

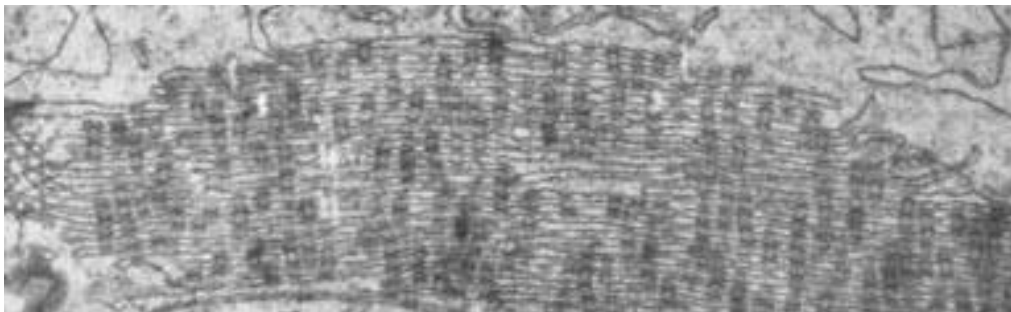


Egg Differentiation & Genetic Abnormalities

The Egg is a Differentiated Cell

The egg is a differentiated cell type. It is specialized in many ways: to receive the sperm during fertilization, to supply the majority of the cytoplasm for early development, to provide half of the genome for the zygote and, especially in lower animals to provide information to initiate the events of early development. The egg specializes early during meiosis and subsequently undergoes unequal cell divisions (releasing smaller polar bodies) so that this differentiated egg cytoplasm is not diminished greatly during meiosis. One aspect of the egg structure is the presence of various "envelopes" that surround it. As we will see, these cellular and non-cellular (extracellular matrix) components are critical to the survival and fertilization of the egg.

- Egg is a specialized cell type
- Comparatively large, round cell
- Growth & Differentiation phases occur during Prophase I of meiosis
- Germinal vesicle is specialized (e.g., minimal "lampbrush chromosomes")
- Surrounded by egg coats: cells (cumulus oophorus; corona radiata) and zona pellucida (protein "shell")
- Specialized organelles: e.g., Annulate lamellae in cytoplasm as shown in figure below:



Electron micrograph of annulate lamellae from human primary oocyte (Hertig, 1968. *Am. J. Anat.* 122: 107-138).

The parallel stacks of nuclear envelope-like membranes lie adjacent to the nucleus which may give rise to them. Evidence indicated the annulate lamellae are essential for the formation of the pronuclei in some mammals.

1° Oocyte: Growth & Differentiation Phase

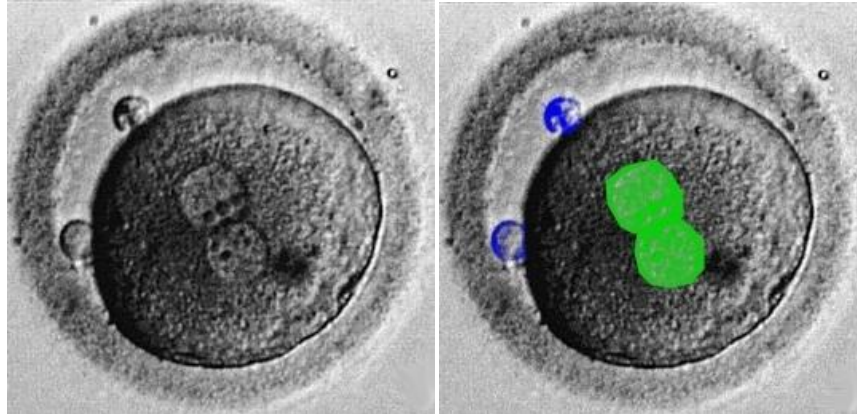
- Many animals have large store of yolk
- Human egg has minimal yolk; yolk proteins made in liver--transported to egg via blood
- Only needs internal nutrients until implantation
- Nutrients from maternal body via placenta
- Chromosomes in germinal vesicle have lateral loops--involved in RNA synthesis
- Egg is surrounded by egg "envelopes"

Meiotic Divisions

- Reduce DNA amount to C=haploid; Chromosome # to n= haploid
- Limits loss of cytoplasm during division: eccentric nucleus leads to large oocyte/ovum & small polar bodies

Egg Differentiation & Genetic Abnormalities

- Polar bodies may be re-absorbed by egg or embryo

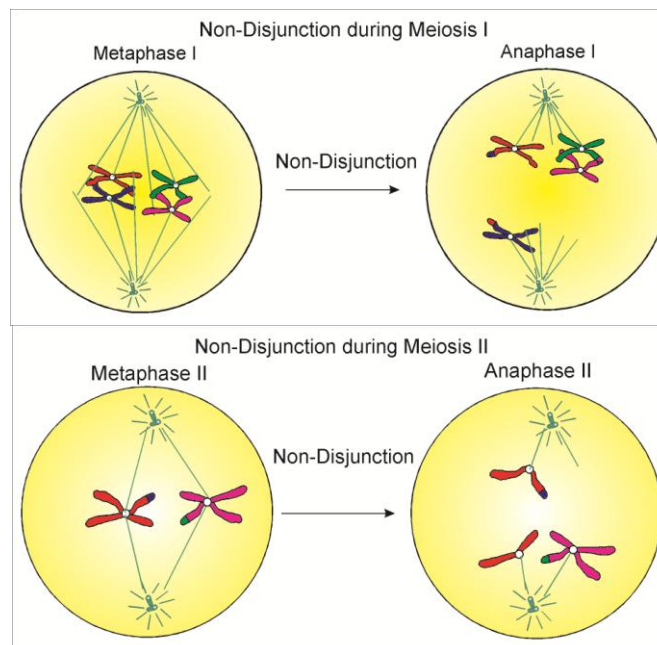


The fusing haploid pronuclei (false coloured green in right panel) are seen in the centre of the egg while the two released pronuclei (false coloured blue in right panel) that resulted from the meiotic divisions are situated outside the egg. Sometimes a third polar body is observed which is due to the division of the first polar body. The polar bodies have no known developmental function other than to reduce the genetic complement of the egg without causing a large reduction in the egg cytoplasm. The zona pellucida surrounds the egg and polar bodies.

Meiosis & Genetic Abnormalities: Non-Disjunction

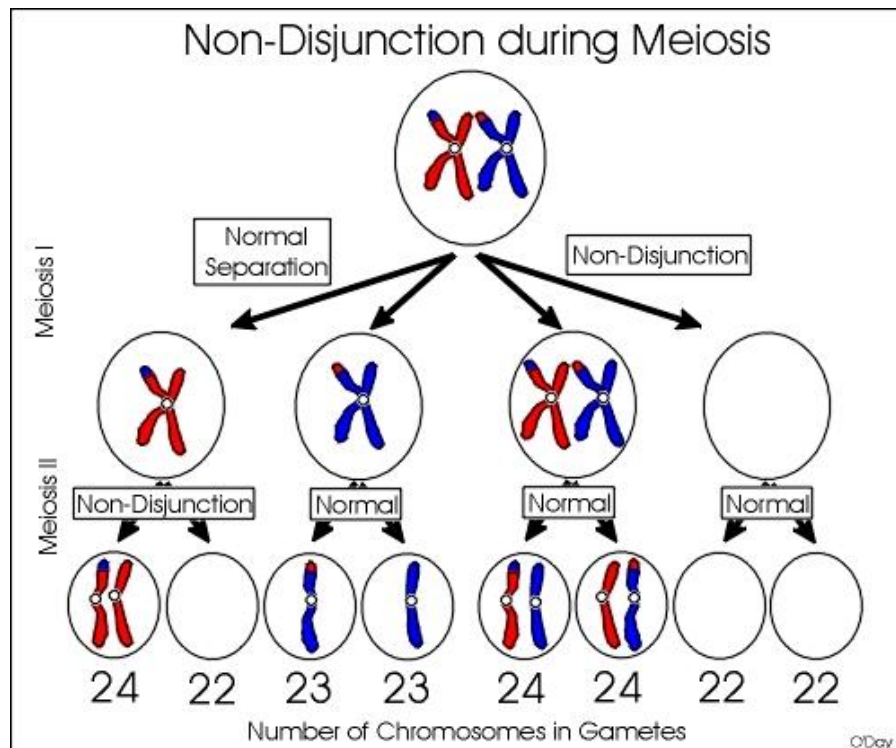
The following sections require a basic understanding of meiosis which you have covered in previous courses.

Non-Disjunction: Chromosomes don't pull apart so one cell gets both sister chromatids (that each become a chromosome) while the other cell doesn't get that chromosome. Non-disjunction can occur during either meiosis I or meiosis II as illustrated in the two following graphics. If it is not clear what is happening here and how you end up with gametes that either have an extra chromosome or lack a chromosome then please review Meiosis.



Egg Differentiation & Genetic Abnormalities

The following figure summarized how gametes end up with one more or one less chromosome when non-disjunction occurs during meiosis.



- Non-disjunction leads to abnormal chromosome numbers
- If one daughter gamete has extra chromosome (i.e., 24 rather than the normal 23) the syndrome is called trisomy (3 copies of the same chromosome) at fertilization e.g., Down Syndrome--trisomy 21: this is due to an extra copy of chromosome 21
- If the daughter gamete has 1 less chromosome (i.e., a total of 22 rather than the normal 23) it is referred to as monosomy (e.g., Turner Syndrome--lacks sex chromosome)
- Most cases of monosomy are not viable

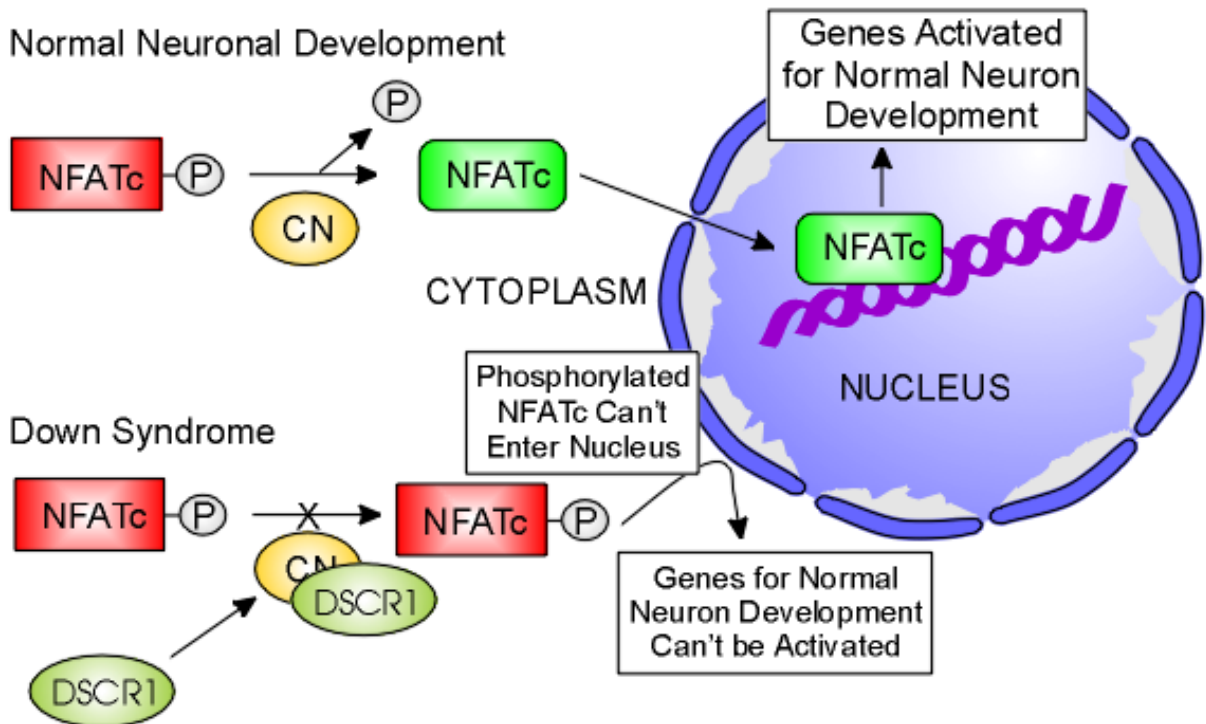
Most cases of non-disjunction are due to the “maternal age effect”. Older women have higher incidences of abnormal chromosome numbers in their eggs due to those eggs being held in a meiotic block (prophase of meiosis I) for an extended period of time. Similarly older men can also produce sperm with abnormal chromosome numbers. This “paternal age effect” however cannot be due to meiotic block since it doesn’t occur in males.

Non-Disjunction: Trisomy 21—Down Syndrome

- Extra chromosome 21
- Affects development of brain, immune system, heart and skeleton
- Mental retardation is the constant hallmark of Down syndrome
- Broad face with flat nasal bridge; wide set eyes; epicanthic folds
- Transverse Simian Crease in hands
- Occurrence: 1 in 700 births

Down Syndrome at the Molecular Level

The role of DSCR1 in neuronal development is just one aspect of Down Syndrome. The extra genes on chromosome 21 have many other functions and effects.



- Gene: *DSCR1* (Down Syndrome Critical Region 1) is found on chromosome 21
- The extra copy of chromosome 21 leads to over-expression of DSCR1 in developing brain cells (neurons)
- DSCR1 protein is an inhibitor of calcineurin (CN), a calcium and calmodulin-dependent protein phosphatase
- In normal neurons, CN removes phosphate groups (i.e., dephosphorylates) NFATc (Nuclear Factor of Activated T cells) allowing it to enter the nucleus to regulate genes required for normal development
- Increased levels of DSCR1 lead to the inhibition of CN which prevents it from dephosphorylating the critical transcription factor NFATc.
- Phosphorylated NFATc can't enter the nucleus to regulate specific genes required for normal brain development

Recently calcineurin, also called protein phosphatase 2B and, more recently, protein phosphatase 3. Calcineurin is the major calmodulin binding protein in the brain.

Non-Disjunction: Monosomy--Turner Syndrome

- Lacks X or Y sex chromosome due to non-disjunction thus is XO after fertilization
- Exhibit female phenotype; sterile
- Short stature, webbed neck; high arched palate
- Cognitive defects (i.e., affects learning)
- Occurrence: 1 in 2500 females



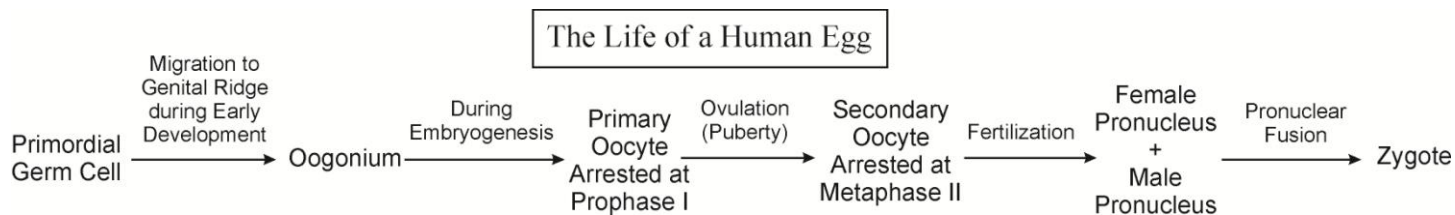
Naturally aborted fetus with Turner Syndrome



The Life of the Human Egg

The human egg goes through a series of starts and stops on its way to becoming prepared for fertilization and subsequently beginning development. During embryonic development the PGCs increase in number by mitosis and migrate into the genital ridge where further mitosis occurs. As the embryo develops, the eggs will begin meiosis progressing to prophase I of meiosis where they become arrested. At puberty, under the influence of hormones, some of the eggs will re-initiate meiosis and will be ovulated or will degenerate. The ovulated oocyte is arrested at metaphase II and will not continue meiosis unless activated by a sperm cell. Fertilization results in the completion of meiosis producing the female haploid pronucleus that will then fuse with the sperm pronucleus. The mechanisms whereby meiosis is arrested and restarted in other animals such as mice and frogs is an exciting area of research that involves signal transduction pathways and various kinases. Little has been done on this subject in human eggs. Remember, the majority of eggs remain locked in prophase I of meiosis during a female's life. Each month only a few eggs are stimulated to move to meiosis II the rest remain in prophase I. The following diagram shows these events as they occur for a single egg.

Egg Differentiation & Genetic Abnormalities



References

Arron et al, 2006. NFAT dysregulation by increased dosage of DSCR1 and DYRK1A on chromosome 21. Nature 1-6.

Cheng et al, 2006. Dosage compensation of the X chromosome and Turner syndrome. Internation Congress Series 1298: 3-8.

Rachidi & Lopes, 2008. Mental retardation and associated neurological dysfunctions in Down syndrome: A consequence of dysregulation in critical chromosome 21 genes and associated molecular pathways. Eur. J. of Paediatric Neurobiology 12: 168-212.



© Copyright 1998-2011 Danton H. O'Day