial germ cells begin nuclear reprogramming. The process includes genetic activation for pluripotent status of the cells and epigenetic modification to reset genomic imprinting status.

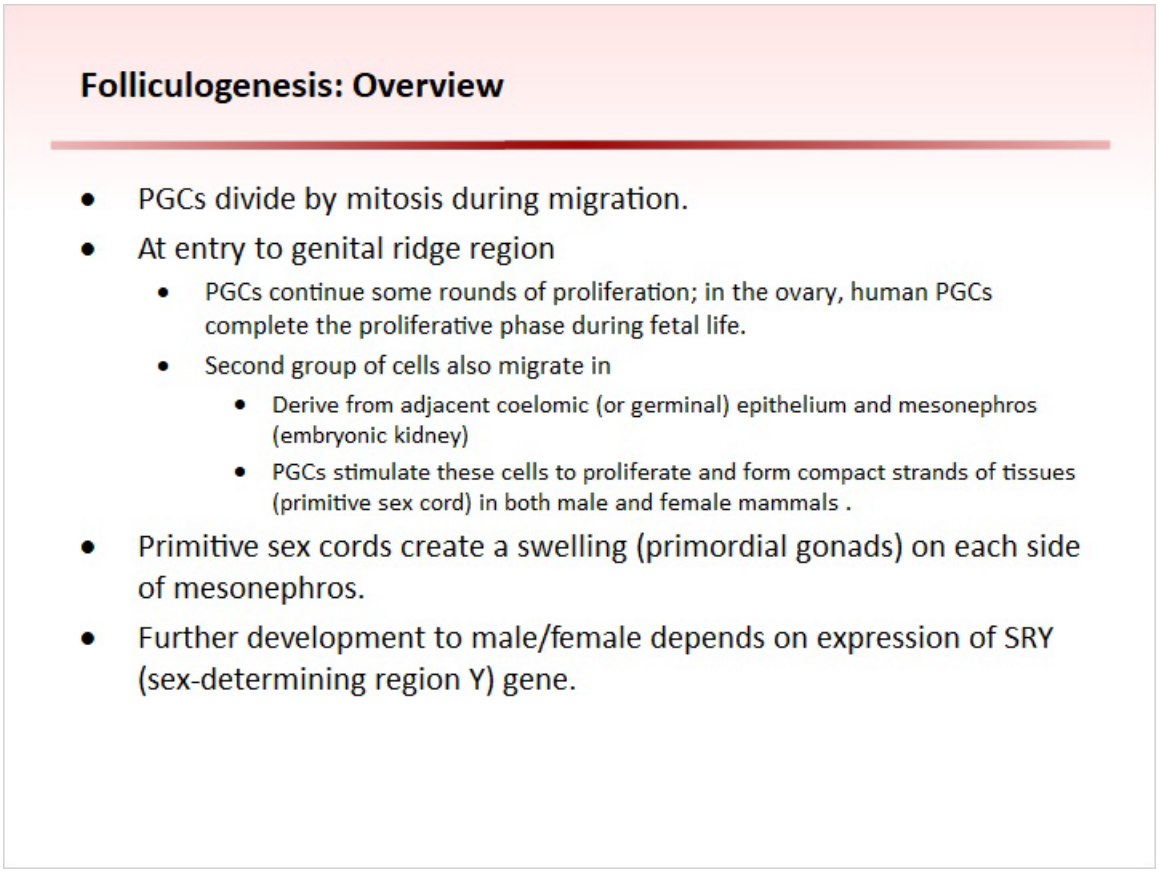
After certain rounds of proliferation of primordial germ cells and under the genetic control of sex determination, these cells differentiate into oogonia in females with XX chromosomes or spermatogonia in males with XY chromosomes.

1.15 II. Folliculogenesis

Notes:

Part 2 will address the process of folliculogenesis.

1.16 Folliculogenesis: Overview



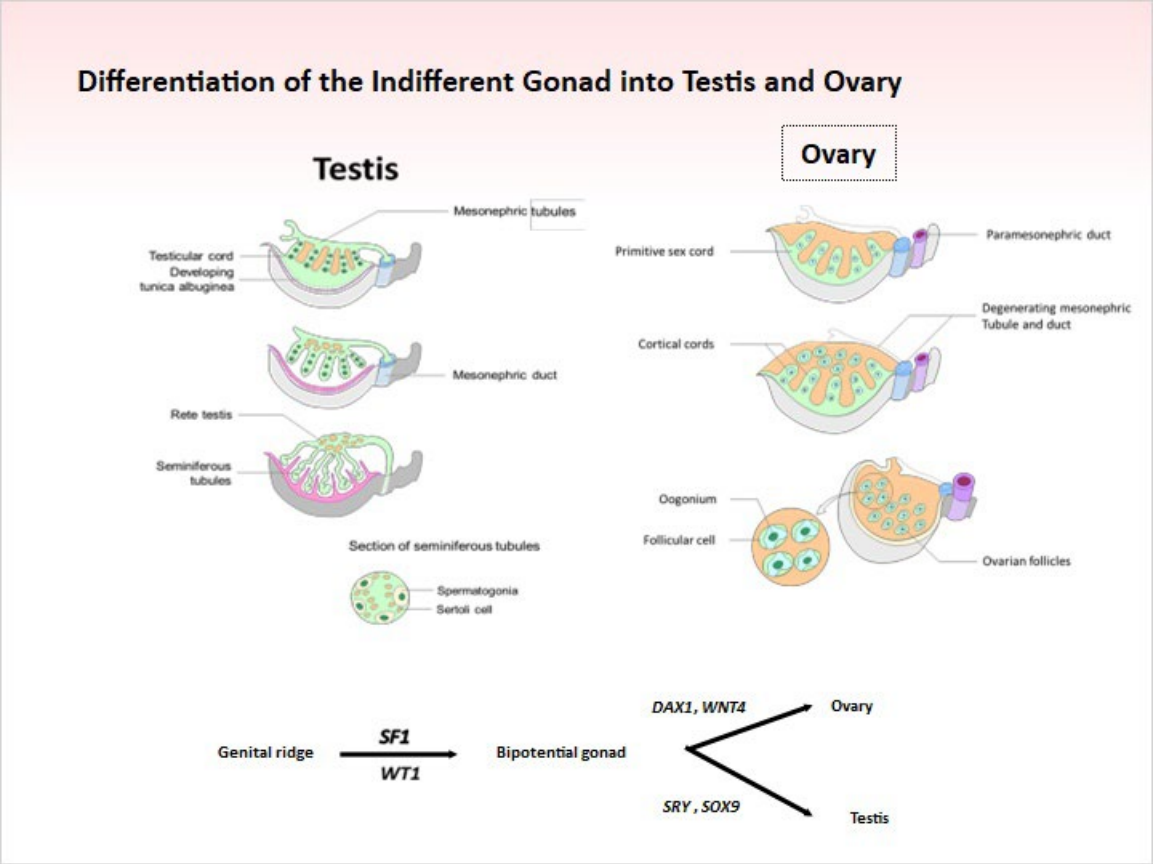
Notes:

PGCs divide by mitosis during migration, and when they arrive in the developing gonads, they continue some rounds of proliferation. In the ovary, human PGCs complete the proliferative phase during fetal life.

When PGCs enter the genital ridge region, a second group of cells also migrate in. They derive from the adjacent coelomic (or germinal) epithelium and mesonephros (embryonic kidney). PGCs stimulate these cells to proliferate and form compact strands of tissues called the primitive sex cords in both male and female mammals.

The primitive sex cords create a swelling on each side of mesonephros. The swellings are the primordial gonads. Further development of these cells depends on the expression of SRY (sex-determining region Y) gene. The primitive sex cords give rise to Sertoli cells in male under the control of SRY gene, or to follicular cells in female. These two types of cells will nourish and regulate the development of gametes.

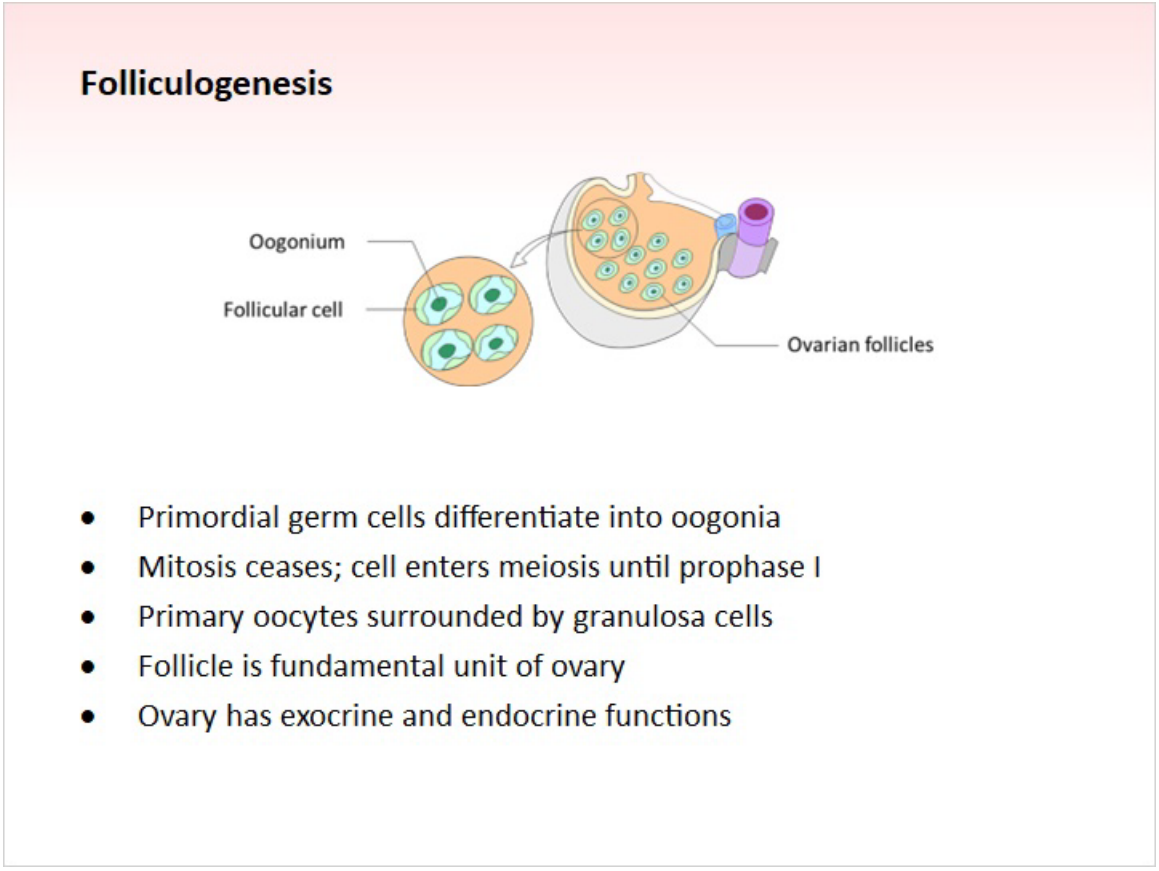
1.17 Differentiation of the Indifferent Gonad into Testis and Ovary



Notes:

This illustrates the process of differentiation of the primordial germ cells into the female ovary. The male and female external genitalia develop from a single bipotential precursor into ovary and testis under the control of several genes: *DAX1*, *WNT4*, *SRY* and *SOX9*.

1.18 Folliculogenesis



Notes:

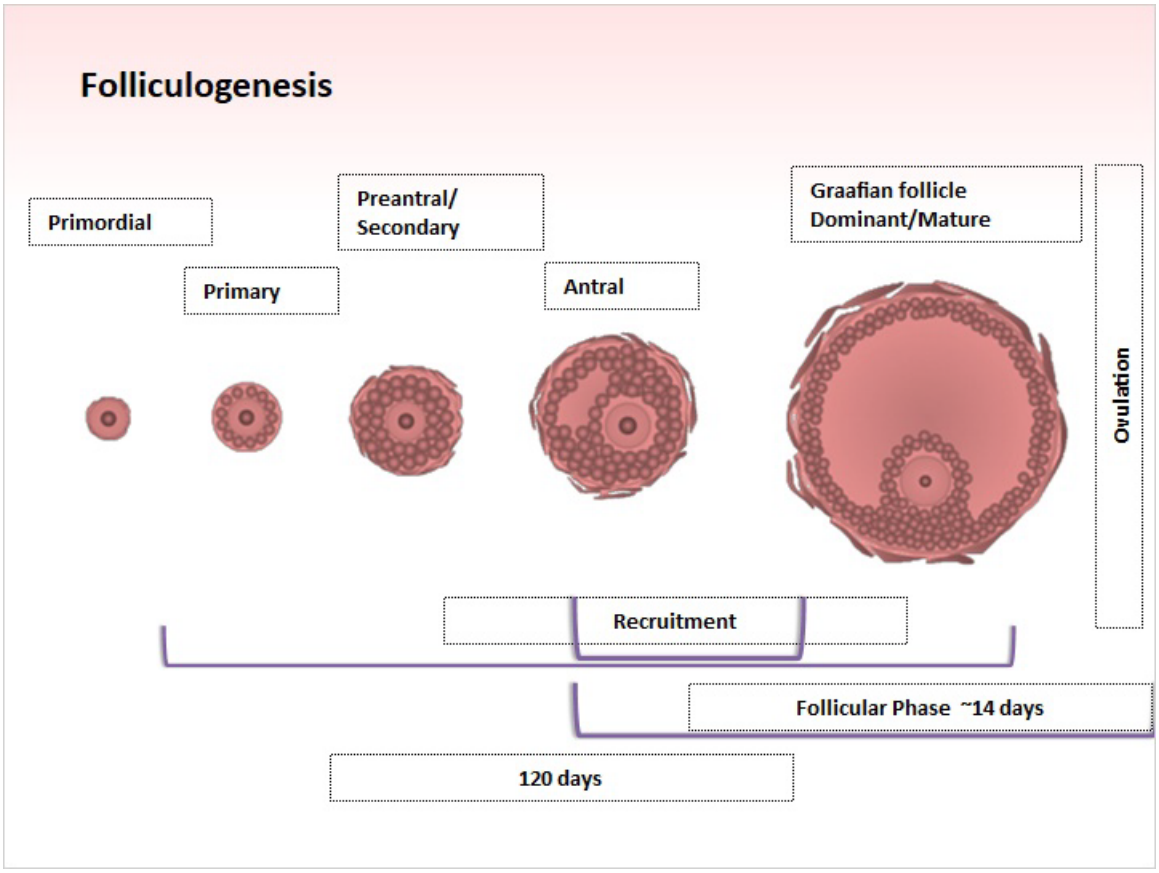
In the female, primordial germ cells differentiate into oogonia when they enter the genital ridge and complete the mitotic proliferation phase.

At the early stage of fetal development in humans/mammals, oogonia cease to divide mitotically and enter meiosis, and then become arrested at prophase I of meiosis. Oogonia become primary oocytes. At this time, oocytes are surrounded by a layer of flattened somatic cells, called granulosa cells.

Growth and differentiation of this oocyte-somatic cell is folliculogenesis. The follicle constitutes the fundamental functional unit of the ovary. The unit containing a primary oocyte with a single layer of flattened granulosa cells is a primordial follicle.

The ovaries have a double function: exocrine and endocrine, with the production of oocytes as well as the sex hormones estrogen and progesterone.

1.19 Folliculogenesis



Notes:

As soon as primordial follicles are formed, follicle growth begins. This continues until the store of follicles is exhausted at menopause in humans.

Primordial follicle is the earliest and also the longest phase of folliculogenesis, as a follicle may stay in the arrested stage for up to 50 years in human ovaries.

When it commences growth under stimulation of hormones at puberty, a primordial follicle passes through 4 important stages until an oocyte is ready to ovulate. These 4 stages are primary follicle, secondary or preantral follicle, antral or tertiary follicle, and the mature Graafian or preovulatory follicle.

1.20 Folliculogenesis: Primordial Follicles

Folliculogenesis: Primordial Follicles

- In humans, a rapid mitotic proliferation of germ cells begins at 6-7 weeks of pregnancy (PGCs migration).
- Formation and differentiation of primordial follicles after PGCs enter genital ridge)
  - Maximum number (6-7x10^6) by 16-20 weeks
  - Number decreases rapidly to 1- 2x10^6 at birth
  - Biological function of this decrease is still unknown

- Primordial follicles
  - 30-60 µm diameter
  - Contain late diplotene-stage primary oocytes with a diameter of 9-25 µm. Oocytes are surrounded by a single layer of flattened pre-granulosa cells.
- First sign of follicle growth is increase in oocyte size; granulosa cells become more cuboidal instead of squamous.
- At this stage, follicle growth is gonadotropin-independent.

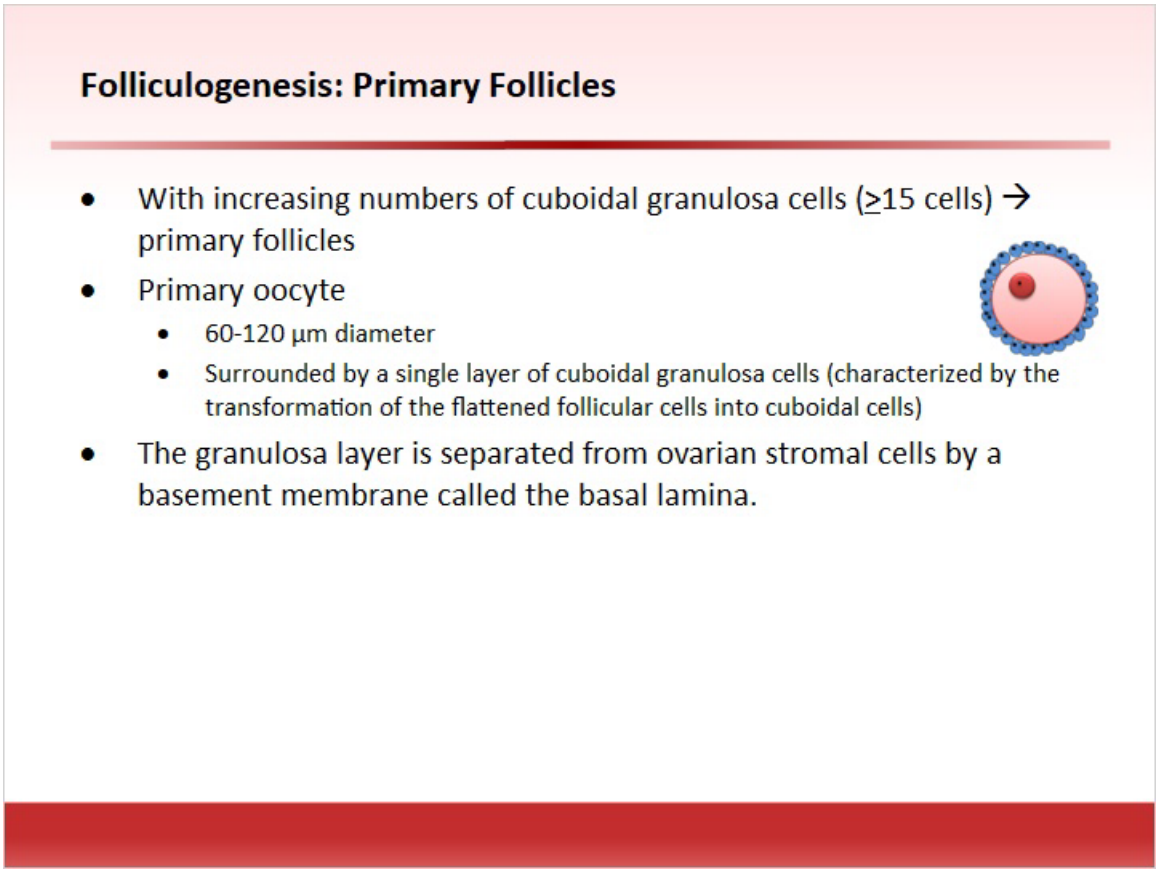
Notes:

In humans, a rapid mitotic proliferation of germ cells begins at 6-7 weeks of pregnancy, which is the time of migration of primordial germ cells.

Formation and differentiation of primordial follicles occur after primordial germ cells enter the genital ridge. The number of primordial follicles peaks around 16 weeks of gestation with a maximum number of 6-7x10^6. Afterward, the number decreases rapidly to 1-2x10^6 at birth. The biological function of this decrease is still unknown but may function to remove defective cells or regulate population size.

Primordial follicles are approximately 30-60 µm in diameter and contain late diplotene-stage primary oocytes with a diameter of 9-25 µm. Oocytes are surrounded by a single layer of flattened pre-granulosa cells. The first sign of follicle growth is an increase in the size of oocytes, and granulosa cells become more cuboidal instead of squamous. At this stage, growth of follicles is independent of gonadotropins.

1.21 Folliculogenesis: Primary Follicles



Notes:

When the number of cuboidal granulosa cells increase and reach 15 cells or more, follicles become primary follicles.

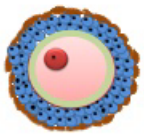
At this stage, the primary oocyte with a diameter of 60-120 µm is surrounded by a single layer of cuboidal granulosa cells. The characteristic of primary follicles is the transformation of the flattened follicular cells into cuboidal cells.

The granulosa layer is separated from ovarian stromal cells by a basement membrane called the basal lamina.

1.22 Folliculogenesis: Preantral Follicles

Folliculogenesis: Preantral Follicles

- Primary follicles >120 µm and surrounded by more than 1 layer of granulosa cells → preantral follicles
- Stage starts at 20-24 weeks' gestation; continuous process until menopause
- Zona pellucida forms around oocyte; is secreted by both oocytes and granulosa cells
- Gap junctions between oocytes and granulosa cells occur
- Thecal layer starts to differentiate from the surrounding stromal cells.
  - Theca cells are vital for successful folliculogenesis; produce androgen → estradiol in granulosa cells
- Oocyte growth is accelerated and reaches its full size at the late preantral stage.



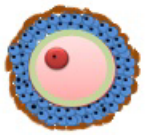
Notes:

When primary follicles increase in size to more than 120 µm and are surrounded by more than one layer of granulosa cells, they become preantral follicles. This stage starts at 20-24 weeks of gestation, and is a continuous process until menopause. The zona pellucida is secreted by both oocytes and granulosa cells and forms around the oocyte. Gap junctions between oocytes and granulosa cells occur. The thecal layer starts to differentiate from the surrounding stromal cells at preantral follicle stage. Thecal cells are vital for successful folliculogenesis and they produce androgen, which is converted to estradiol in granulosa cells. Oocyte growth is accelerated and it reaches its full size at the late preantral stage.

1.23 Folliculogenesis: Preantral Follicles

Folliculogenesis: Preantral Follicles

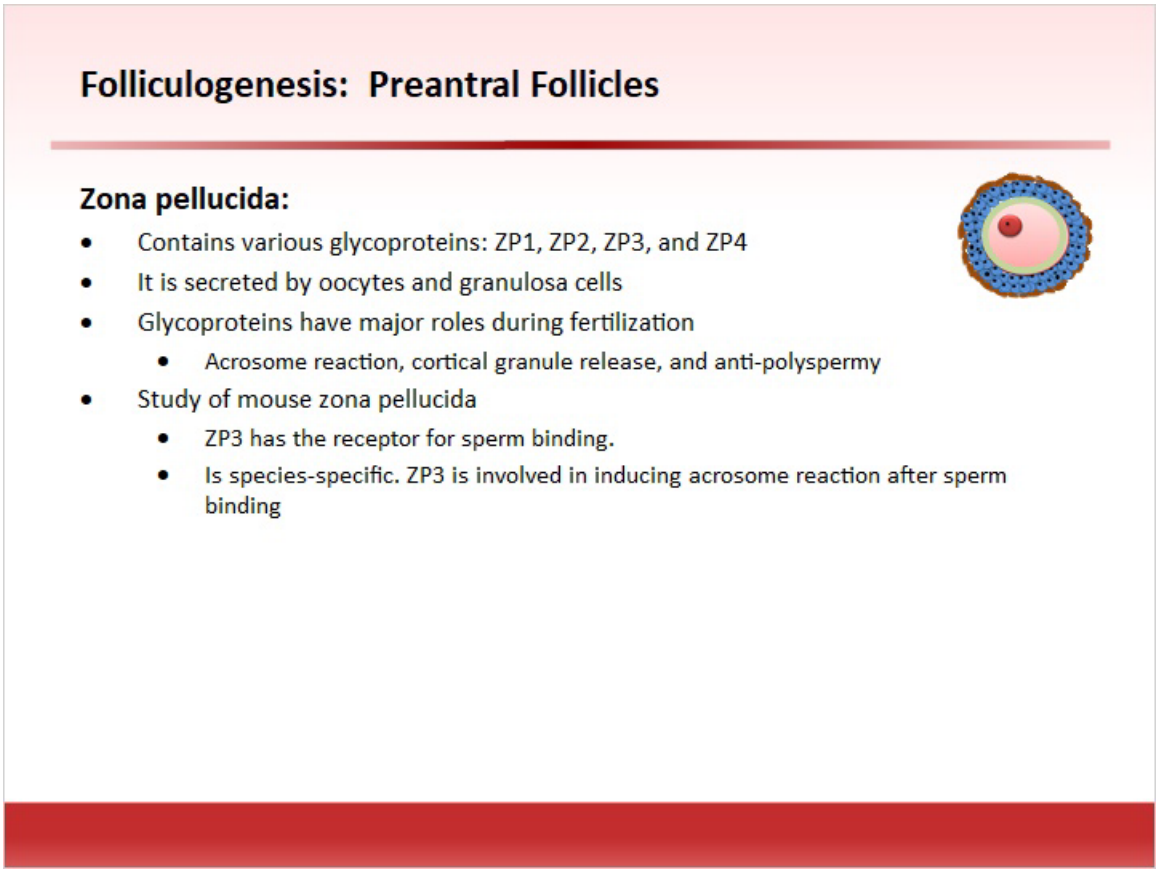
- The development of preantral follicles is dependent on some hormones and growth factors:
  - Follicle-stimulating hormone (FSH) promotes granulosa cell growth and inhibits apoptosis through the expression of genes for cell proliferation and differentiation.
  - IGF-1 is produced by the granulosa cells and helps to amplify the follicular response to FSH.
  - Granulosa cells produce all 3 steroids: estrogen, androgen, and progesterone at the end stage



Notes:

The development of preantral follicles is dependent on some hormones and growth factors. Follicle-stimulating hormone (FSH) promotes granulosa cell growth and inhibits apoptosis by promoting the expression of genes for cell proliferation and differentiation. Insulin growth factor-1 is produced by the granulosa cells and helps to amplify the follicular response to FSH. Granulosa cells produce all 3 steroids: estrogen, androgen, and progesterone at the end stage.

1.24 Folliculogenesis: Preantral Follicles



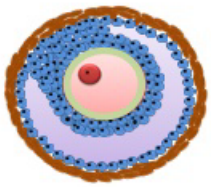
Notes:

Zona pellucida formation is another feature of preantral follicle stage. The zona pellucida contains various glycoproteins: ZP1, ZP2, ZP3, and ZP4. These glycoproteins have major roles during fertilization, including acrosome reaction, cortical granule release, and anti-polyspermy. The study using mouse zona pellucida shows that ZP3 has the receptor for sperm binding. This ZP and sperm binding is species-specific. ZP3 is involved in inducing the acrosome reaction after sperm binding.

1.25 Folliculogenesis: Antral Follicles

Folliculogenesis: Antral Follicles

- Estrogen and FSH → production of follicular fluid in intercellular spaces of the granulosa layer → cavity called the antrum (hence "antral follicles")
- Antrum:
  - Multiple numbers of antra. They localize among granulosa cells and accumulate fluid when follicles reach 200-400 µm in diameter.
  - Follicular fluid is an ultrafiltrate of plasma and contains amino acids, electrolytes, proteins, gonadotropins, locally secreted proteoglycans, and steroids, etc.
  - Fluid pockets are coalesced with eccentric displacement of oocyte to form a single antrum: Graafian follicle
- Granulosa cells continue to proliferate to form several layers (>600 cells): cells surrounding the oocytes differentiate as cumulus cells.
- Follicles increase rapidly in volume because of the rapid multiplication of the follicular cells → ~ 50 million.
- Follicle size continues to increase → preovulatory or mature follicle



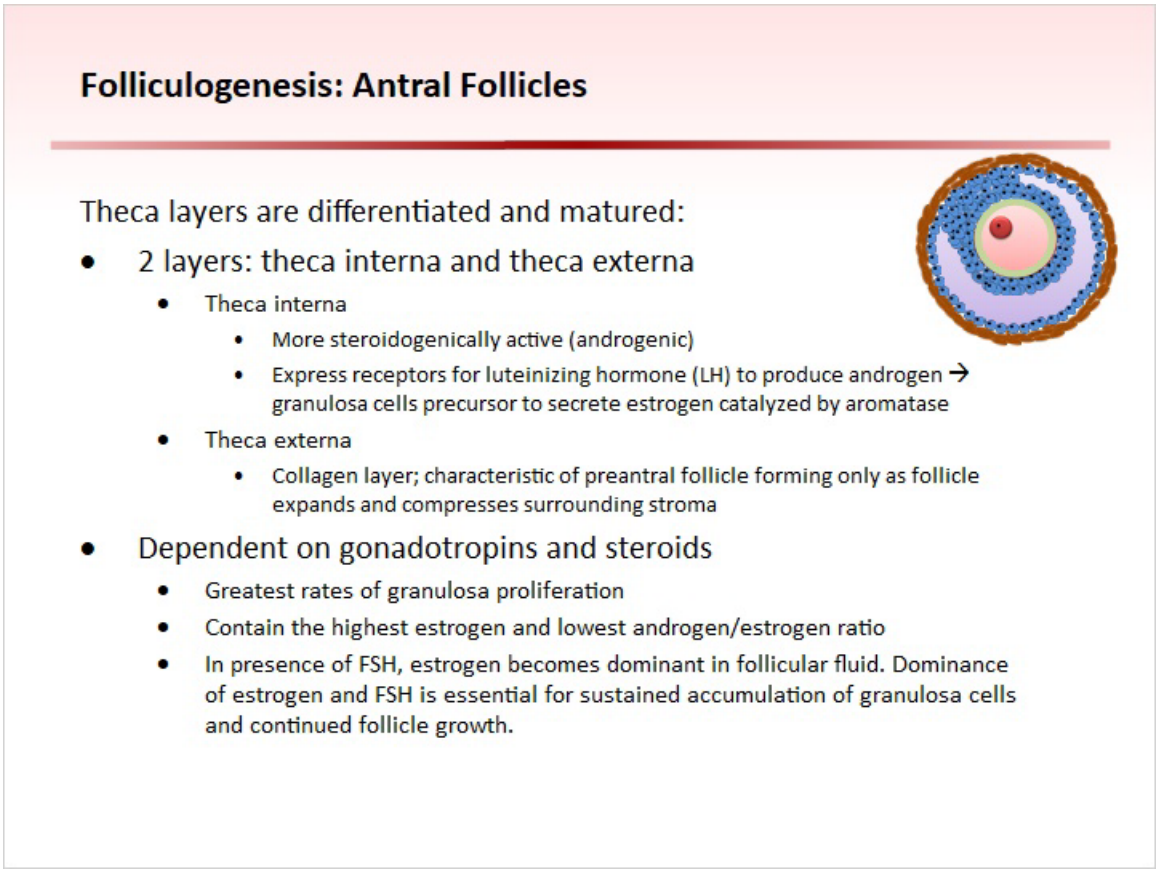
Notes:

Under the influence of estrogen and FSH, follicular fluid starts to accumulate in the intercellular spaces of the granulosa layer and a large cavity filled with fluid is formed, called the antrum; these are "antral follicles."

There are multiple numbers of antra in the beginning of this stage. They localize among granulosa cells and accumulate fluid when follicles reach 200-400 µm in diameter. Follicular fluid is an ultrafiltrate of plasma and contains a number of substances including amino acids, electrolytes, proteins, gonadotropins, locally secreted proteoglycans, and steroids.

Later the fluid pockets are coalesced with eccentric displacement of the oocyte to form a single antrum. The granulosa cells continue to proliferate to form several layers with more than 600 cells; cells surrounding the oocytes differentiate as cumulus cells. Follicles increase in volume because of the rapid multiplication of the granulosa cells and cumulus cells. At the end of the follicle's development, these cell numbers will reach about 50 million. The follicle increases in size and becomes a preovulatory or mature follicle.

1.26 Folliculogenesis: Antral Follicles



Notes:

During the development of antral follicles, theca layers are differentiated and matured. Basically, theca cells differentiate into two distinguishing layers: theca interna lying on the basement membrane, and a more fibrous outer theca externa.

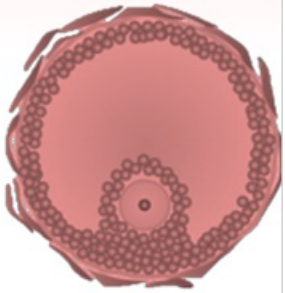
Theca interna is more steroidogenically active, and it is androgenic. The theca interna cells express receptors for luteinizing hormone (LH) to produce androgen, which gives the granulosa cells the precursor to secrete estrogen. Androgen is converted to estrogen catalyzed by aromatase. The theca externa is a collagen layer, and it is also a characteristic of the forming preantral follicle. The follicle expands and surrounding stroma is compressed to become the theca externa.

Antral follicles are also dependent on gonadotropins and steroids. They have the greatest rates of granulosa proliferation and contain the highest estrogen and lowest androgen/estrogen ratio. In the presence of FSH, estrogen releases and becomes dominant in follicular fluid. The dominance of estrogen and FSH is essential for sustained accumulation of granulosa cells and continued follicle growth.

1.27 Folliculogenesis: Graafian Follicles

Folliculogenesis: Graafian Follicles

- With increased size and volume of follicular fluid → mature
- Contain large amounts of hypoxanthine, and adenosine (hold the oocyte in meiotic arrest) and hyaluronate (a glycosaminoglycan)

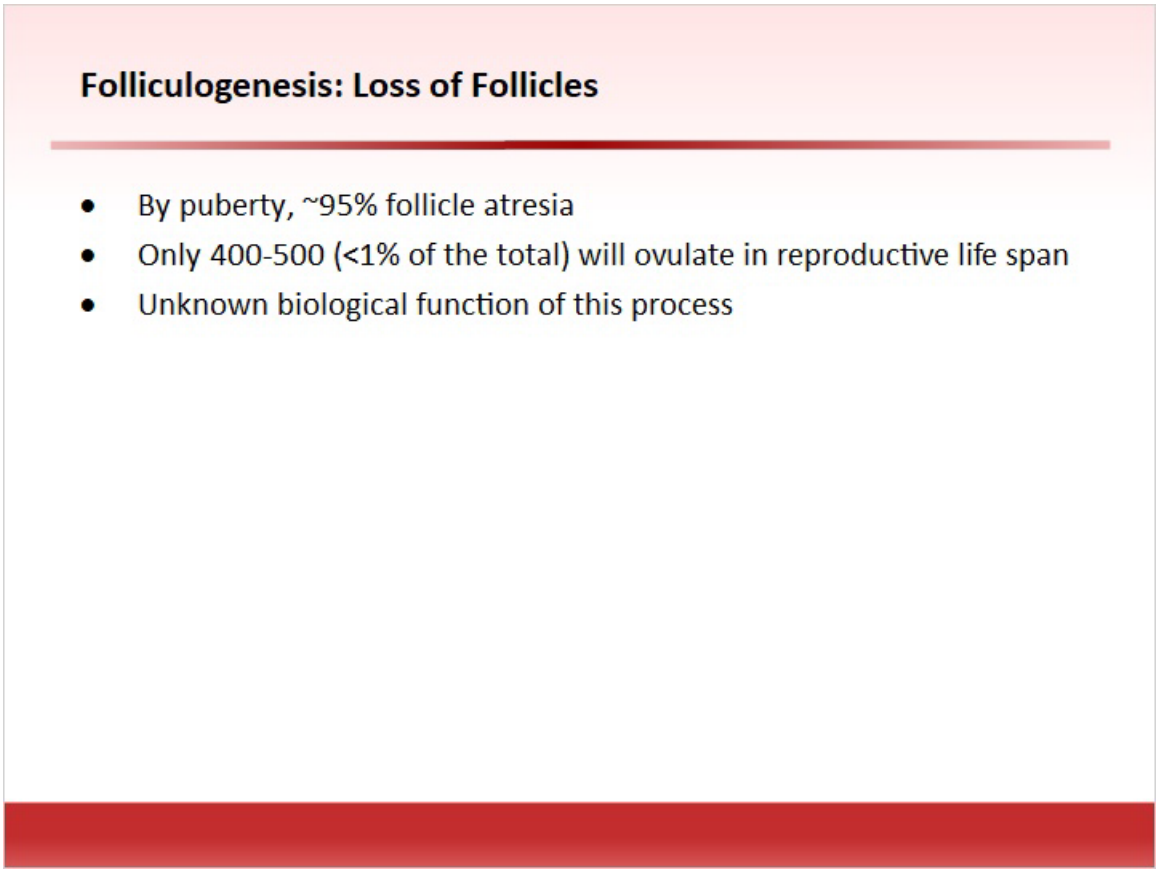


- Granulosa cells enlarge, acquire liquid inclusion, → 2 cm
- Vacuolated and richly vascular theca
- Oocyte → 120 µm in diameter; completes first meiotic division
- Follicle produces increasing estrogen, reaches peak before ovulation
- LH surge → luteinization of granulosa cells of dominant follicles → resulting in the production of progesterone
- Follicle itself is ready to ovulate.

Notes:

With increased size and volume of follicular fluid, the follicles become mature and are called Graafian follicles. They are named after the Dutch anatomist, Regnier de Graaf, who discovered mature ovarian follicles. Graafian follicles contain large amounts of hyaluronate, hypoxanthine, and adenosine. The last two substrates have been shown to hold the oocyte in meiotic arrest. Granulosa cells enlarge, acquire liquid inclusion and follicle size reaches around 2 cm in diameter. At this time, the theca becomes vacuolated and richly vascular. The oocyte grows to around 120 µm in diameter and proceeds to complete its first meiotic division. The follicle produces increasing estrogen, which reaches a peak before ovulation. The surge of LH occurs, which promotes luteinization of the granulosa cells of the dominant follicles, resulting in the production of progesterone. Now the follicle itself is ready to ovulate.

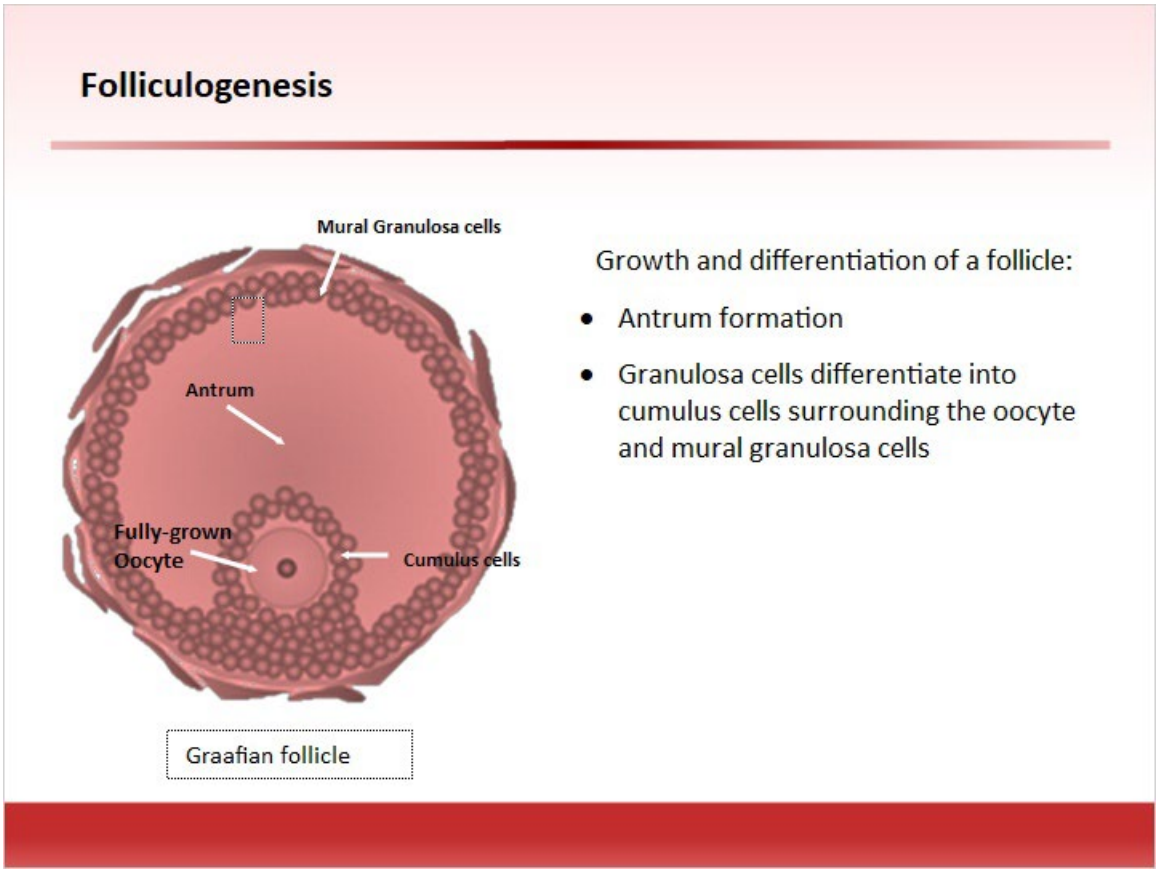
1.28 Folliculogenesis: Loss of Follicles



Notes:

By the onset of puberty, about 95% of all follicles have been lost through follicle atresia, only 400 to 500 of which will in fact ovulate in the course of a reproductive life span. This is less than 1% of the total numbers of follicles. The biological function of this process is unknown.

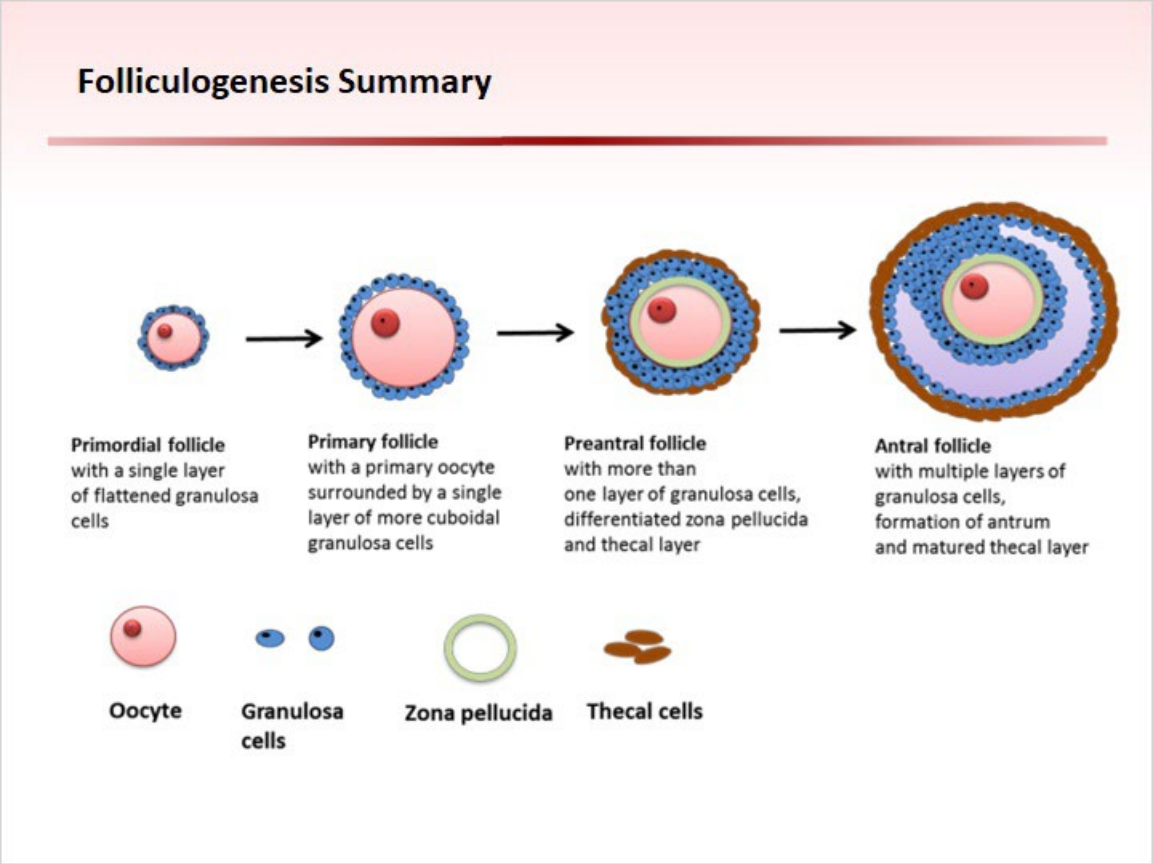
1.29 Folliculogenesis



Notes:

As the follicle grows and differentiates, the antrum forms and granulosa cells differentiate into cumulus cells surrounding the oocyte and mural granulosa cells.

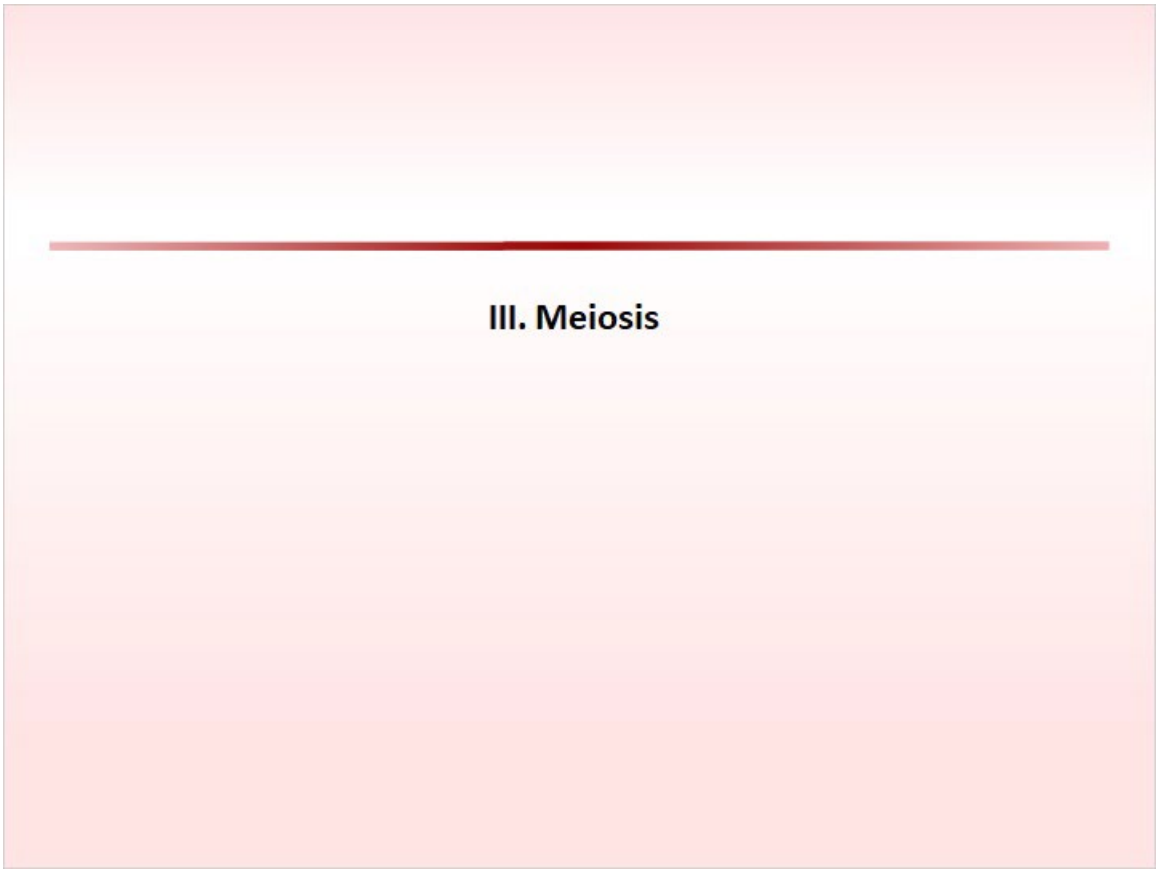
1.30 Folliculogenesis Summary



Notes:

To summarize, folliculogenesis begins with the primordial follicle with a single layer of flattened granulosa cells. The primary follicle has a primary oocyte surrounded by a single layer of more cuboidal granulosa cells. The preantral follicle has more than one layer of granulosa cells, a differentiated zona pellucida, and thecal layer. The antral follicle has multiple layers of granulosa cells, a formed antrum, and matured thecal layer.

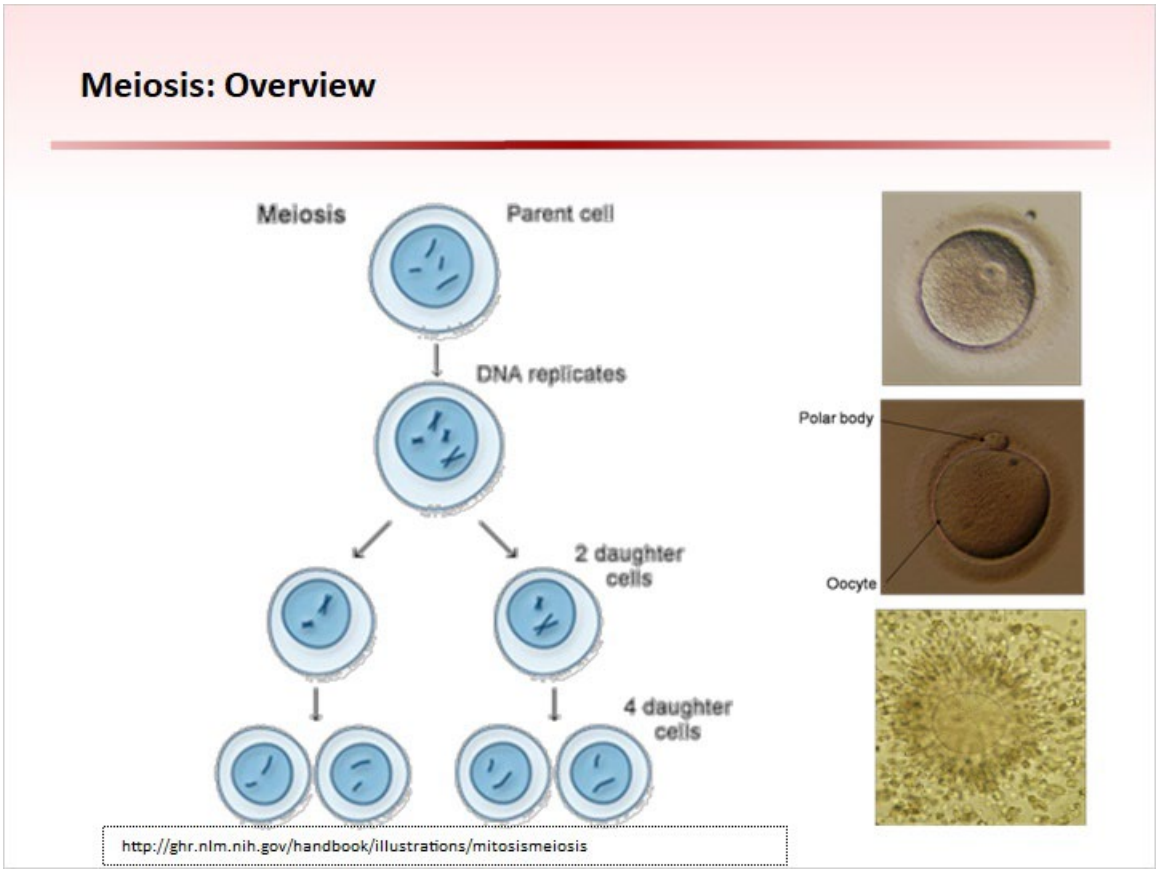
1.31 Untitled Slide



Notes:

Part 3 addresses meiosis, a process to form germ cells.

1.32 Meiosis: Overview

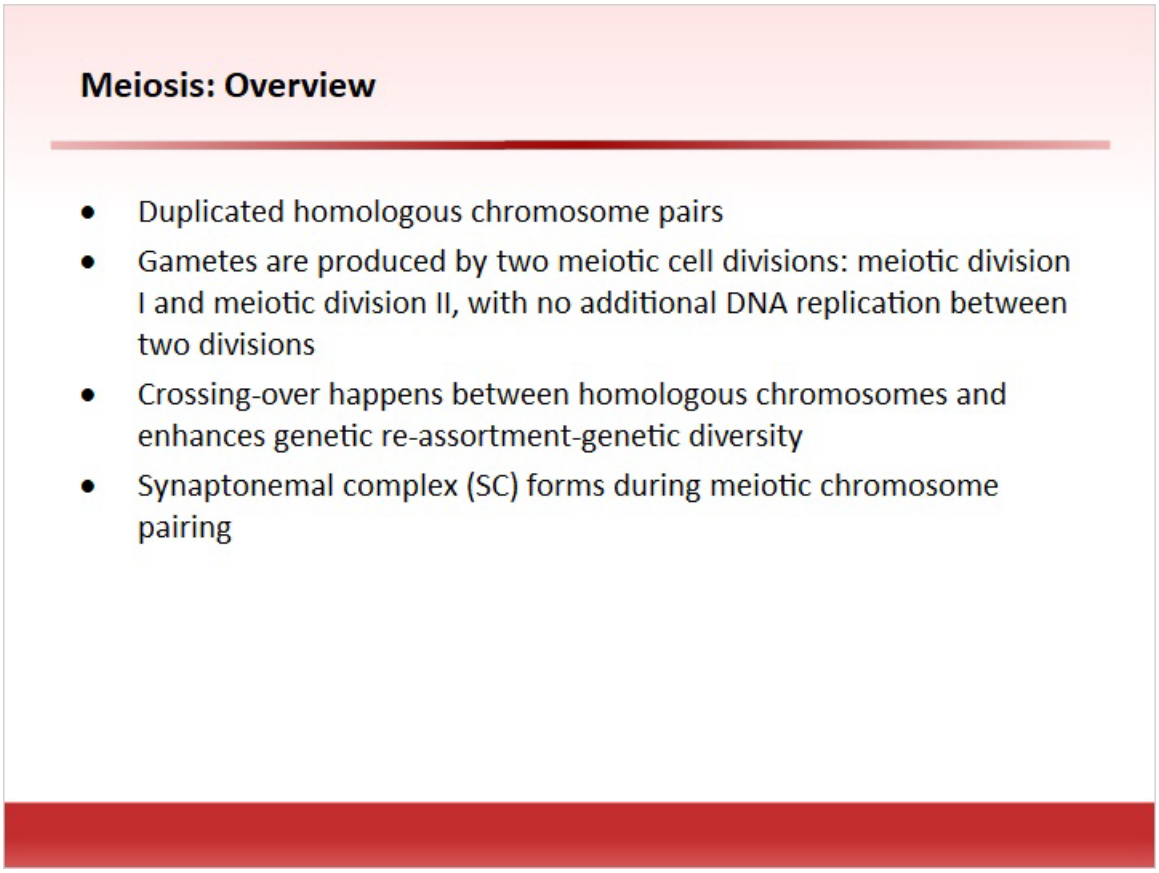


Notes:

Recall that somatic cells in humans usually reproduce by mitosis with each daughter cell being an identical replicate of the mother cell. Germ cells are haploid and they are produced by meiosis, a special type of reduction division. This type of division only occurs in germ cells in ovaries and testes.

After meiotic divisions, the genomic DNA content and the corresponding chromosome numbers of the gametes must be reduced by half. The genetic composition of each chromosome is modified as a result of the exchange of pieces of homologous chromosomes known as genetic recombination.

1.33 Meiosis: Overview



Notes:

Some main events occur during the process of meiosis.

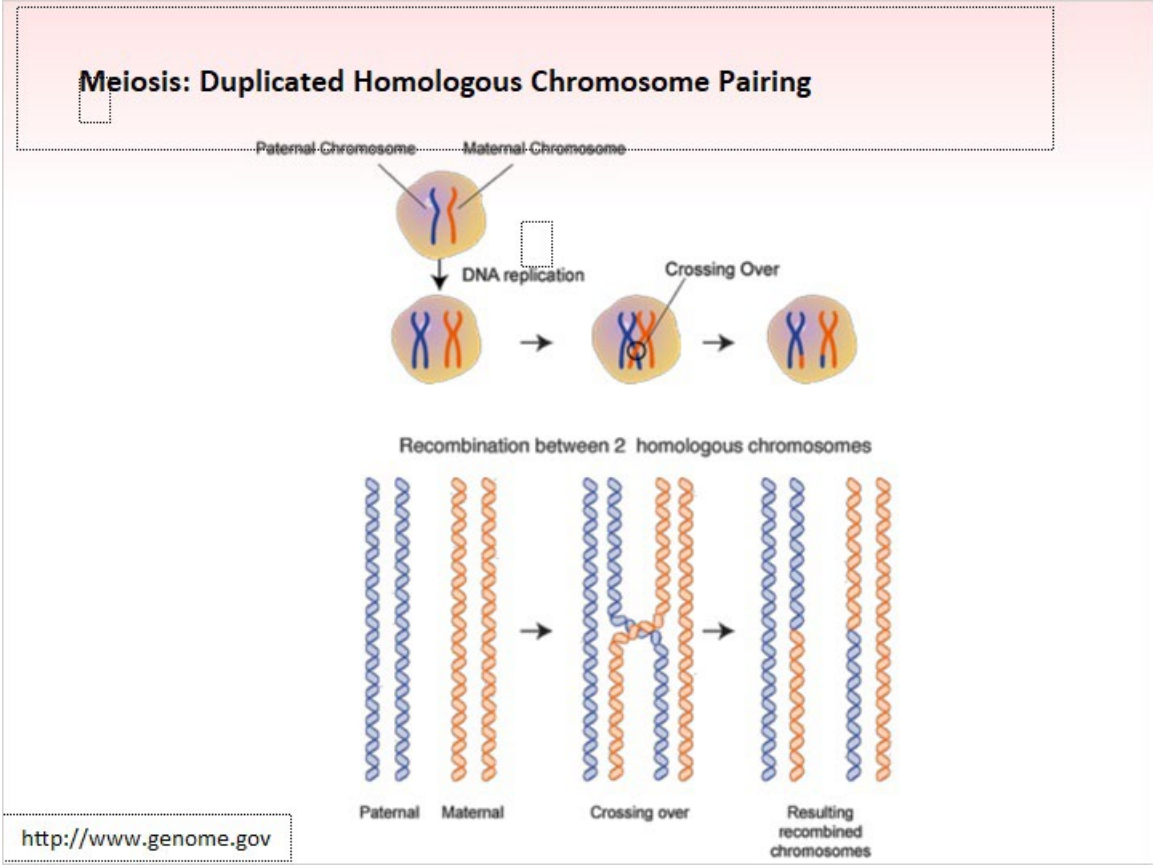
There is a duplicating of homologous chromosome pairs at the metaphase of meiotic division.

Gametes are produced by two meiotic cell divisions: meiotic division I and meiotic division II, with no additional DNA replication between two divisions.

Crossing-over happens between homologous chromosomes and enhances genetic re-assortment, which results in genetic diversity.

A synaptonemal complex forms during meiotic chromosome pairing, which ensures the completion of crossing-over between homologous chromosomes.

1.34 Meiosis: Duplicated Homologous Chromosome Pairing



Notes:

During the process of meiosis, pairing of duplicated homologous chromosomes is an important event that ensures completion of genetic recombination.

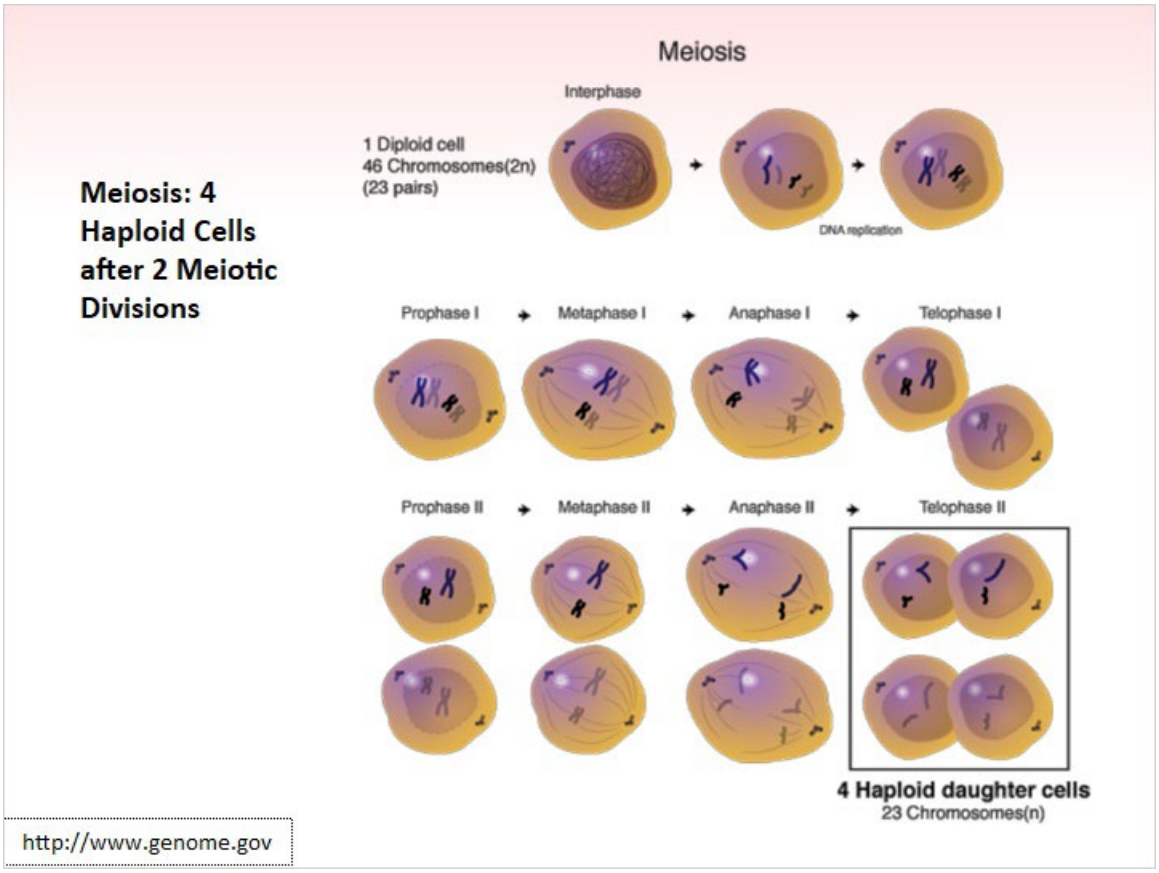
This figure shows one pair of homologous chromosomes.

After DNA duplication, each pair of homologous chromosomes contains 4 sister chromatids and forms a bivalent.

The homologs recognize each other and become physically connected side-by-side along their whole length. They line up on the equator of spindle. The sister chromatids are tightly connected along their entire length by a protein called cohesion. The mechanism for recognizing and pairing of homologous chromosomes is still not clear.

The pairing of homologous chromosomes allows genetic recombination to occur.

1.35 Meiosis: 4 Haploid Cells after 2 Meiotic Divisions



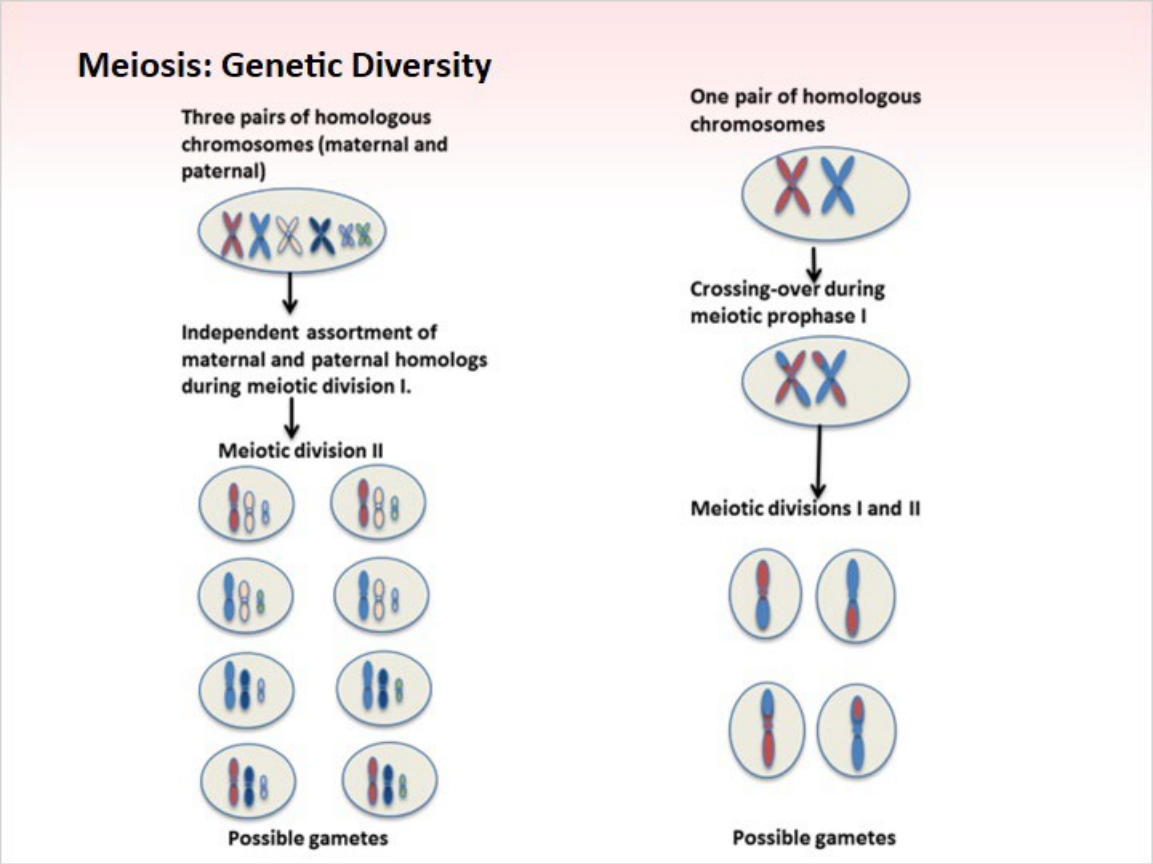
Notes:

In this figure, 4 haploid cells or germ cells are formed after 2 meiotic divisions.

At anaphase of division I, homologs are separated, and each daughter cell inherits 1 homolog, which contains 2 copies of sister chromatids. Crossing-over occurred between the homologs at this stage.

The second division occurs right after the first division without DNA replication. The chromosome aligns on the second spindle, and the sister chromatids separate into 2 cells. Each cell contains haploid DNA content. At the end of the second division 4 haploid cells are formed.

1.36 Meiosis: Genetic Diversity

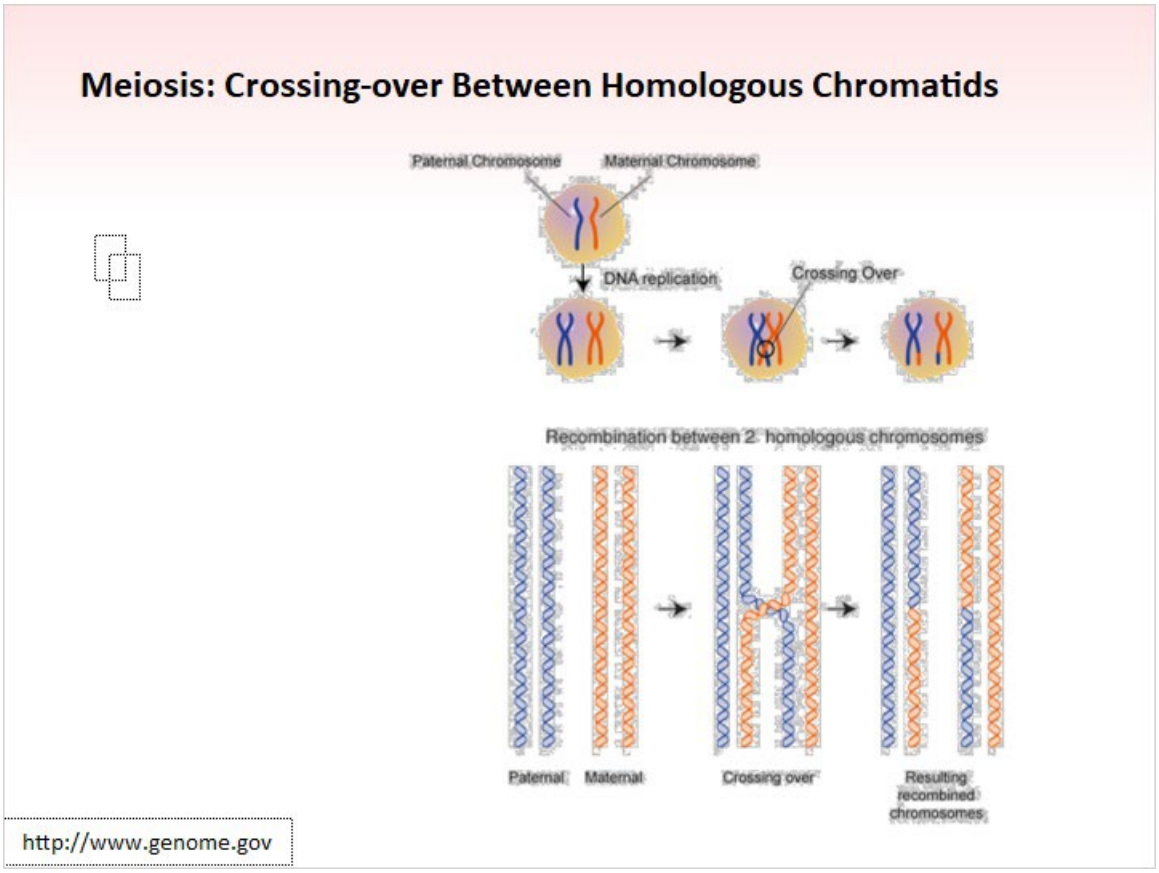


Notes:

This figure shows 2 randomizing genetic re-assortments during meiosis. The graphic on the left shows the independent assortment of the maternal and paternal homologs during the first meiotic division. This cell contains 3 pairs of chromosomes; after randomized sorting in the first meiotic division, 8 possible gametes are produced.

On the right, a crossing-over during the prophase I of meiosis exchanges segments of homologs resulting in many small differences in DNA sequences between 2 homologs. On average, there are between 2 and 3 crossover events occurring on each pair of homologs.

1.37 Meiosis: Crossing-over Between Homologous Chromatids

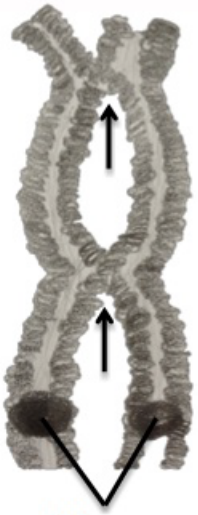


Notes:

During crossing-over, the DNA double helix is broken in both maternal and paternal chromatids, and fragments exchange in a reciprocal fashion, which is known as genetic recombination.
The consequence of this event is visible under the microscope later in prophase I. Bivalent chromosomes are highly condensed and homologs are connected at specific points, called the chiasma (plural: chiasmata), where crossover occurs.

1.38 Meiosis: Crossing-over Between Homologous Chromatids

Meiosis: Crossing-over Between Homologous Chromatids



Centromeres

A pair of homologs.

With permission from H. Yin

- Chiasmata play a role in holding homologs together properly until anaphase I when they are pulled into 2 daughter cells; ensures genetic integrity of daughter cells
- Before anaphase I, spindle fibers from 2 opposite poles pull 2 duplicated homologs in opposite direction.
- Chiasmata resist this pull by a tension to ensure proper division.
- Some chromosome pairs lack chiasmata→ abnormal chromosome segregation (nondisjunction)

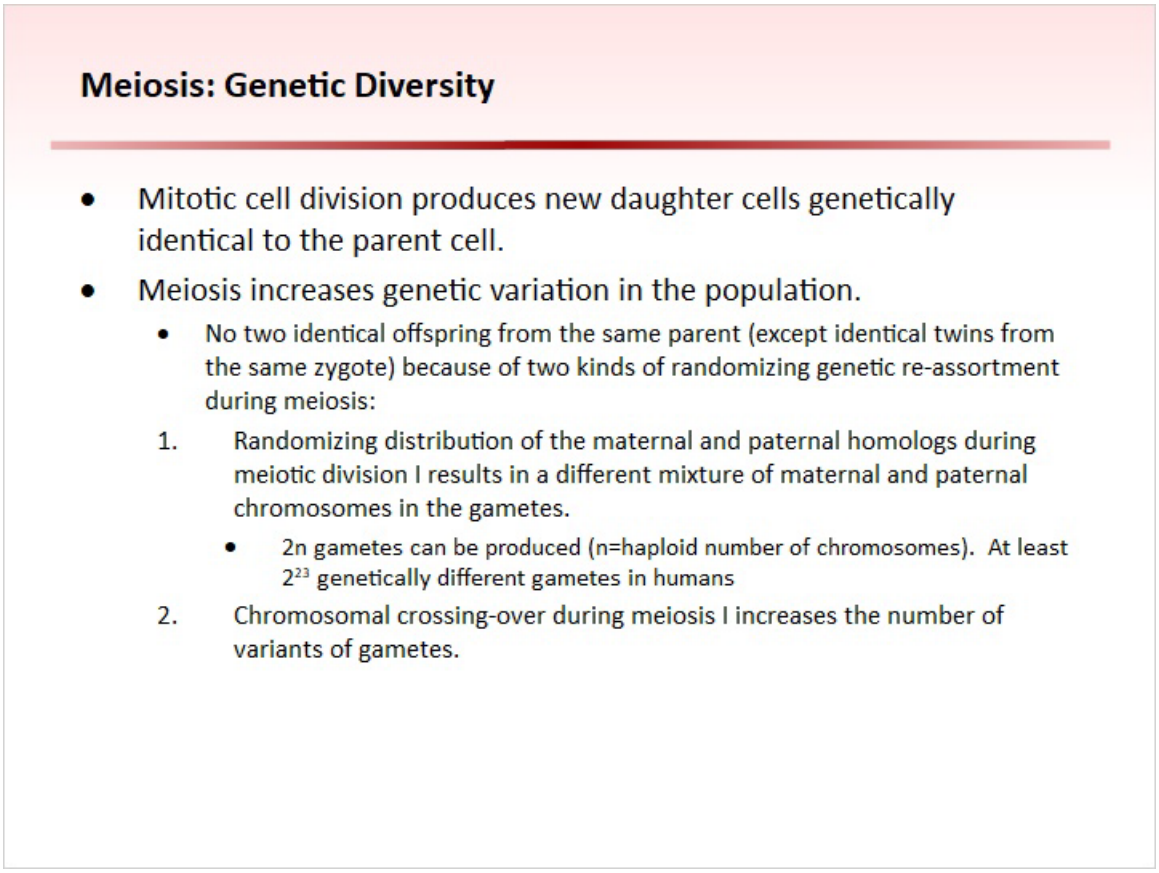
Notes:

In this figure is a pair of homologs: Centromeres (or kinetochores, the protein structure on the 2 sides of centromeres) are visible in dark circles (this is a pair of acrocentric chromosomes); the black arrows point to chiasmata.

Chiasmata help to hold the homologs together properly until anaphase I when they are pulled into 2 daughter cells. This holding ensures genetic integrity of the daughter cells.

Before anaphase I, the spindle fibers from the 2 opposite poles attaching to kinetochores pull 2 duplicated homologs in the opposite direction. The chiasmata resist this pull by a tension to ensure proper division. In mutants with reduced frequency of meiotic crossover, some chromosome pairs lack chiasmata or lack tension, which causes abnormal chromosome segregation, which is non-disjunction. The resultant gametes contain too many or too few chromosomes such as Down syndrome with three number 21 chromosomes, or Turner syndrome with a single X chromosome.

1.39 Meiosis: Genetic Diversity

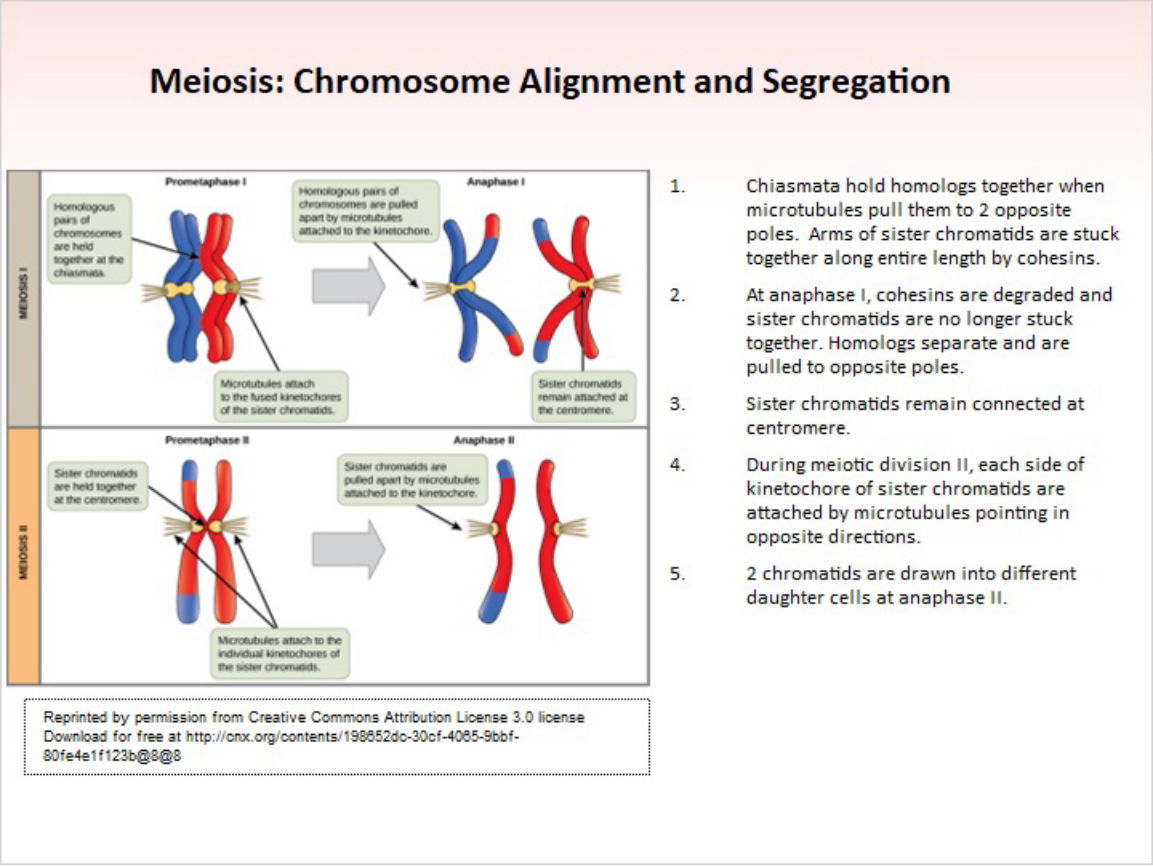


Notes:

Mitotic cell division produces new daughter cells that are genetically identical to the parent cell. However, meiosis increases genetic variation in the population. There are no two identical offspring from the same parent unless they are identical twins from the same zygote. There are two kinds of randomizing genetic re-assortment during meiosis to give genetic diversity:

1. One is randomizing distribution of the maternal and paternal homologs during the first meiotic division. It results in a different mixture of maternal and paternal chromosomes in the gametes. In principle, 2n gametes can be produced, in which "n" stands for haploid number of chromosomes. For example in humans, there are at least 2^{23} genetically different gametes.
2. The other is that chromosomal crossing-over during meiosis I increases the number of variants of gametes.

1.40 Meiosis: Chromosome Alignment and Segregation



Notes:

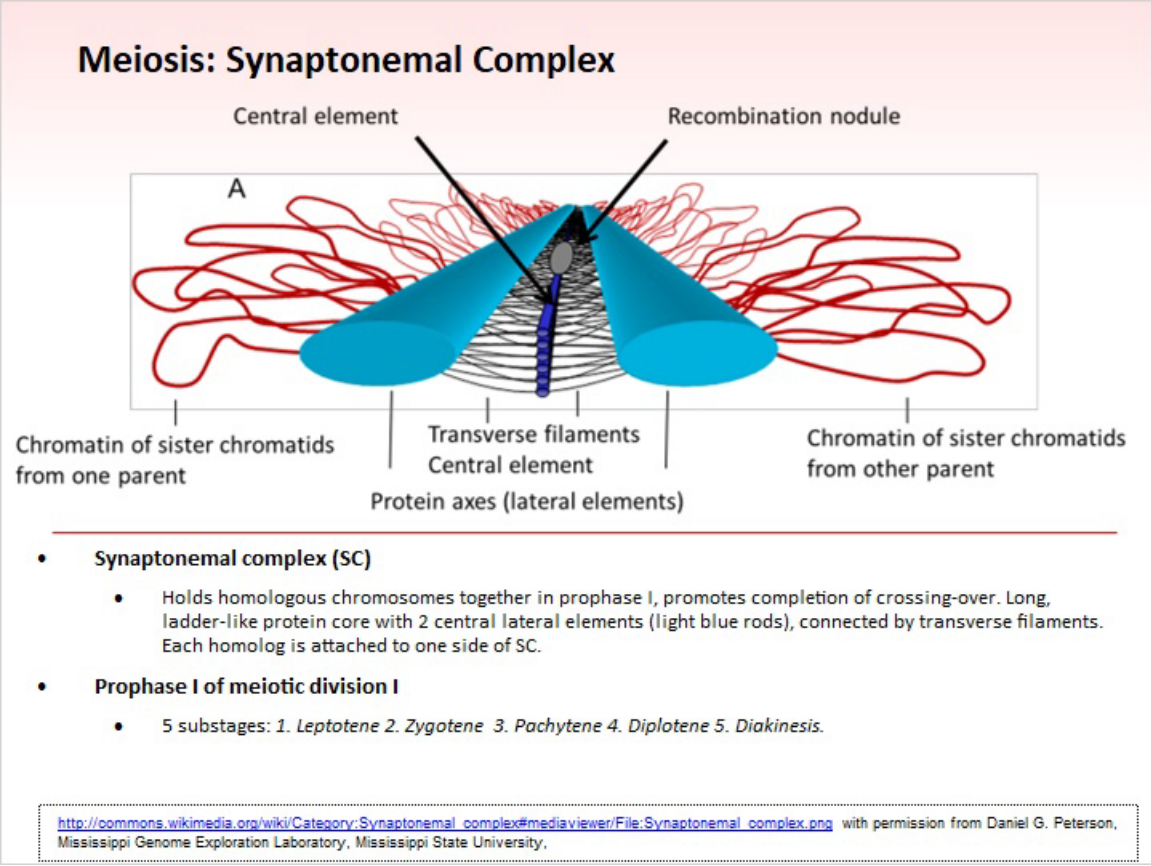
This is a closer look at chromosome alignment and segregation in the first and second meiotic division.

During the metaphase of the first meiotic division, chromosomes align on the spindle equator, and microtubules from the two opposite poles attached to kinetochores pull 2 duplicated homologs in the opposite direction, and chiasmata hold the homologs together. The arms of sister chromatids are stuck together along the entire length by a protein called cohesins.

At anaphase I, cohesins are degraded and sister chromatids are no longer stuck together. The homologs are pulled to opposite poles and separate. Sister chromatids still remain connected at the centromere.

During the second meiotic division, each side of the kinetochore of the sister chromatids are attached by microtubules pointing in opposite directions. Then, 2 chromatids are drawn into different daughter cells at anaphase II.

1.41 Meiosis: Synaptonemal Complex



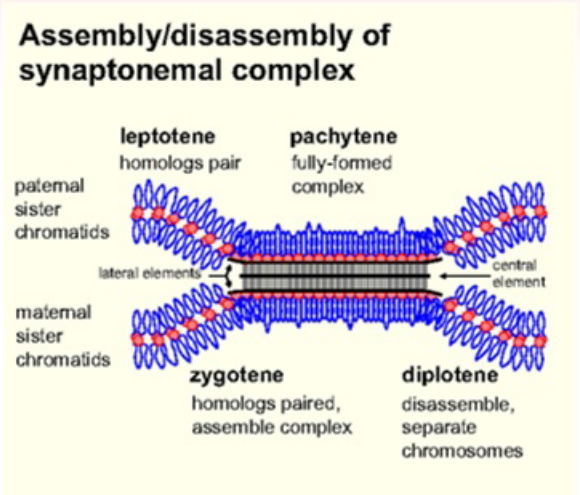
Notes:

During meiotic division, a functional protein structure called the synaptonemal complex holds homologous chromosomes together in prophase I and promotes the completion of crossing-over. It consists of a long, ladder-like protein core, which is made up of 2 central lateral elements seen in the figure, connected by transverse filaments. Each homolog is attached to one side of this complex.

Before studying the formation and functions of synaptonemal complex, it is important to know that prophase of the first meiotic division is prolonged prophase I, which can last months or years in humans. It is divided into 5 substages: 1. Leptotene 2. Zygotene 3. Pachytene 4. Diplotene 5. Diakinesis.

1.42 Meiosis: Synaptonemal Complex – Prophase I

Meiosis: Synaptonemal Complex - Prophase I



1. Single bivalent at leptotene, 2 sister chromatids condense and their loops each extend from a common protein axis (red).
2. At later stage of zygotene, SC starts to form.
3. Pachytene stage-period with a fully formed SC.
4. Subsequent diplotene stage is a prolonged period, chromosomes decondensed and very active in transcription
5. Diplotene ends with diakinesis-transition to metaphase in which chromosomes are recondensed and transcription stops

Notes:

These 5 substages of prophase I are defined by the morphological changes associated with the assembly and disassembly of synaptonemal complex. There is a single bivalent at leptotene; the two sister chromatids condense, and their loops each extend from a common protein axis, shown in the red color.

At the later stage of zygotene, the synaptonemal complex starts to form.

The pachytene stage is defined as the period with a fully formed synaptonemal complex.

Subsequent diplotene stage is a prolonged period, during which the chromosomes are decondensed and very active in transcription.

Diplotene ends with diakinesis, the transition to metaphase, in which chromosomes are recondensed and transcription stops.

1.43 Mitosis vs. Meiosis

Mitosis vs. Meiosis

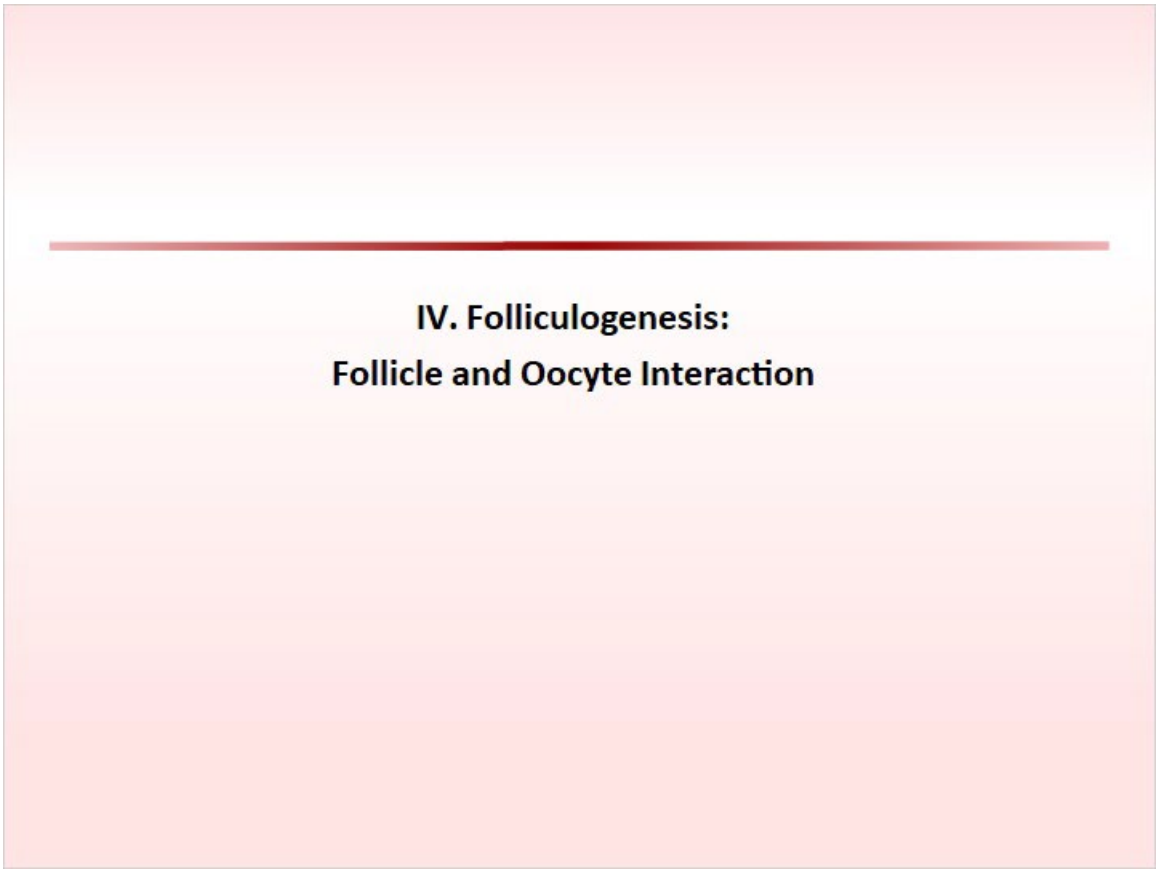
	Mitosis	Meiosis
Purpose	Produce somatic cells, a process of cell duplication	Produce reproductive cells: oocytes and sperm
Process	Cell duplication (DNA content: diploid → diploid)	Reduction division (DNA content: diploid → haploid)
Number of divisions	One-time DNA replication and one division	One-time DNA replication and two divisions
Product	1→2 daughter cells, daughter cells genetically identical to each other and mother cell	1→4 cells (gametes) daughter cells genetically different to mother cell

Notes:

This table helps to summarize and compare mitosis and meiosis.

Duplication of somatic cells occurs in mitosis, and gametes are produced in meiosis. The processes are also different: mitosis produces genetic identical daughter cells while haploid oocytes or sperm are produced in meiosis. One division results in 2 daughter cells in mitosis; 2 divisions are required to produce 4 germ cells in meiosis.

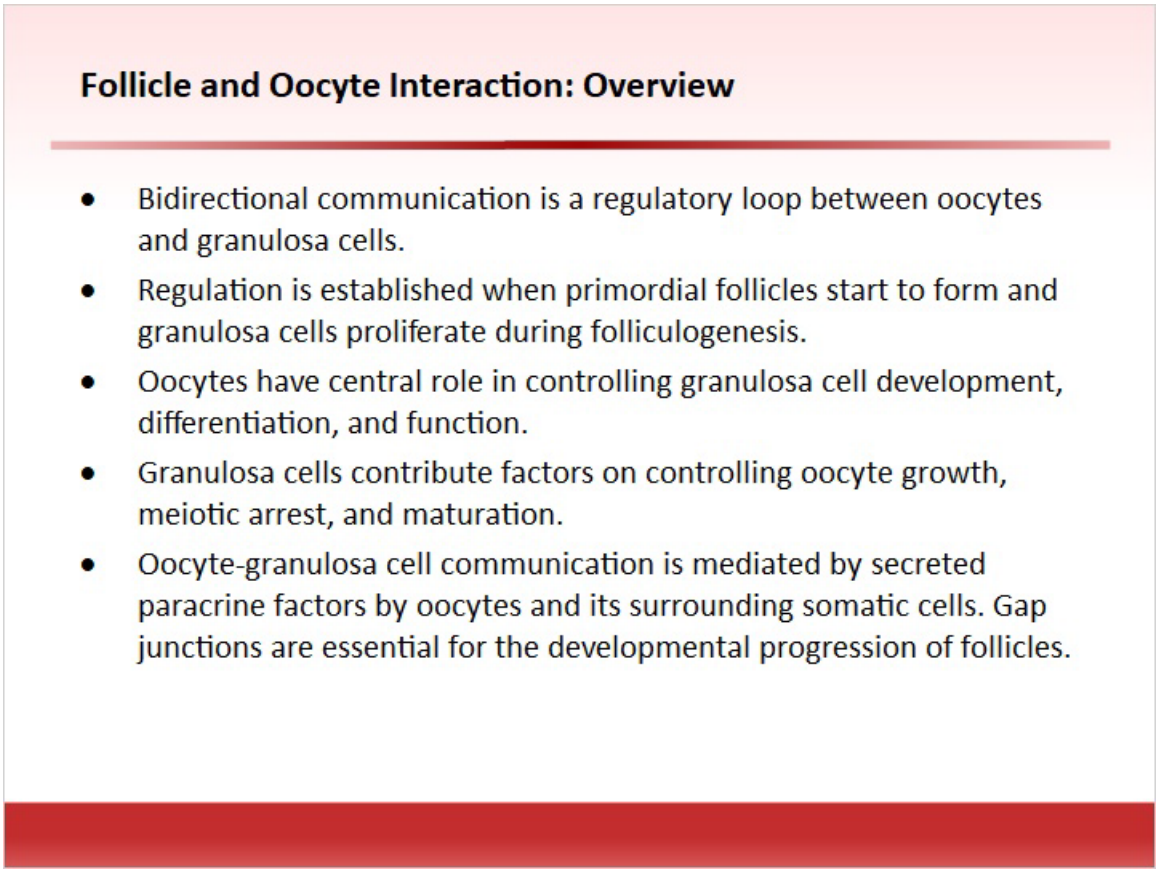
1.44 Untitled Slide



Notes:

Follicle and oocyte interaction during folliculogenesis will be addressed in this section.

1.45 Follicle and Oocyte Interaction: Overview



Notes:

During folliculogenesis, oogenesis, and early embryonic development, a regulatory loop with bidirectional communication between oocytes and granulosa cells is essential for the development.

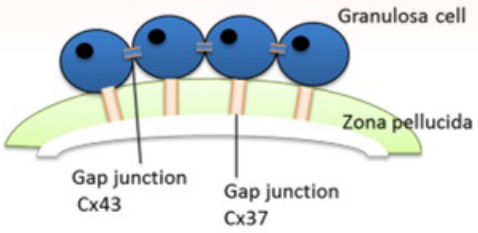
This regulation is established when primordial follicles start to form and granulosa cells proliferate during the ensuing stages of folliculogenesis.

In this regulatory loop, oocytes have the central role in controlling granulosa cell development, differentiation, and function from the time of follicular organization and continuing throughout ovulation. Granulosa cells contribute factors on controlling oocyte growth, meiotic arrest, and maturation.

Oocyte-granulosa cell communication is mediated by secreted paracrine factors by oocytes and its surrounding somatic cells. Gap junctions are formed between oocyte and granulosa cells, and between granulosa cells. This structure plays an essential role in the developmental progression of follicles.

1.46 Follicle and Oocyte Interaction: Gap Junctions

Follicle and Oocyte Interaction: Gap Junctions

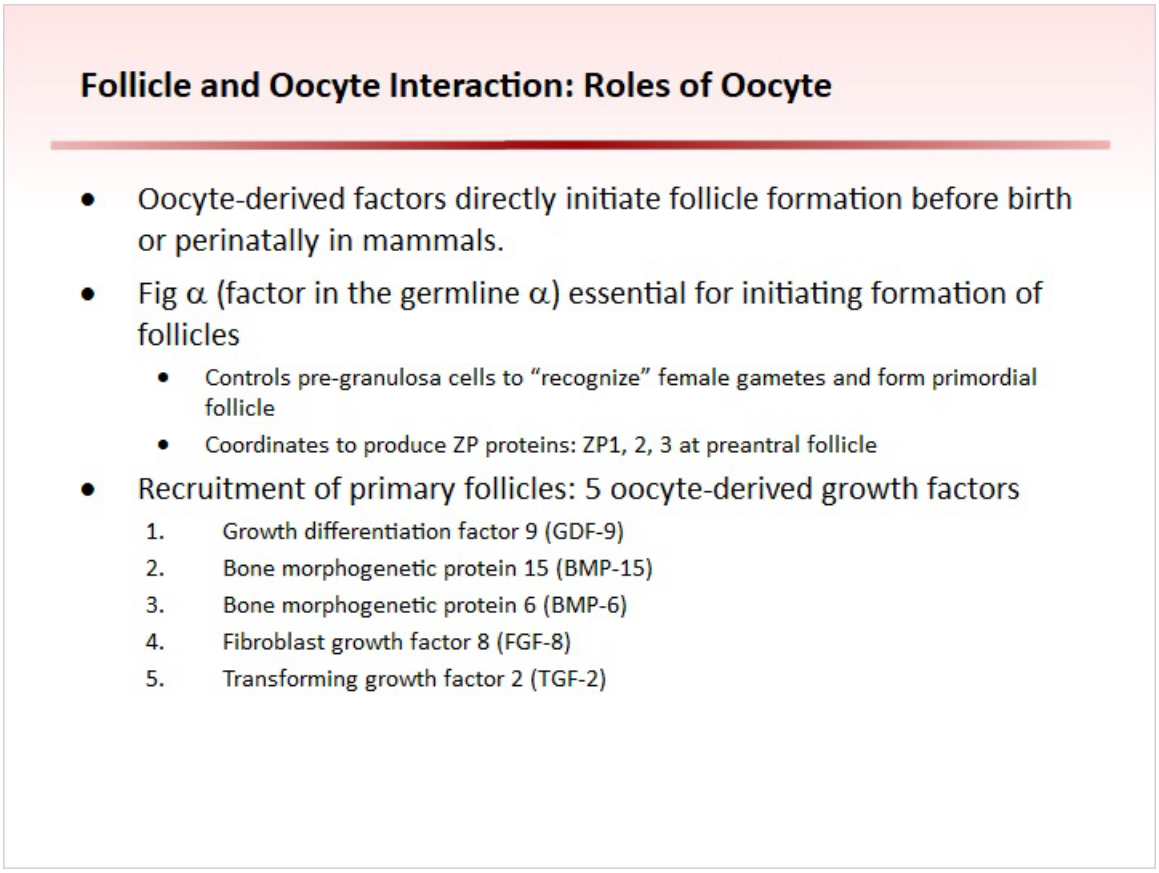


- Bidirectional communication between granulosa cells and oocytes
  - Granulosa-granulosa cells (homologous junctions)
  - Granulosa-oocyte (heterologous junctions)
- Channels permit exchange of nutrients, ions, and regulatory molecules
- Spanned by channel-forming proteins: connexins
  - Cx37: couples oocyte to granulosa cells
  - Cx43: couples granulosa cells

Notes:

Gap junctions are exchange channels for this bidirectional communication between granulosa cells and oocytes. These channels are formed between granulosa-granulosa cells, which are homologous junctions, and granulosa-oocyte, which are heterologous junctions. These channels permit the exchange of nutrients, ions, and regulatory molecules between these two cell types. Gap junctions are spanned and formed by channel-forming proteins called connexins. There are two types of connexins: Cx37, which couples the oocyte to granulosa cells, and Cx43, which couples granulosa cells together.

1.47 Follicle and Oocyte Interaction: Roles of Oocyte



Notes:

The oocyte plays central roles in this follicle and oocyte interaction. Oocyte-derived factors directly initiate follicle formation before birth or perinatally in mammals. Fig α (factor in the germline α) is essential for initiating formation of follicles. It controls pre-granulosa cells to recognize female gametes and form the primordial follicle. It coordinates to produce zona pellucida proteins: ZP1, 2, 3 at the preantral follicle stage.

The recruitment of primary follicles is promoted by other factors secreted by the oocyte. At least 5 oocyte-derived growth factors are involved in the stage:

Growth differentiation factor 9 (GDF-9)

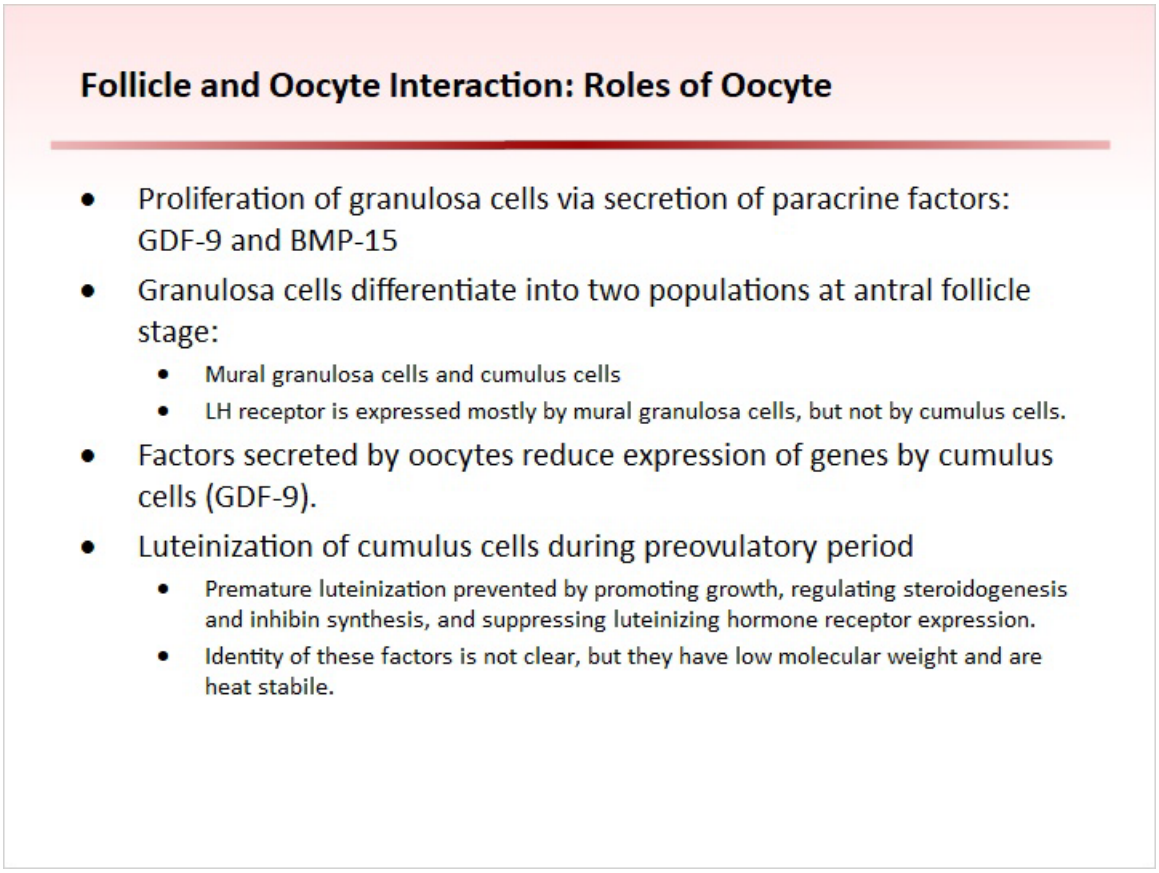
Bone morphogenetic protein 15 (BMP-15)

Bone morphogenetic protein 6 (BMP-6)

Fibroblast growth factor 8 (FGF-8)

Transforming growth factor 2 (TGF-2)

1.48 Follicle and Oocyte Interaction: Roles of Oocyte



Notes:

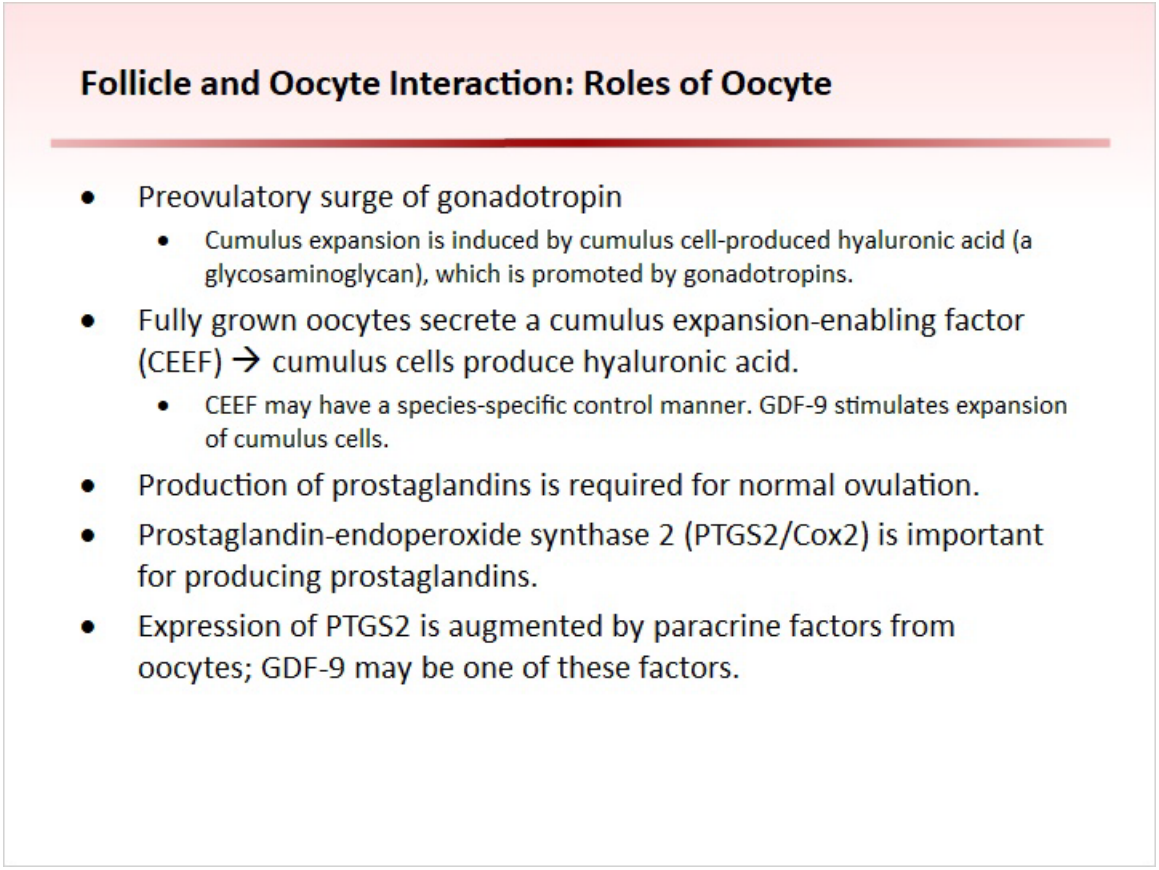
There are other important roles of the oocyte in this regulatory loop.

Proliferation of granulosa cells is probably regulated by the oocyte via the secretion of one or more paracrine factors: GDF-9 and BMP-15.

It promotes granulosa cells to differentiate into two populations at antral follicle stage: mural granulosa cells and cumulus cells. They are distinguished at the molecular level: the LH receptor is expressed mostly by mural granulosa cells, but not by cumulus cells. One or more factors secreted by oocytes probably reduce the expression of genes by cumulus cells; GDF-9 is one of these factors.

Luteinization of cumulus cells is the last differentiation, which takes place during the preovulatory period when progesterone is secreted in large amounts. The oocyte-cumulus cell interaction prevents luteinization of cumulus cells prematurely by promoting growth, regulating steroidogenesis and inhibin synthesis, and suppressing luteinizing hormone receptor expression on granulosa cells, which suppresses secretion of progesterone before the LH surge. The identity of these factors is not clear, but they have low molecular weight and are heat stabile. Possibly they are oocyte-secreted factors.

1.49 Follicle and Oocyte Interaction: Roles of Oocyte



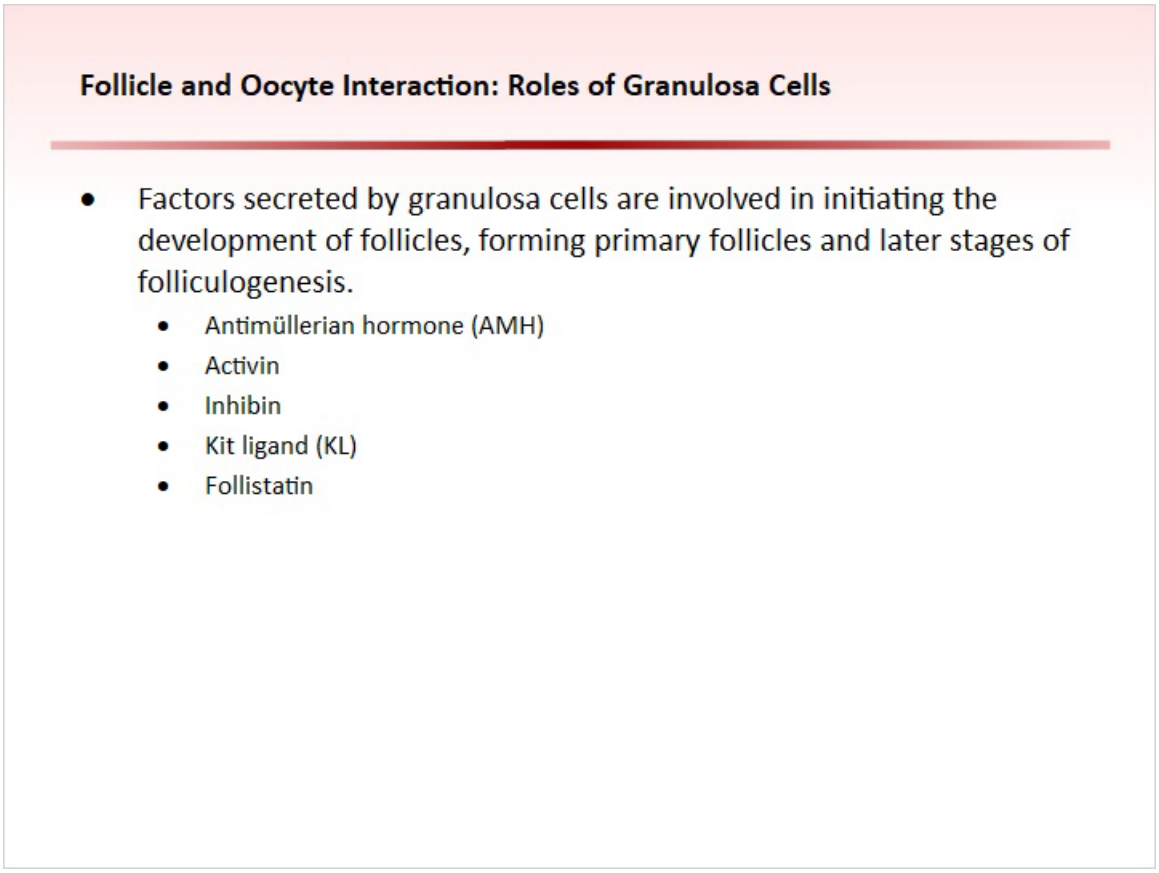
Notes:

The preovulatory surge of gonadotropin is essential for a cascade of processes in ovulation. Cumulus expansion, an important phenomenon for ovulation, is induced by cumulus cell-produced hyaluronic acid, which is a glycosaminoglycan and promoted by gonadotropins. This phenomenon is regulated by oocyte-derived factors.

The fully-grown oocytes secrete a cumulus expansion-enabling factor: CEEF, which enables cumulus cells to produce hyaluronic acid. CEEF may have a species-specific control manner. GDF-9 stimulates the expansion of cumulus cells.

The production of prostaglandins is required for normal ovulation. The prostaglandin-endoperoxide synthase 2, (PTGS2, also called Cox2), is important for producing prostaglandins. The expression of PTGS2 is augmented by paracrine factors from oocytes: GDF-9 may be one of these factors.

1.50 Follicle and Oocyte Interaction: Roles of Granulosa Cells



Notes:

This section will address the roles and functions of granulosa cells in this bidirectional communication.

The following factors secreted by granulosa cells are involved in initiating the development of follicles, forming primary follicles, and later stages of folliculogenesis:

Antimüllerian hormone (AMH)

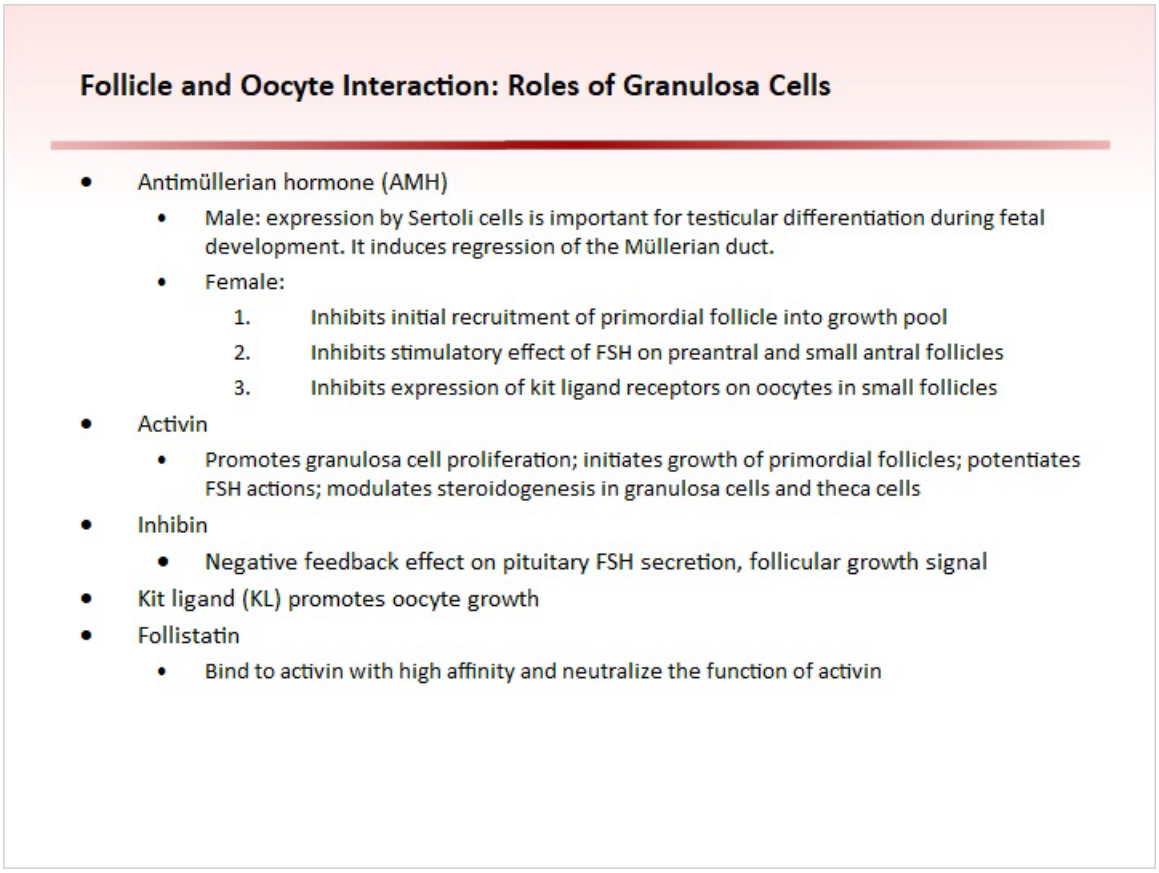
Activin

Inhibin

Kit ligand (KL)

Follistatin

1.51 Follicle and Oocyte Interaction: Roles of Granulosa Cells



Notes:

In men, antimüllerian hormone expression by Sertoli cells is important for testicular differentiation during fetal development. It induces regression of the müllerian duct (this duct otherwise gives rise to the oviduct, uterus, and upper part of the vagina).

In females, antimüllerian hormone is produced by follicular granulosa cells. It inhibits initial recruitment of the primordial follicle into the growth pool and inhibits the stimulatory effect of FSH on the growth of preantral and small antral follicles. It also inhibits expression of kit ligand receptors on oocytes in small follicles. It prevents premature recruitment and growth of follicles.

Activin is also produced by granulosa cells and has important regulating factors for folliculogenesis and oogenesis. It promotes granulosa cell proliferation and initiates the growth of primordial follicles. Activin potentiates FSH actions by increasing FSH receptors on granulosa cells and it modulates steroidogenesis in granulosa cells and theca cells in the later stages of folliculogenesis.

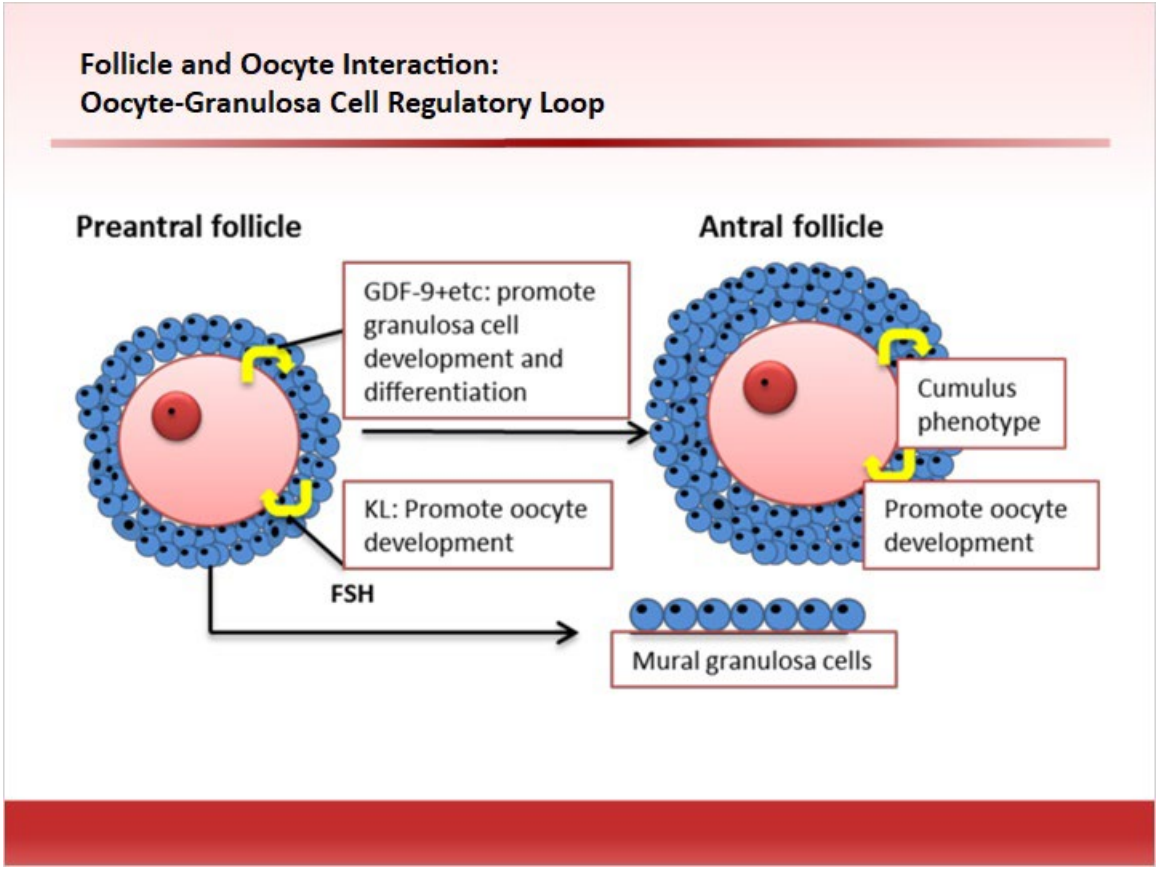
Inhibin is mainly secreted by granulosa cells and has a negative feedback effect on pituitary FSH secretion. This feedback is selective, but not on LH secretion. Inhibin functions as a follicular growth signal.

Kit ligand is produced by preantral and early antral follicles and promotes oocyte growth until it reaches a specific size. The expression of Kit ligand by granulosa cells and its receptor by oocytes implies a functional relationship. The regulation of oocytes on expression of Kit ligand is probably via GDF-9. This GDF-9 from fully grown oocytes, but not from medium-sized oocytes, suppresses Kit ligand expression in cumulus cells. This slows and terminates oocyte growth and forms an oocyte-granulosa cell regulatory loop.

In addition, FSH stimulates Kit ligand expression in preantral follicles, yet oocyte growth is independent of FSH.

Follistatin: it is produced by the granulosa cells and usually next to the cells producing activin. It binds to activin with high affinity and neutralize the function of activin.

1.52 Follicle and Oocyte Interaction:



Notes:

This is a short summary of the oocyte-granulosa cell regulatory loop.

GDF-9 and other factors derived from the oocyte regulate the differentiation of granulosa cells.

Signals from granulosa cells, such as Kit ligand, regulate the growth and differentiation of oocytes.

FSH stimulates follicle differentiation and aromatization of androgens in granulosa cells after the preantral follicle stage.

Factors from the oocyte influence granulosa cell development, differentiation, and function.

These interactions form an oocyte-granulosa cell regulatory loop, which operates in concert with gonadotropins and other factors to promote the transition to antral follicular development.

In antral follicles, cumulus cells are essential for promoting the development of oocyte competence to undergo fertilization and embryogenesis.

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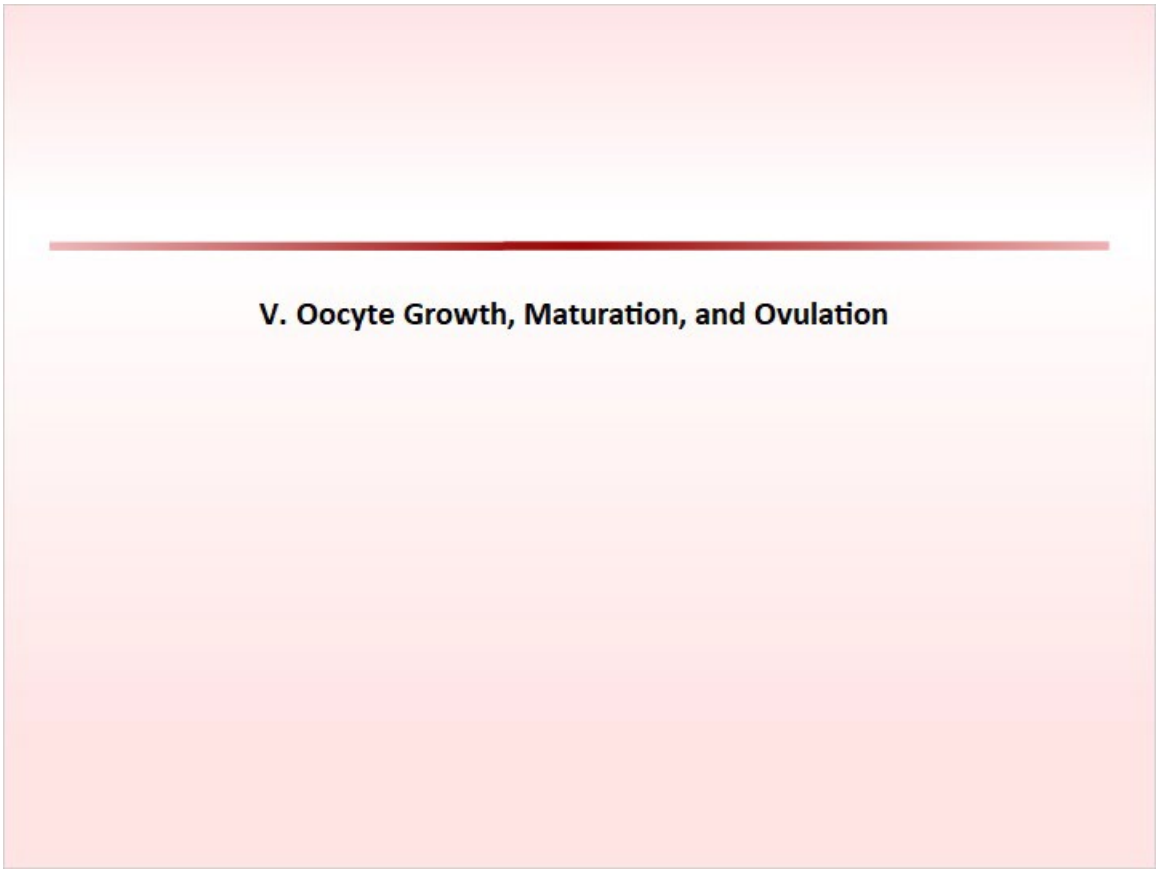
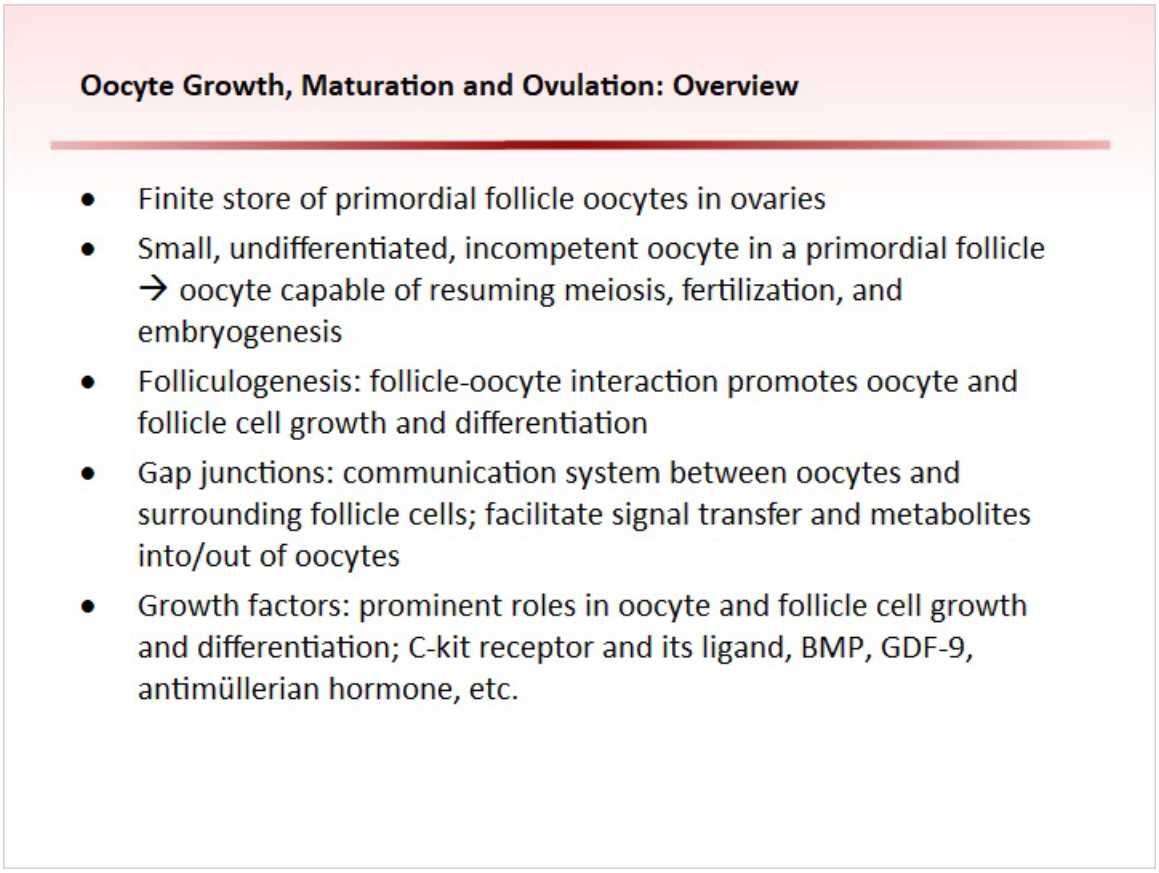


Notes:

The last section of this module will discuss oocyte growth, maturation, and ovulation.

1.54 Oocyte Growth, Maturation and Ovulation: Overview



Notes:

Recall that mammalian females contain a finite store of primordial follicle oocytes in the ovaries at birth. The oocyte changes from a small, undifferentiated, incompetent oocyte in a primordial follicle to one capable of resuming meiosis, fertilization, and embryogenesis.

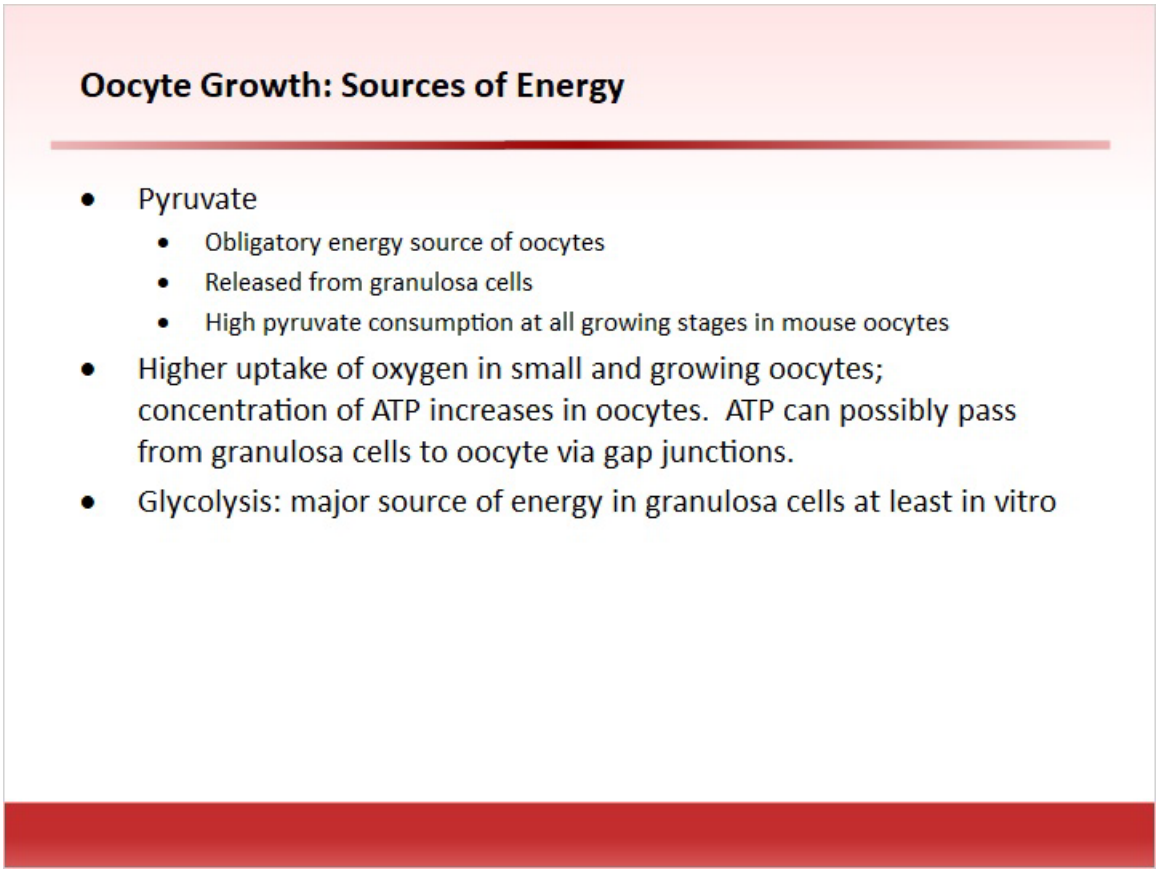
During folliculogenesis, follicle-oocyte interaction promotes oocyte and follicle cell growth and differentiation.

Gap junctions are the communication channels between oocytes and their surrounding follicle cells; they facilitate signal transfer and metabolites into and out of oocytes.

The growth factors and other factors play prominent roles in oocyte and follicle cell growth and differentiation. These include factors that were discussed earlier: C-kit receptor and its ligand, BMP, GDF-9, antimüllerian hormone, etc.

But there are other factors and changes determining the growth competence of oocytes.

1.55 Oocyte Growth: Sources of Energy



Notes:

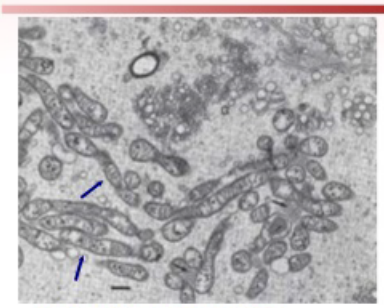
Pyruvate is an obligatory energy source of oocytes and is released from granulosa cells. It is also an energy source for zygotes and early embryo development. Research shows that high pyruvate consumption is shown at all growing stages in mouse oocytes.

Small and growing oocytes have a higher uptake of oxygen, which is the potential for ATP production (assuming 1 mole of fully oxidized pyruvate yields 12.25 moles of ATP). Thus the concentration of ATP increases in oocytes. ATP can possibly pass from granulosa cells to the oocyte via gap junctions.

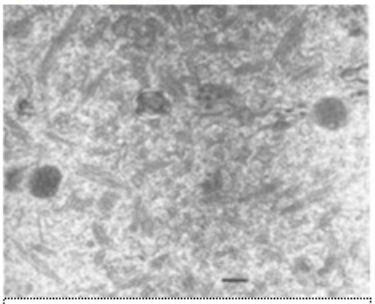
In vitro studies have shown that glycolysis is a major source of energy in granulosa cells.

1.56 Morphology and Structure Changes

Morphology and Structure Changes during Oocyte Growth



Mitochondria in a monkey oocyte by EM (Blue arrows) (Courtesy of RG Gosden)



Bundles of fibrous lamellae in the cytoplasm of a full-grown oocyte from hamster by EM (Courtesy of RG Gosden)

- Other morphology and structure changes may reflect increased energy and synthetic requirement of the oocyte
  - Elongated forms of mitochondria (energy)
  - Dividing mitochondria (energy)
  - Smooth endoplasmic reticulum (SER) (lipid synthesis)
  - Rough endoplasmic reticulum (RER) (protein synthesis)
- Other membranous cytoplasmic (ooplasmic) organelles
  - Golgi increases in abundance and migrates to cell periphery and becomes vesicular: for protein and lip modification and sortation
- Vesicles: export (secretion) and import (endocytosis) proteins and other molecules
- "Nuage" (French for "cloud"): small electron dense masses often close to mitochondria (rich in ribonucleoproteins or RNPs)
- Fibrous lamellae: increasing abundance in rodent oocytes (nearly 10% volume)

Notes:

There are morphology and structure changes during oocyte growth. The growing oocytes in primary follicles increase the abundance of elongated forms of mitochondria and dividing mitochondria, which indicate the increasing energy demand. There are also increasing amounts of smooth and rough endoplasmic reticulum (SER, RER), which reflect increased lipid and protein synthesis.

Other membranous cytoplasmic (ooplasmic) organelles are seen in growing oocytes. Golgi increase in abundance, migrate to the cell periphery, and become vesicular, which plays a role for protein and lipid modification and sortation. Vesicles are seen in the ooplasm; these are both the export and import of proteins and other molecules. "Nuage" (French for "cloud") are found: these are small electron dense masses often close to mitochondria that are rich in ribonucleoproteins (RNPs). Fibrous lamellae show increasing abundance in rodent oocytes, which takes nearly 10% volume of ooplasm.

1.57 Oocyte Growth

Oocyte Growth

Nucleus

- Initially small with several small nucleoli, expands enormously (nucleoli also), and reaches >4 μm in mature oocyte
- Oocyte remains in prophase I of meiosis throughout its growth; no further DNA synthesis. In many species, it migrates to the periphery as the oocyte enlarges, with numerous nuclear pores.

Synthesis of mRNAs and proteins in growing oocytes

- Oocytes accumulating mRNAs, ribosomes, polypeptides, and organelles during growth phase; crucial for oocyte competence and early embryo development
- First signs of RNA synthesis at preantral follicle stage. Early antral follicles are transcriptionally active until follicles reach Graafian follicle stage.

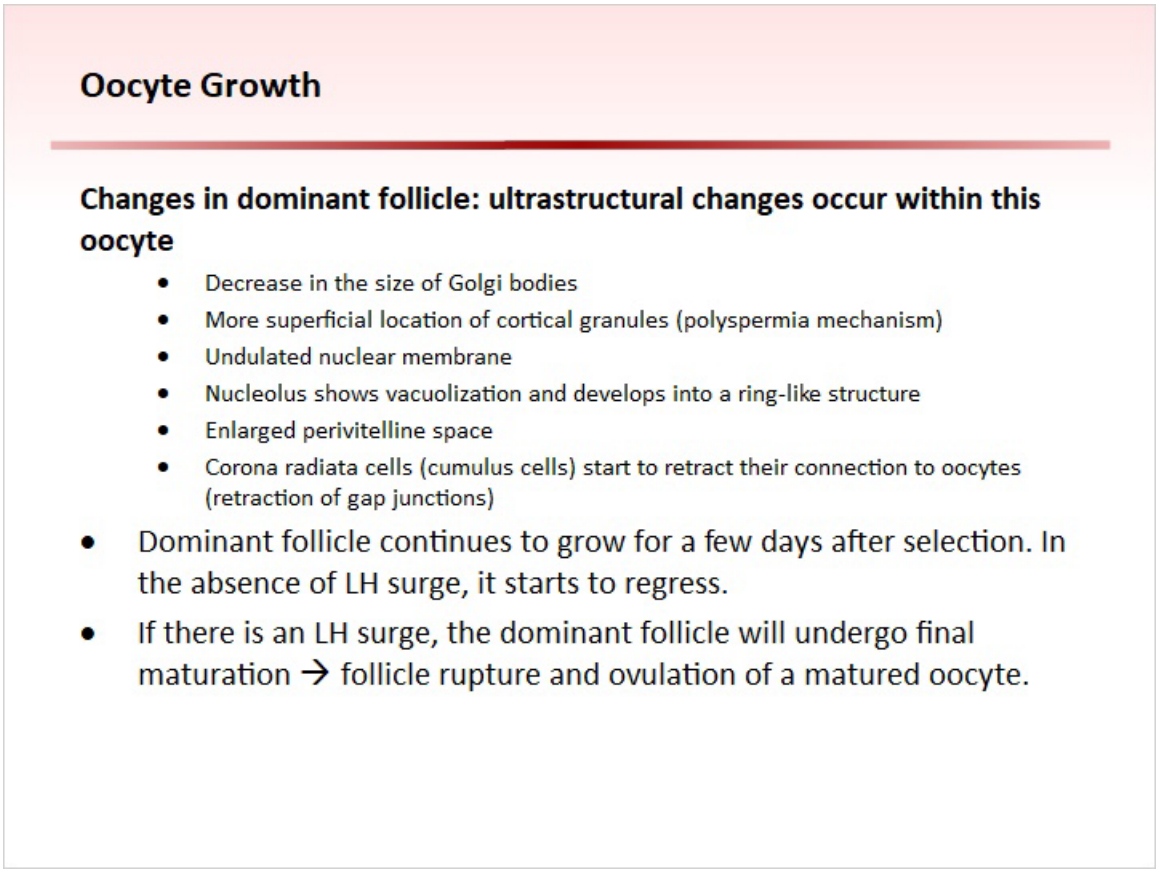
Notes:

The nucleus also undergoes some morphology and structural changes during oocyte growth:

The nucleus is initially small with several small nucleoli and expands enormously as do nucleoli, and it reaches more than 4 μm in diameter in the mature oocyte. The oocyte arrests in prophase I of meiosis throughout its growth and there is no further DNA synthesis. In many species, the nucleus migrates to the periphery as the oocyte enlarges. It has numerous nuclear pores.

Oocytes accumulate mRNAs, ribosomes, polypeptides, and organelles during the growth phase, which is a crucial step for oocyte competence and early embryo development. These oocytes show the first signs of RNA synthesis at the preantral follicle stage. Early antral follicles are transcriptionally active until follicles reach the Graafian follicle stage.

1.58 Oocyte Growth



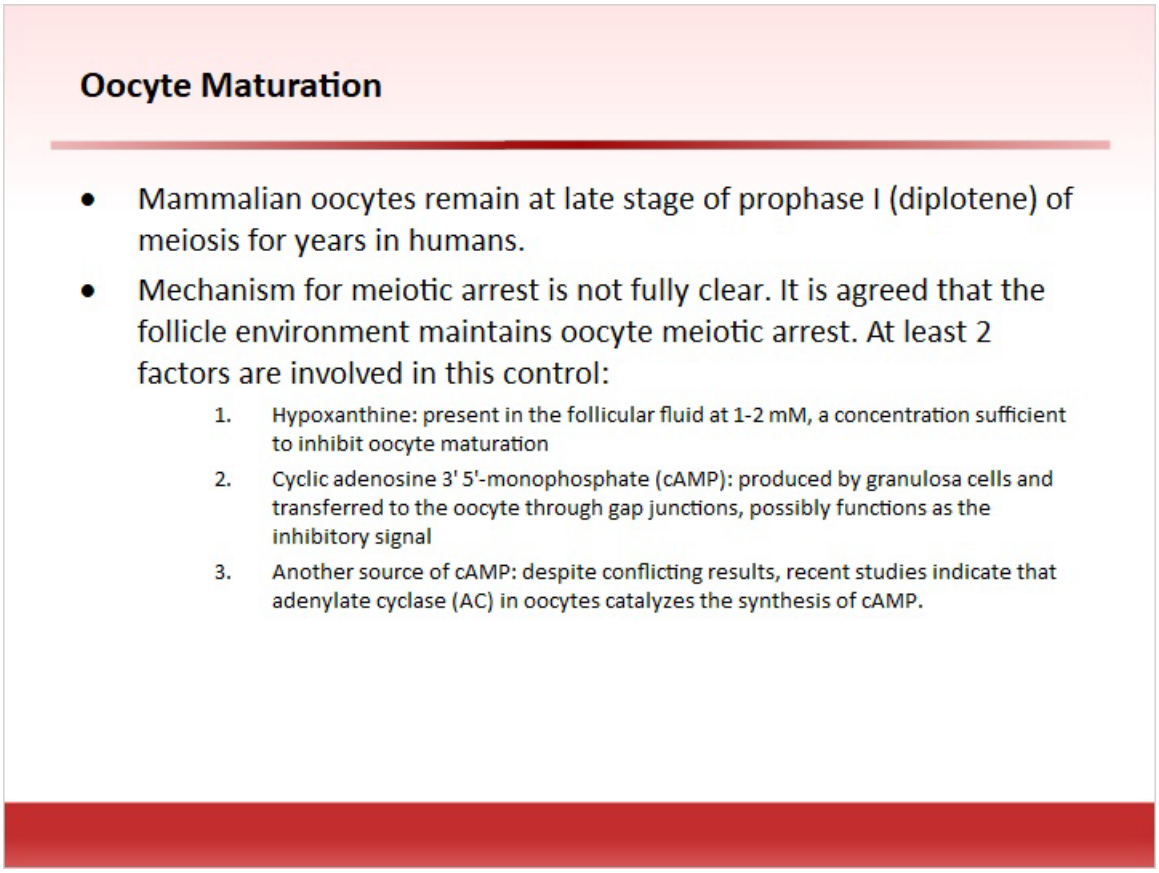
Notes:

When follicles reach the late stage, only one follicle increases in size and becomes larger than the other, which is called a dominant follicle. Several ultrastructural changes occur within this oocyte. There is a decrease in the size of Golgi bodies, and more cortical granules are gathered under ooplasmic membrane, which will function in the polyspermia mechanism after the first sperm enters the oocyte.

The nuclear membrane becomes undulated and the nucleolus shows vacuolization and develops into a ring-like structure. The perivitelline space of the oocyte is enlarged and corona radiata cells (also known as cumulus cells) start to retract their connection to the oocyte, which causes the gap junctions to retreat between these two types of cells.

The dominant follicle continues to grow for a few days after selection and in the absence of an LH surge, it starts to regress. If there is an LH surge, the dominant follicle will undergo final maturation, culminating in follicle rupture and the ovulation of a matured oocyte.

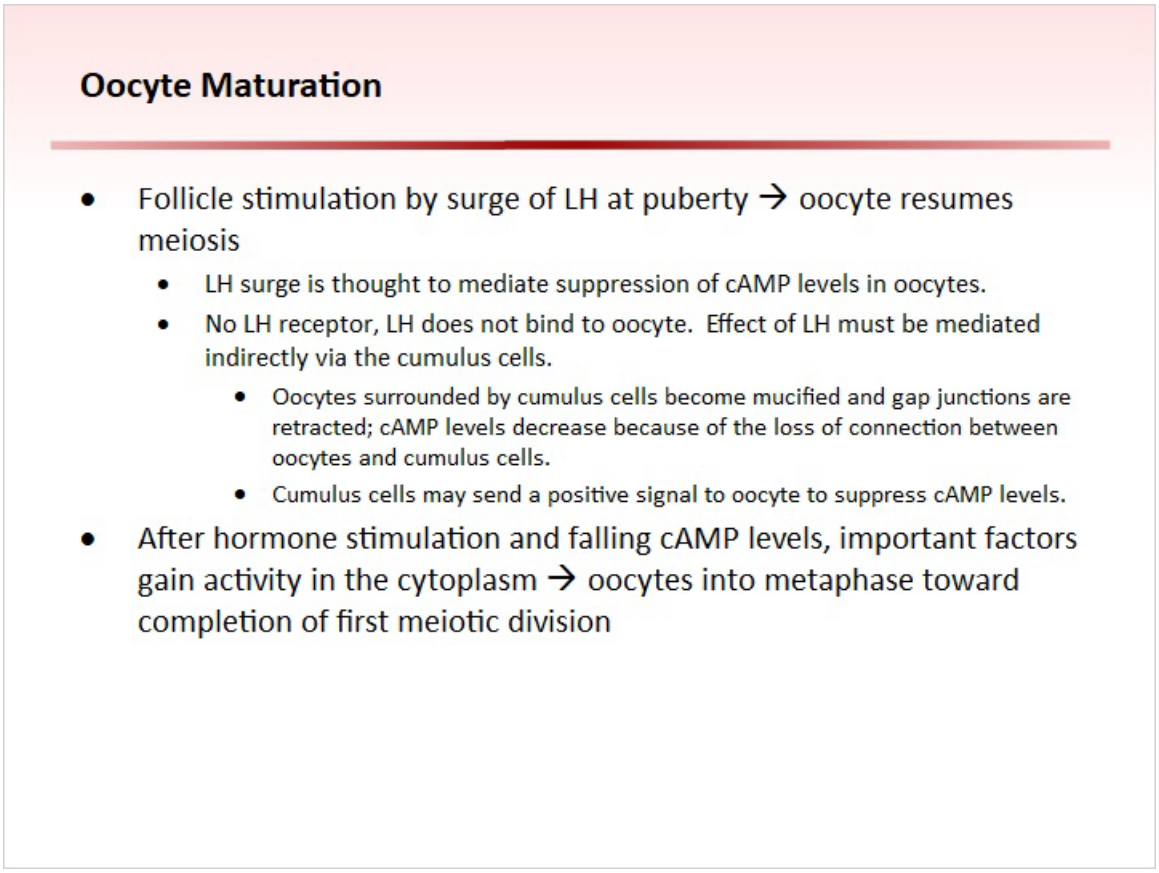
1.59 Oocyte Maturation



Notes:

Oocytes remain at late stage of prophase I (diplotene stage) of meiosis for years in humans. The mechanism for meiotic arrest is not fully clear. It is agreed that the follicle environment maintains oocyte meiotic arrest. At least two factors are involved in this control. Hypoxanthine presents in the follicular fluid at 1-2 mM. This concentration is sufficient to inhibit oocyte maturation. Cyclic adenosine 3' 5'-monophosphate (cAMP) is produced by granulosa cells and transferred to the oocyte through gap junctions; it possibly functions as the inhibitory signal. Despite conflicting results, recent studies indicate that adenylate cyclase (AC) in oocytes catalyzes the synthesis of cAMP.

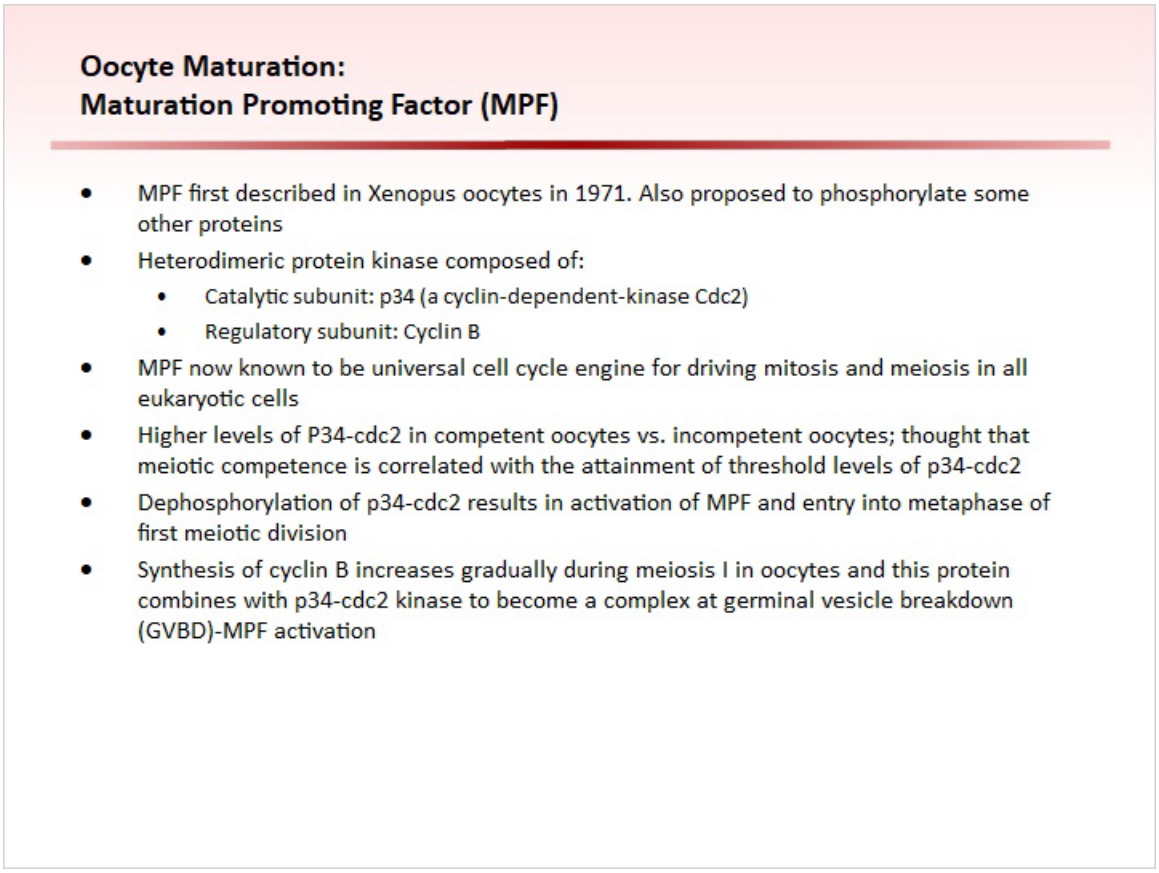
1.60 Oocyte Maturation



Notes:

With follicle stimulation by the surge of LH at puberty, the oocyte resumes meiosis. The LH surge is thought to mediate suppression of cAMP levels in oocytes. The oocyte does not have a receptor for LH and thus it doesn't bind to the oocyte and the effect of LH must be mediated indirectly via the cumulus cells. Oocytes surrounded by cumulus cells become mucified and gap junctions are retracted; cAMP levels decrease because of the loss of connection between oocytes and cumulus cells. Cumulus cells may also send a positive signal to the oocyte to suppress cAMP levels. After hormone stimulation and falling cAMP levels, important factors gain activity in the cytoplasm, which drive oocytes into metaphase and toward the completion of the first meiotic division.

1.61 Oocyte Maturation:



Notes:

The next steps involve maturation promoting factor (MPF) and cytostatic factor (MOS and MAP kinase).

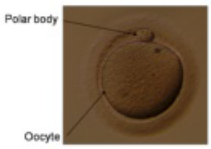
The activity of MPF was first described in *Xenopus* oocytes by Masui and Markert in 1971. Their study also proposed that MPF could also phosphorylate some other proteins. Later studies showed that it is a heterodimeric protein kinase composed of a catalytic subunit p34 (a cyclin-dependent-kinase Cdc2) and a regulatory subunit cyclin B. MPF is now known to be the universal cell cycle engine for driving mitosis and meiosis in all eukaryotic cells.

P34-cdc2 shows higher levels in competent oocytes compared with incompetent oocytes. It has been suggested that meiotic competence is correlated with the attainment of threshold levels of p34-cdc2. Dephosphorylation of p34-cdc2 results in the activation of MPF, which promotes the entry into metaphase of the first meiotic division. Synthesis of cyclin B increases gradually during meiosis I in oocytes and this protein makes a complex with p34-cdc2 kinase at the germinal vesicle breakdown stage, in which MPF gains its activity.

1.62 Oocyte Maturation:

Oocyte Maturation:
Maturation Promoting Factor (MPF)

- Once it becomes activated, MPF initiates meiotic events:
  1. Chromosome condensation
  2. Germinal vesicle breakdown (GVBD)
  3. Spindle assembly



- First polar body is extruded and oocyte completes first division of meiosis. MPF is inactivated between two rounds of meiosis, which is regulated by a translation-dependent mechanism that determines the level of cyclin B synthesis.
- Cyclin B degradation is a proteolytic process involving ubiquitin pathway regulated throughout the cell cycle; cyclins remain stable in interphase and are degraded during a short interlude just before the metaphase-anaphase transition.
- Protein synthesis is needed for the next round of meiotic resumption (cyclins).

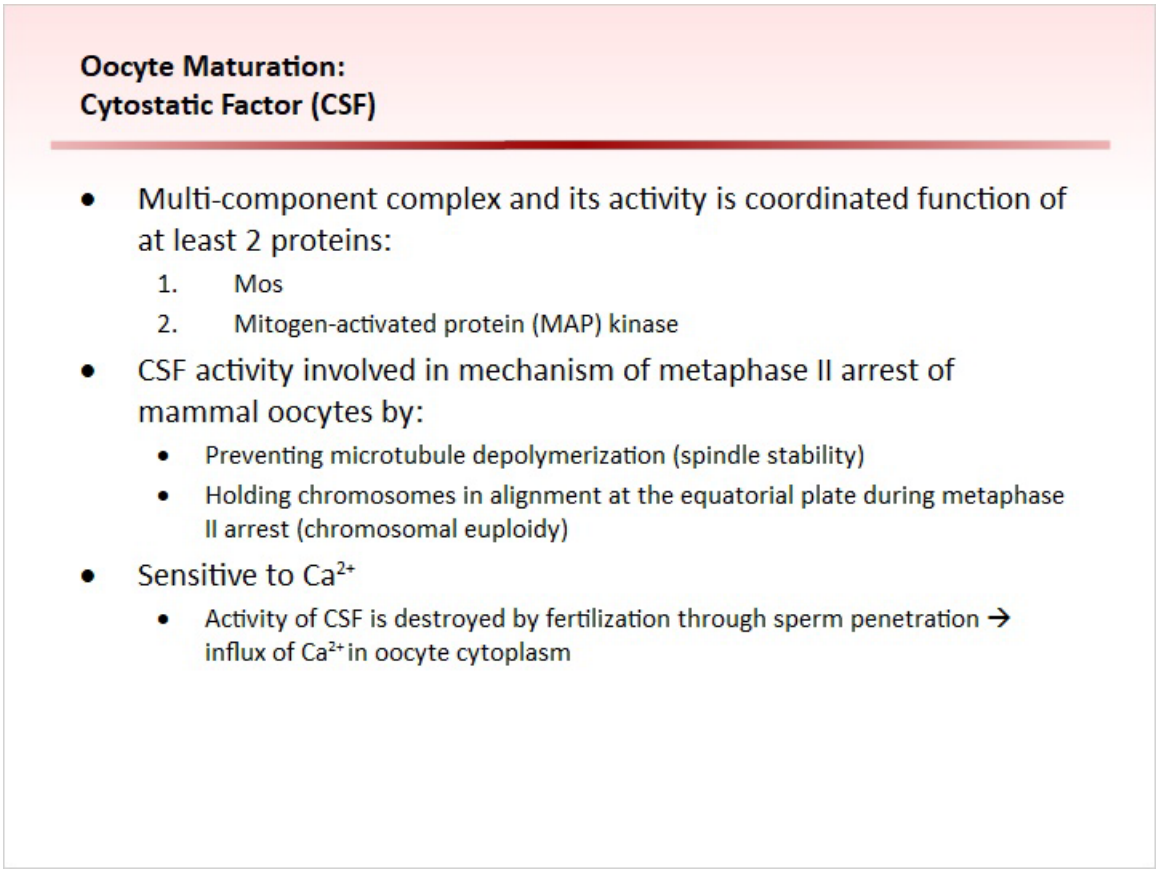
Notes:

Once it becomes activated, MPF initiates other meiotic events: chromosome condensation, germinal vesicle breakdown, and spindle formation.

The first polar body is extruded, and the oocyte finishes the first meiotic division. MPF is inactivated between two rounds of meiosis. This is regulated by a translation-dependent mechanism that determines the level of cyclin B synthesis.

Cyclin B degradation is a proteolytic process involving the ubiquitin pathway that is regulated throughout the cell cycle, in which the cyclins remain stable in interphase and are degraded during a short interlude just before the metaphase-anaphase transition. So protein synthesis is needed for the next round of meiotic resumption.

1.63 Oocyte Maturation:



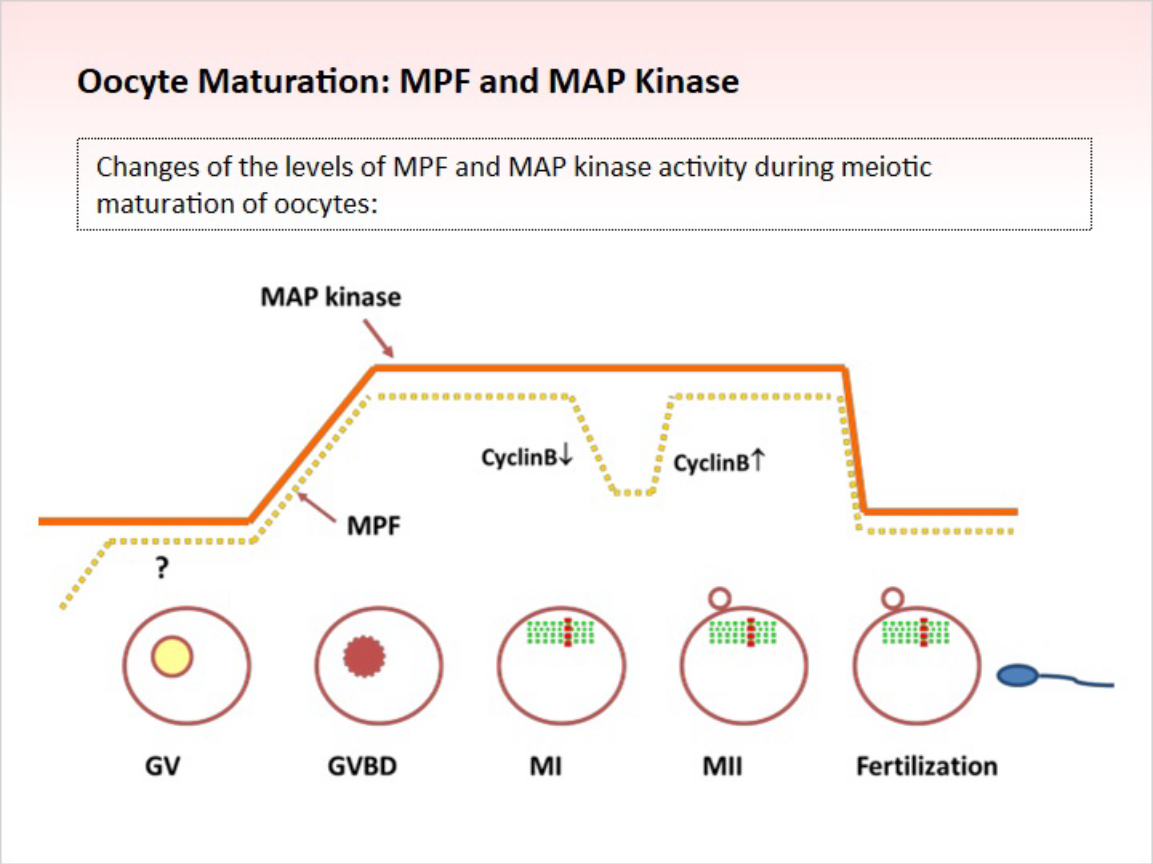
Notes:

The activity of cytostatic factor was also first described in *Xenopus* oocytes by Masui and Markert in 1971. Cytostatic factor is a multi-component complex and its activity is the coordinated function of at least two proteins: Mos and mitogen-activated protein (MAP) kinase.

Later studies showed that cytostatic factor activity is involved in the mechanism of metaphase II arrest of mammal oocytes by preventing microtubule depolymerization, which maintains spindle stability, and by holding the chromosomes in alignment at the equatorial plate during metaphase II arrest, which ensures chromosomal euploidy.

Cytostatic factor is sensitive to Ca^{2+}. Its activity is destroyed by fertilization through sperm penetration, which brings an influx of Ca^{2+} in oocyte cytoplasm.

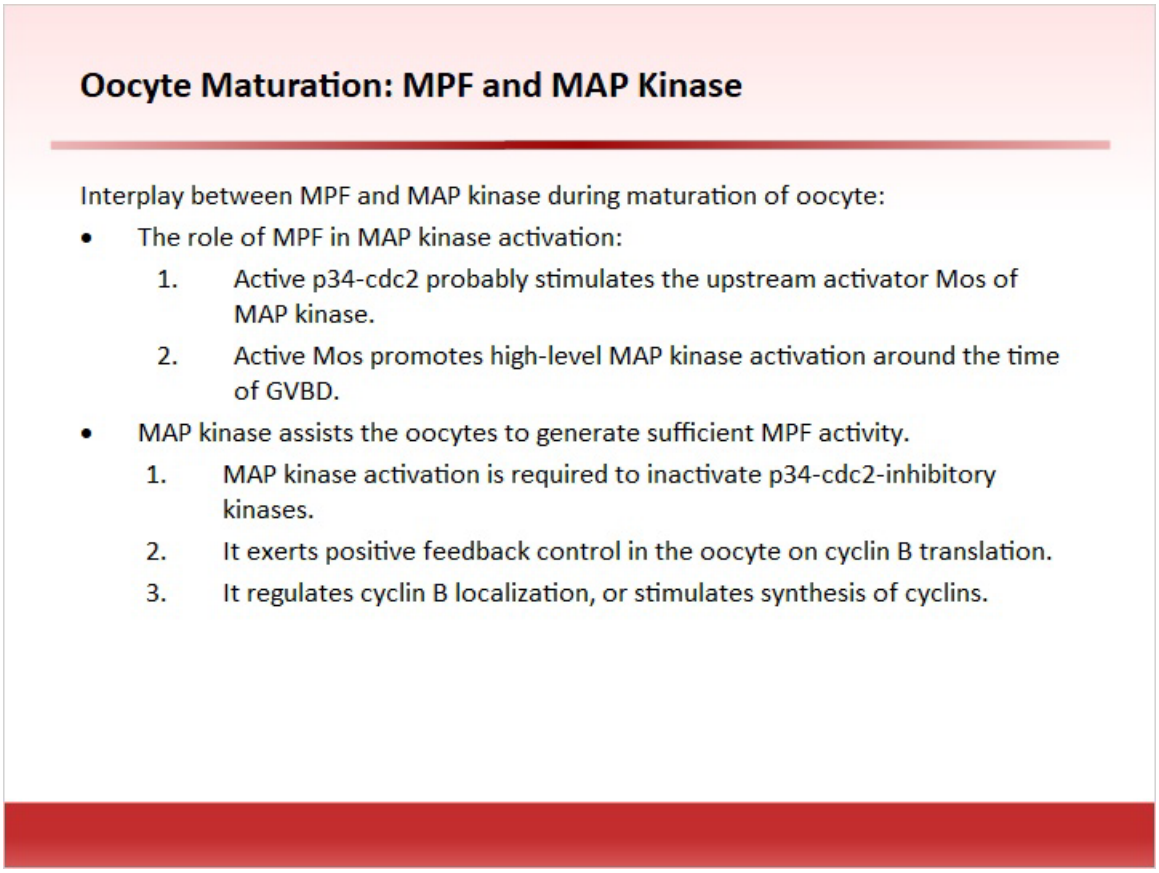
1.64 Oocyte Maturation: MPF and MAP Kinase



Notes:

This chart summarizes the changes of the levels of MPF and MAP kinase activity during meiotic maturation of the oocyte.

1.65 Oocyte Maturation: MPF and MAP Kinase



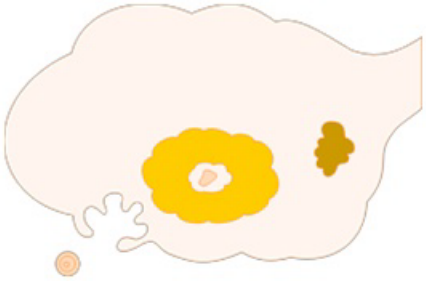
Notes:

MPF and MAP kinase interact together during maturation of the oocyte. Active p34-cdc2 probably stimulates the upstream activator Mos of MAP kinase, and active Mos promotes high-level MAP kinase activation around the time of GVBD. MAP kinase also assists the oocytes to generate sufficient MPF activity. Activation of MAP kinase is required to inactivate p34-cdc2-inhibitory kinases. It exerts positive feedback control in the oocyte on cyclin B translation. In the end, MAP kinase regulates cyclin B localization, or stimulates synthesis of cyclins.

1.66 Oocyte Ovulation

Oocyte Ovulation

- In response to the LH surge, the meiotic block is broken, and oocytes complete the first meiotic division and are arrested at metaphase II.
- The oocytes will be ovulated at this stage.
- The details of the mechanism of ovulation are still unknown.
- Some studies have shown that the two gonadotropins (FSH and LH) act together during this process.
    - LH induces the activities of collagenase, plasminogen, and prostaglandin, which cause the burst of the follicle wall.



Notes:

In response to the LH surge, the meiotic arrest is broken: oocytes complete the first meiotic division and are arrested at metaphase II. The oocytes will be ovulated at this stage. The details of the mechanism of ovulation are still not clear. Some studies have shown that the two gonadotropins (FSH and LH) act together during this process. LH induces the activities of collagenase, plasminogen, and prostaglandin, which cause the burst of the follicle wall for the mature oocyte escaping the ovary.

1.67 Thank you!

Notes:

Thank you for participating in this educational activity.