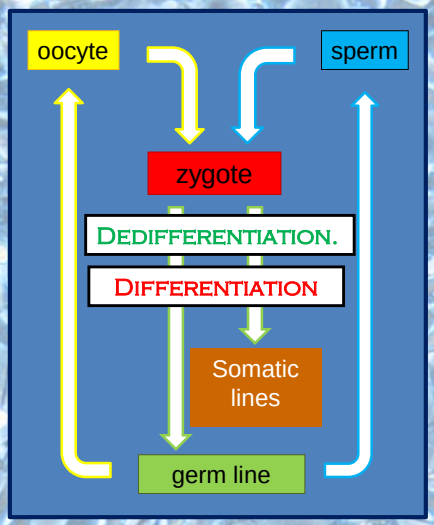
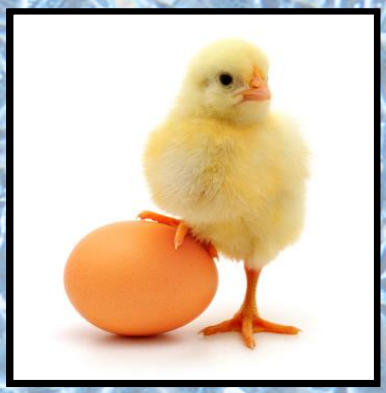
Potency of Cells

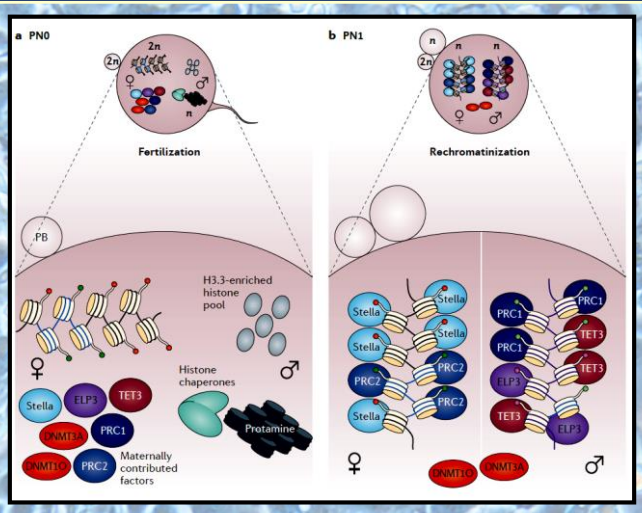
2018. Április 25.

The Fundamental Cycle





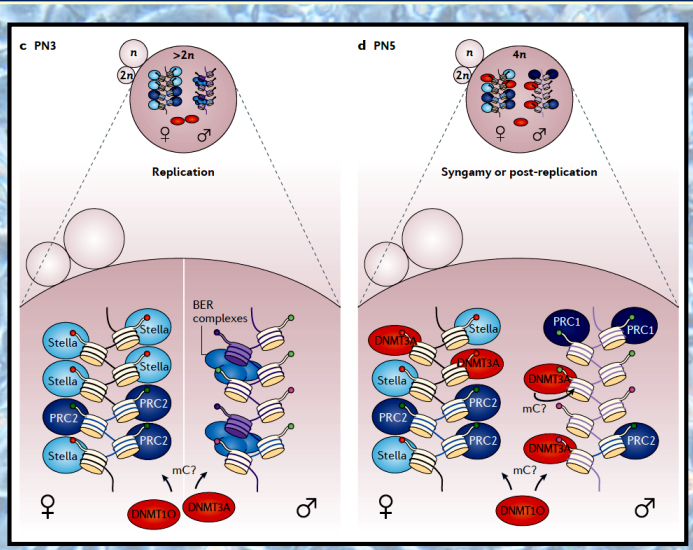
Global DNA Demethylation in the Zygote



Zachary et al., *Nature Rev. Genetics*, 2013

ELP3: histone acetyltransferase elongator complex protein 3
Tet1/2/3: ten-eleven translocation family of proteins
PRC1: polycomb repressive complex 1
PRC2 and Stella: epigenetic silencers

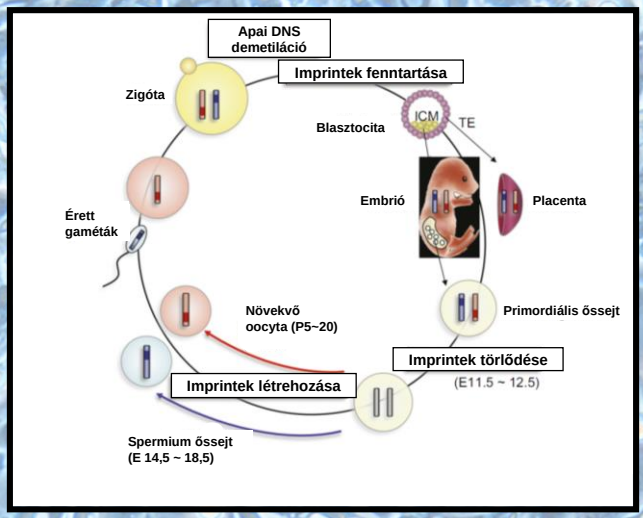
Global DNA Demethylation in the Zygote



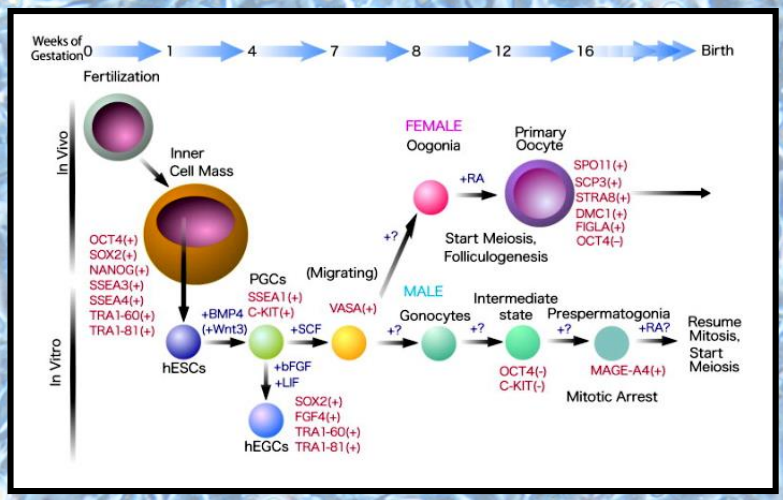
Zachary et al., *Nature Rev. Genetics*, 2013

BER: base excision repair

Dedifferentiation of Progenitor Germ Cells



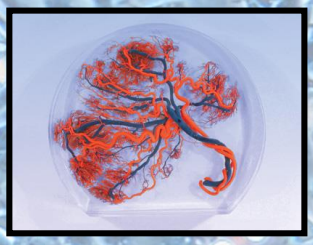
Differenciation of EGCs



Hayashi et al., *EMBO and Ster, 2012*

What is the ‚potency of cell'?

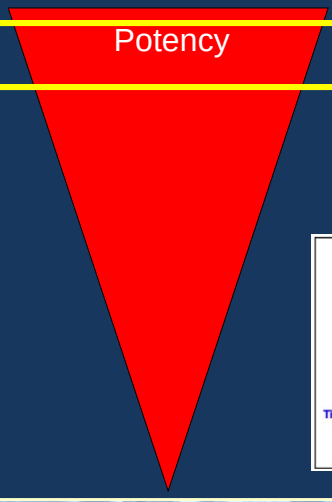
Cell potency is a cell's ability to differentiate into other cell types.
The more cell types a cell can differentiate into, the greater its potency.
Potency is also described as the gene activation potential within a cell.

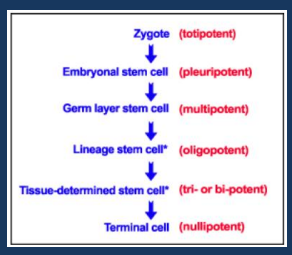


Potency

The range of commitment options available to a cell

- Totipotent
- Pluripotent
- Multipotent
- Oligopotent
- Unipotent





Totipotency: What it is and what it is not?

Totipotent cells are capable of developing into a complete organism or differentiating into any of its cells or tissues of given organism.

DNA demethylation : active and passive

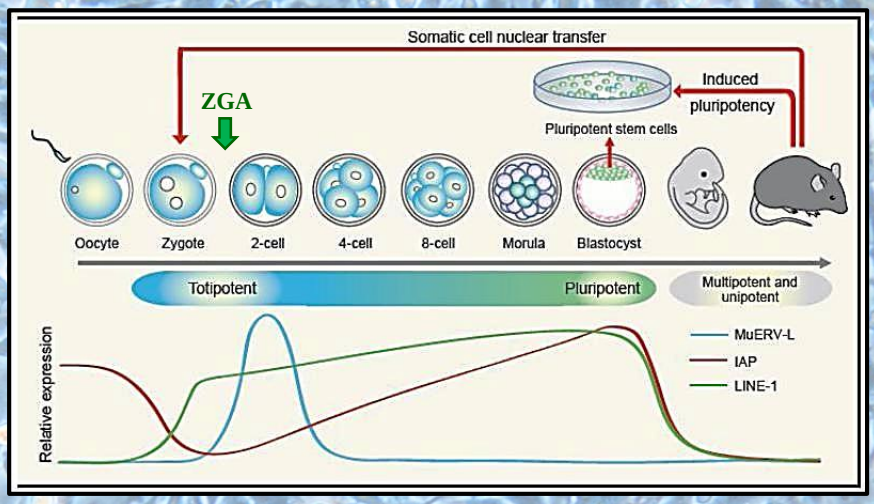
Under special conditions….

Tumor cells

Embryonic development

Reproductive adult

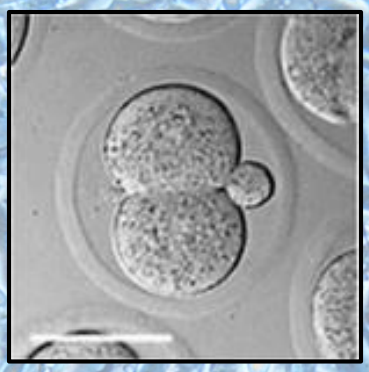
From totipotent to pluripotent: ZGA



Lu and Zhang, Nat Sci Rev, 2015

MuERV-L: murine endogenous retrovirus with leucine tRNA primer
IAP: intracisternal A-particle, **LINE-1**: long interspersed nuclear element 1 (transposable elements)

Loss of totipotency



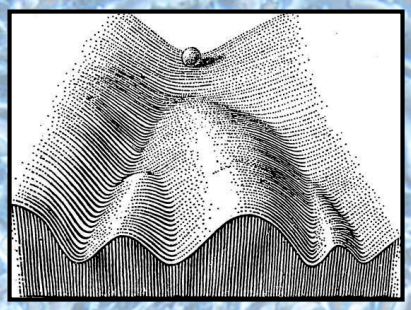
oct4 (homeobox) expression and *high* mobility of oct4

⇩

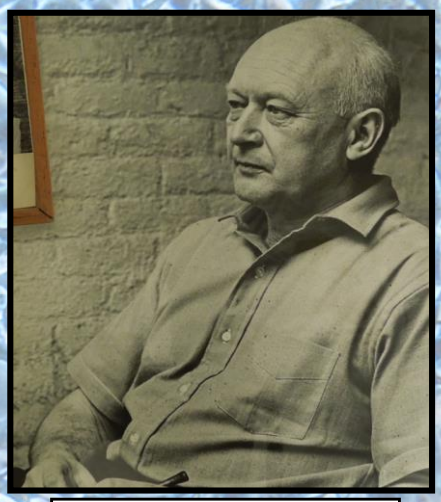
ICM

Cdx2 (homeobox) expression and *low* mobility of oct4 ⇨ **Trophoblast**

Epigenetic landscape



Mutation can modulate the epigenetic landscape.



Conrad Hal Waddington (1905–1975)

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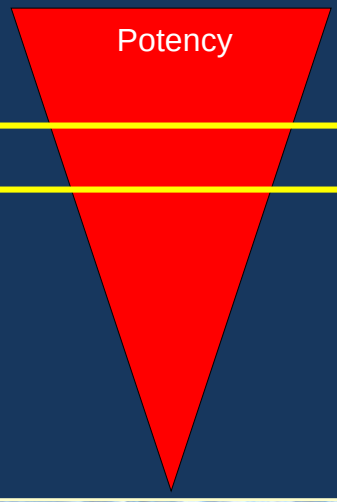
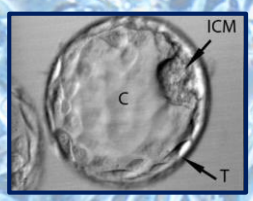


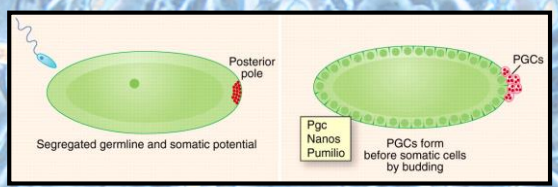
Pluripotency

Pluripotency refers to a stem cell that has the potential to differentiate into any of the three germ layers.

?



ICM: inner cell mass (embryoblast) ⇨ Germ layers

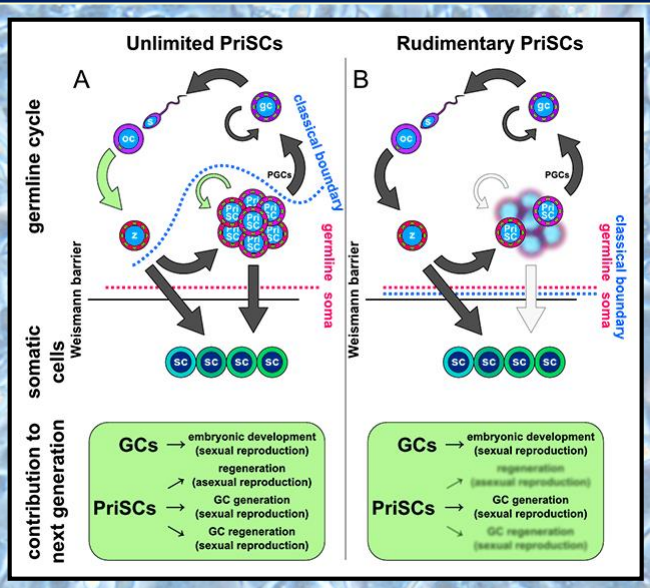


Segregated germ line potencial

⇩

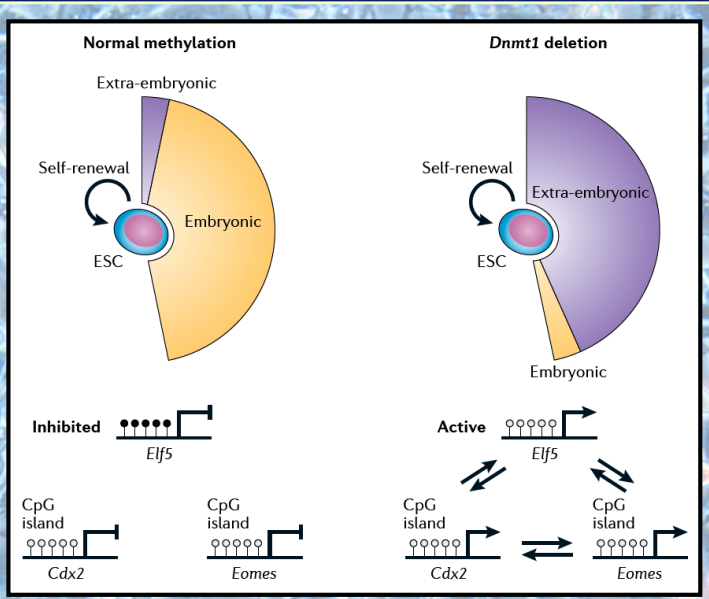
4th germ layer

Weismann barrier



Solana, EvoDevo, 2013

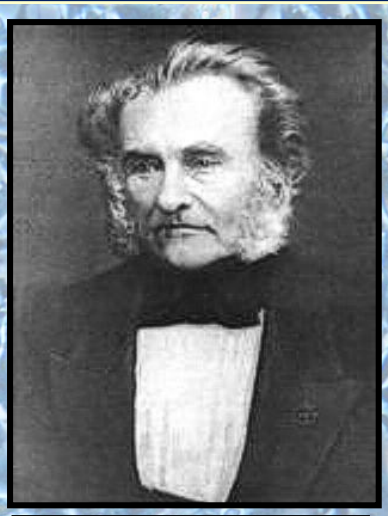
Lineage restriction



Zachary et al., *Nature Rev. Genetics, 2013*

Germ layers

Caspar Friedrich Wolff (1735 – 1794)

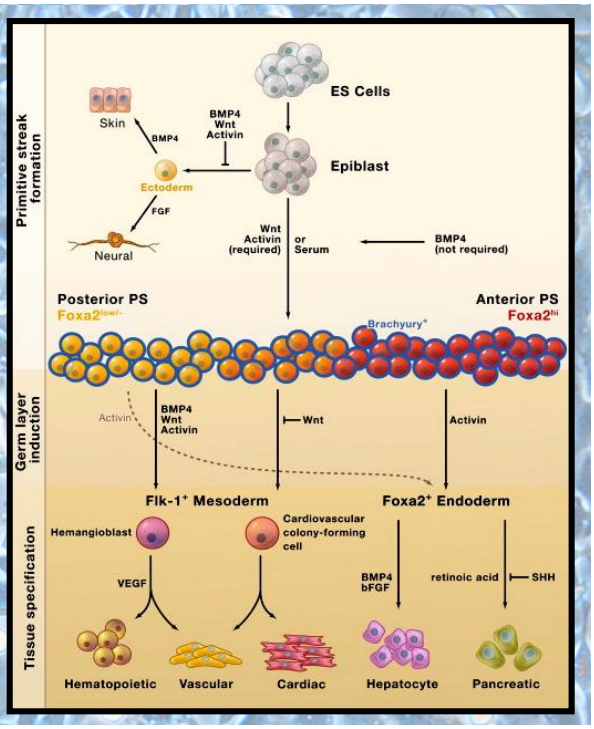


Heintz Christian Pander (1794 – 1865)

Germ layer determinants

PS: primitive streak

Flk1: Fetal Liver Kinase 1
Foxa2: forkhead box protein A
VEGF: Vascular endothelial growth factor



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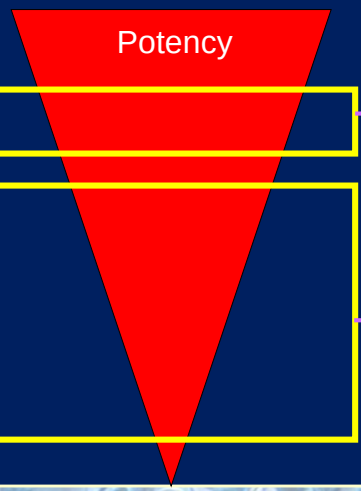


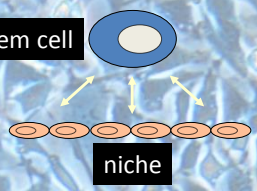
Embryonic

Amniotic

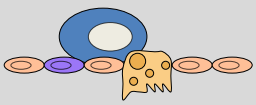
Adult

Stem cell niches

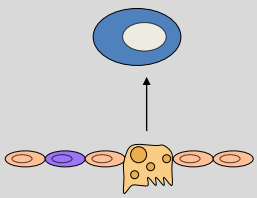
Niche
Microenvironment around stem cells that provides support and signals regulating self-renewal and differentiation



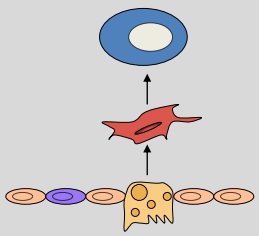
Direct contact



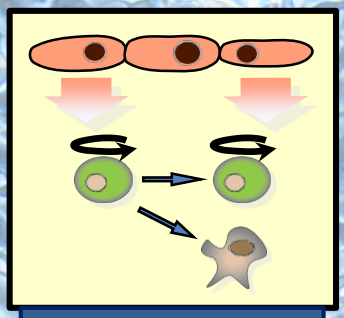
Soluble factors



Intermediate cell



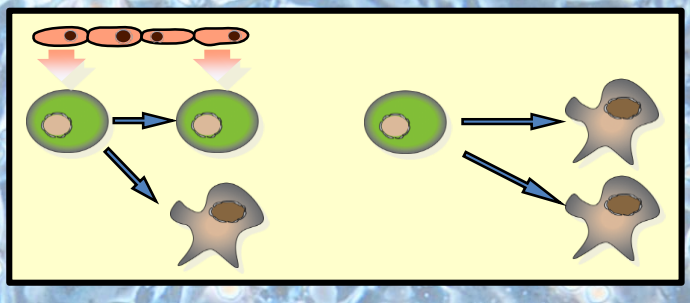
Signals from Niche



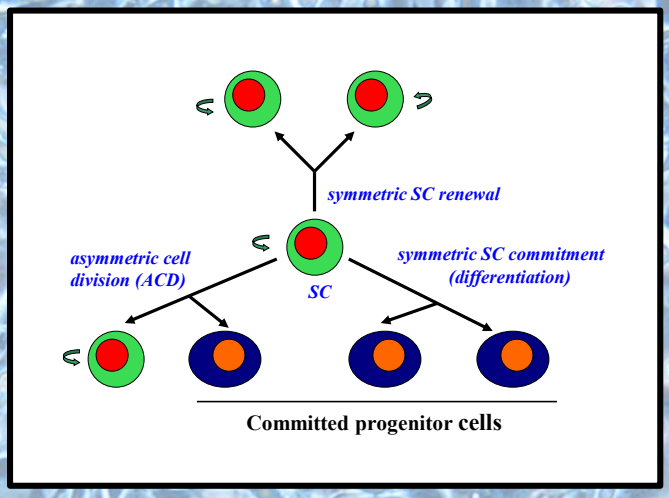
Signals from niches maintain adult stem cells and tissues.

- Signals are local; niches have a limited capacity and cells compete for the signals
- The signals control tissue homeostasis, also after damage.

In the absence of niche signals, adult stem cells will differentiate, by default.

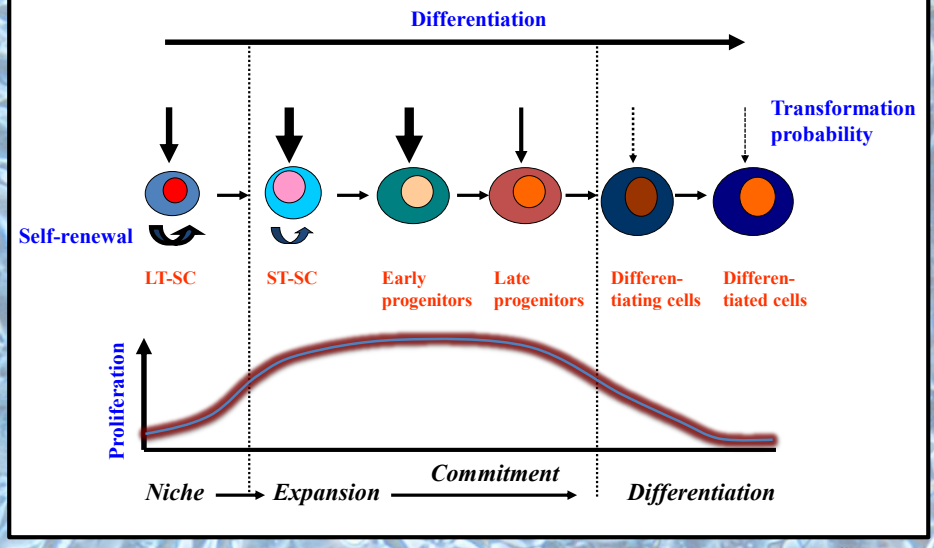


Alternate Stem Cell Fates



Tang, *Cell Res.* 2012

Cell Lineage Development



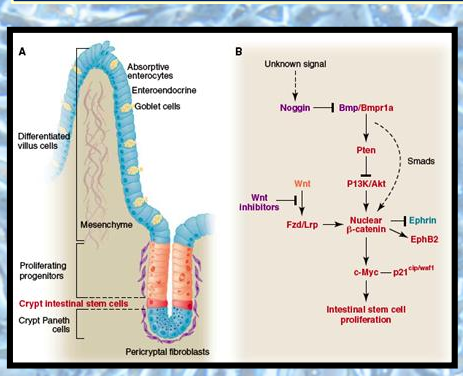
Tang, *Cell Res.* 2012

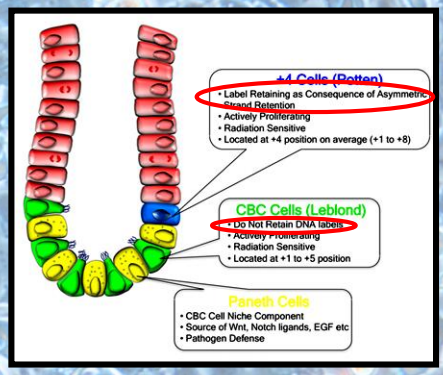
Motivation for Asymmetric Strand Segregation

- Adult rat contains $6x10^{10}$ cells
- In its small intestine, a rat sheds over 10^{13} epithelial cells during its lifetime.
- Requires 10^3 symmetric cell doublings from embryo to adult followed by 10^{13} asymmetric cell doublings during its lifetime
- How do epithelial cells minimize mutations that lead to cancer?

Cairns, *Nature*, 1975

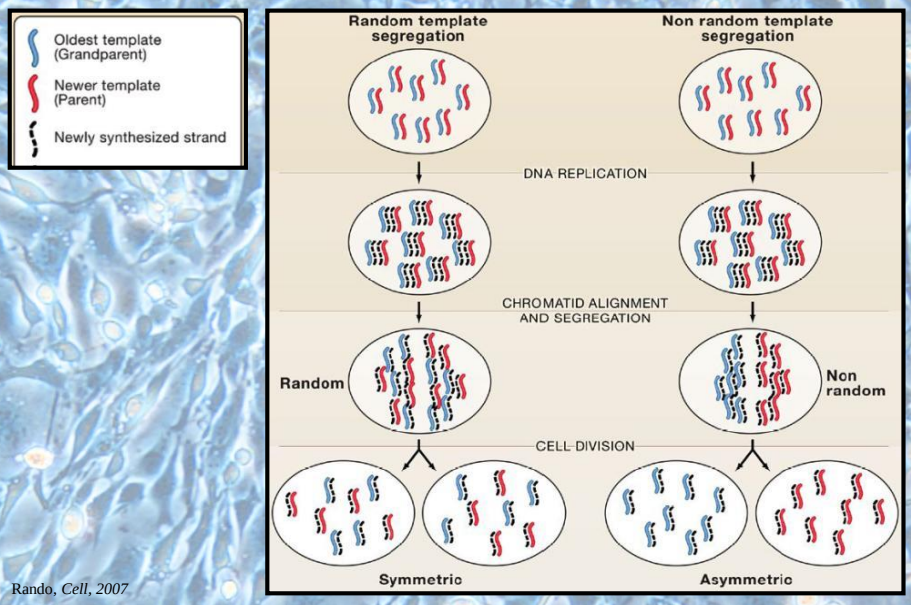
Stem Cell Niche in Small Intestine





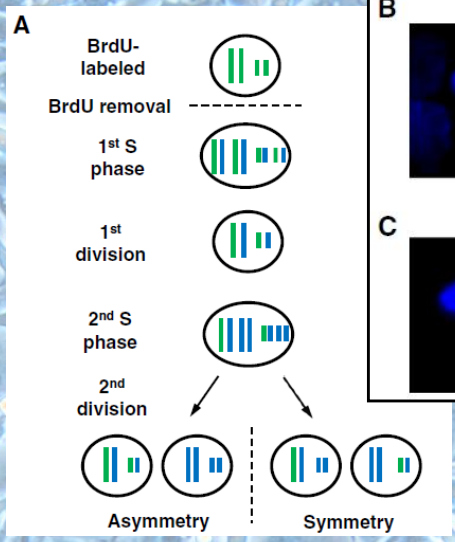
Barker et al., *Cell Stem Cell, 2012*

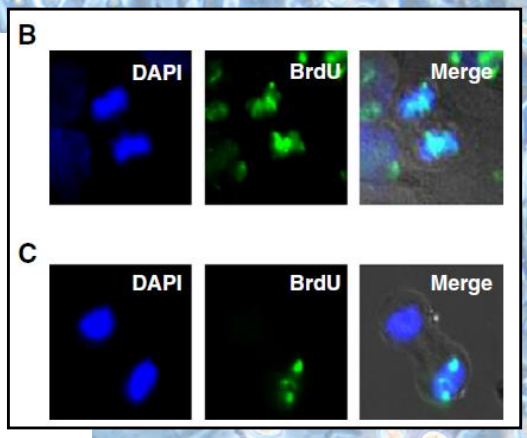
Asymmetric Segregation of Grandparental DNA Strands?



Rando, *Cell, 2007*

Asymmetrical segregation of DNA in human breast cancer cells





Liu et al., *Molecular Cancer 2013*

Duplicating Muscle Cell Pairs Display Asymmetric DNA Labeling Patterns

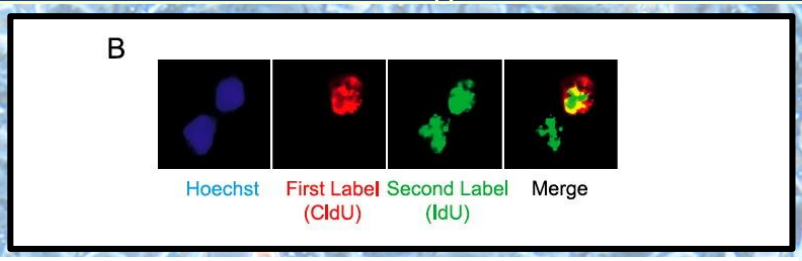
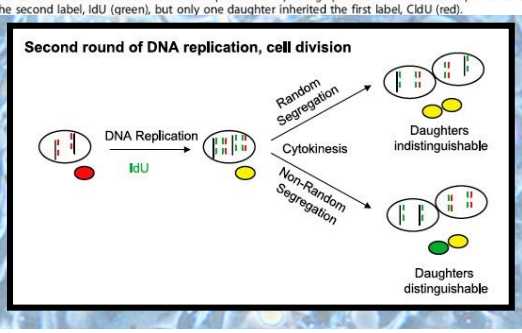
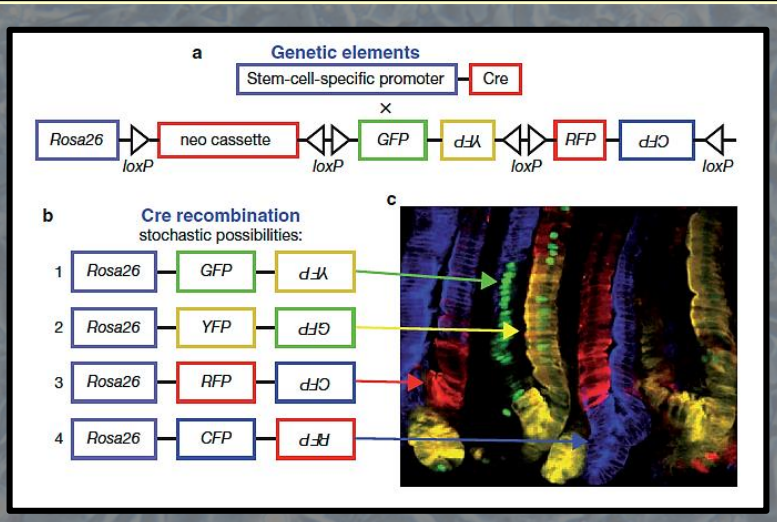


Figure 2. Evidence of Co-Segregation of DNA Template Strands during Muscle Progenitor Cell Division
(B) Cell pairs were immunostained for CldU and IdU. Shown is a representative photograph of an immunostained pair of cells, in which both daughter cells were labeled with the second label, IdU (green), but only one daughter inherited the first label, CldU (red).



Conboy et al, *Plos, 2007*

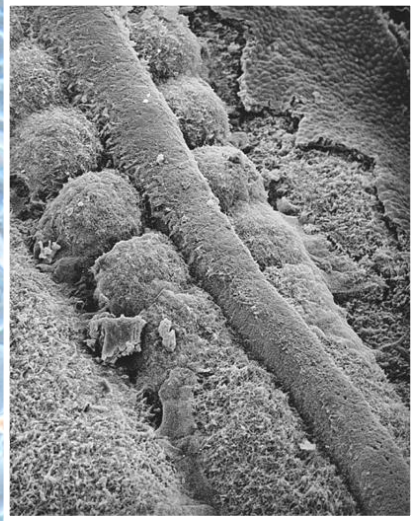
„Ferreting out stem cells from their niches”

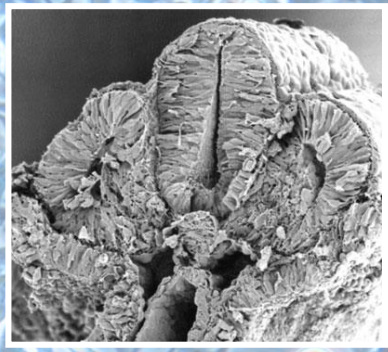


Fuchs and Horsley, *Nature Cell Biol., 2011*

Skeletal Muscle Stem Cells

Somitogenesis

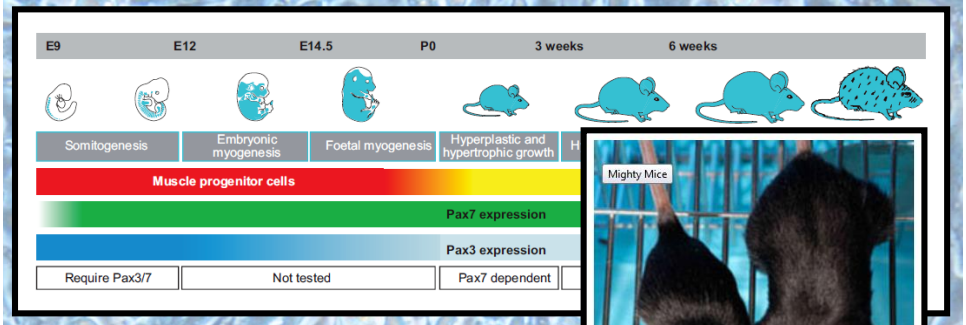




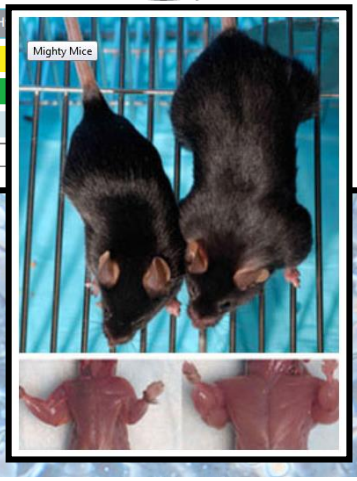
Pax3 ⟶ Pax7 ⟶ MyoD

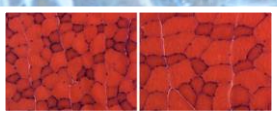
PAX3 + PAX7+PAXBP1 ⟶ HMT

Steps of myogenesis



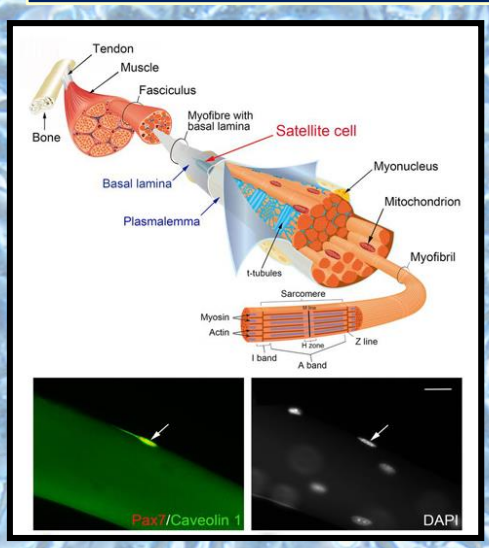
Myostatin / ActivinA ➡ Activin receptor 2B pathway

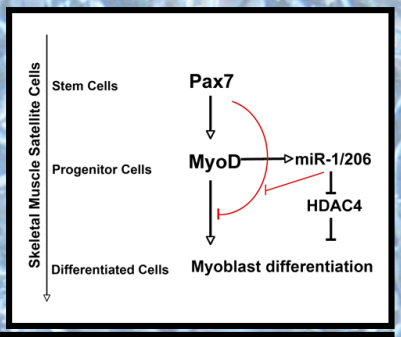


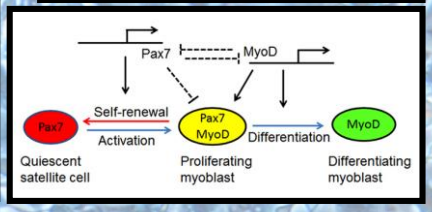


Lee et al., *PNAS, 2012*

Myosatellite cells

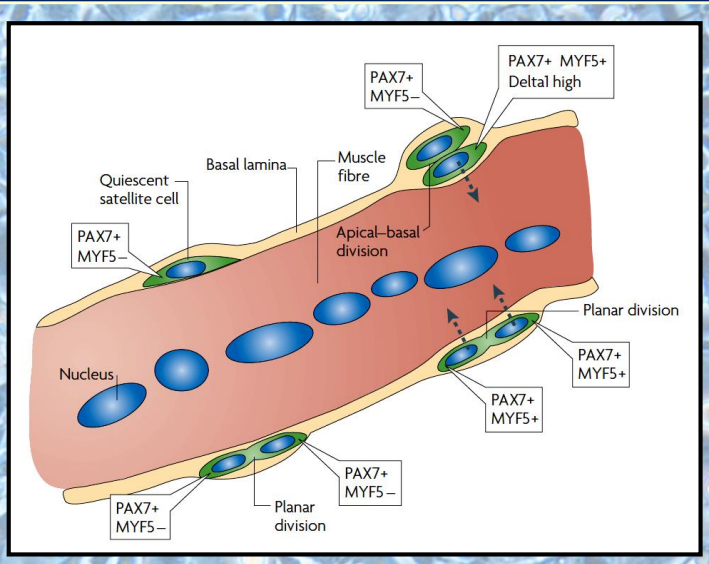






Relaix and Zammit, *Development*, *2012*

Myogenesis in adults

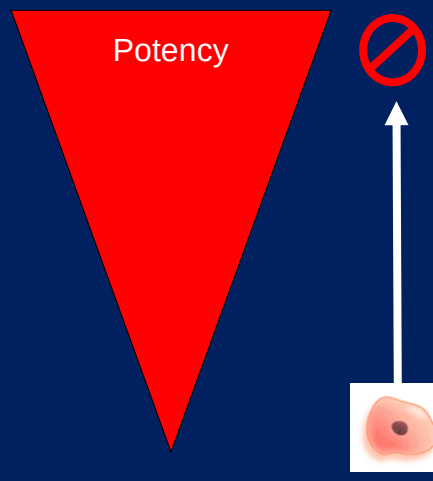


MYF5: myogenic factor 5

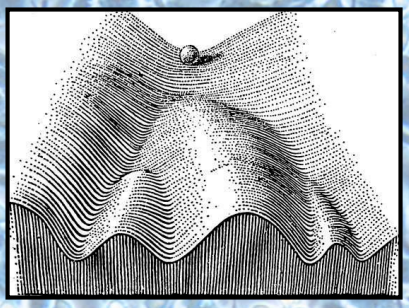
Stem Cells Reprogramming

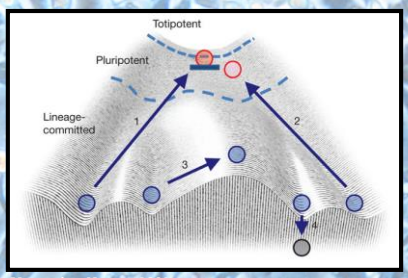
There is no way back?

- Totipotent
- Pluripotent
- Multipotent
- Oligopotent
- Unipotent

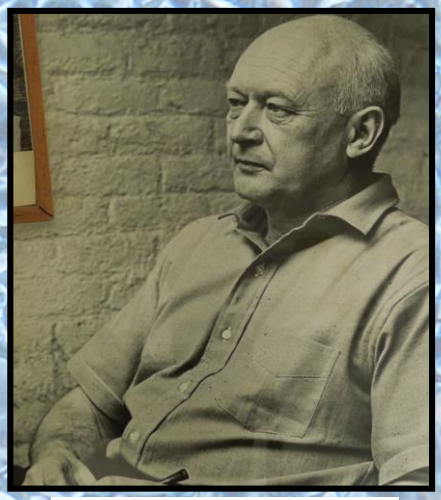


Epigenetic landscape



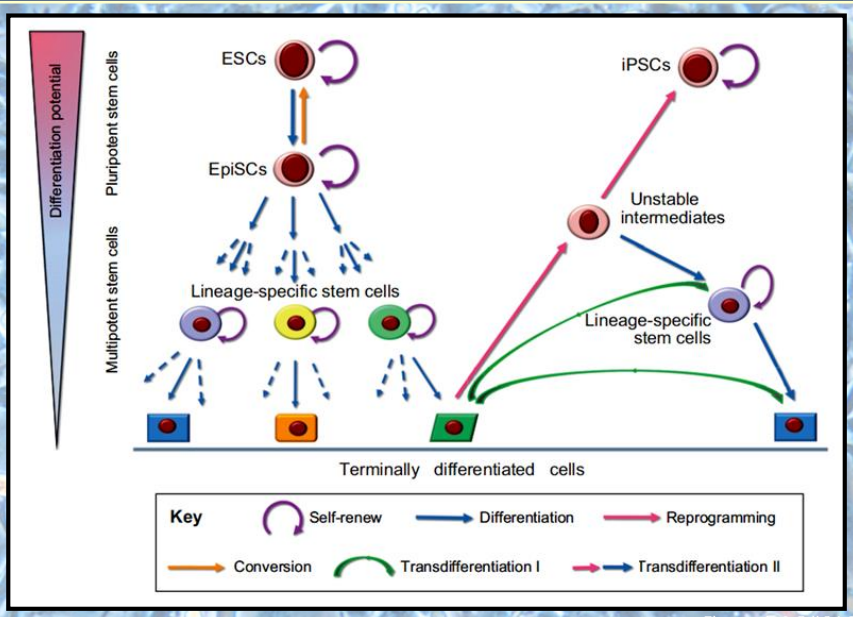


Yamanaka, *Nature*, 2009



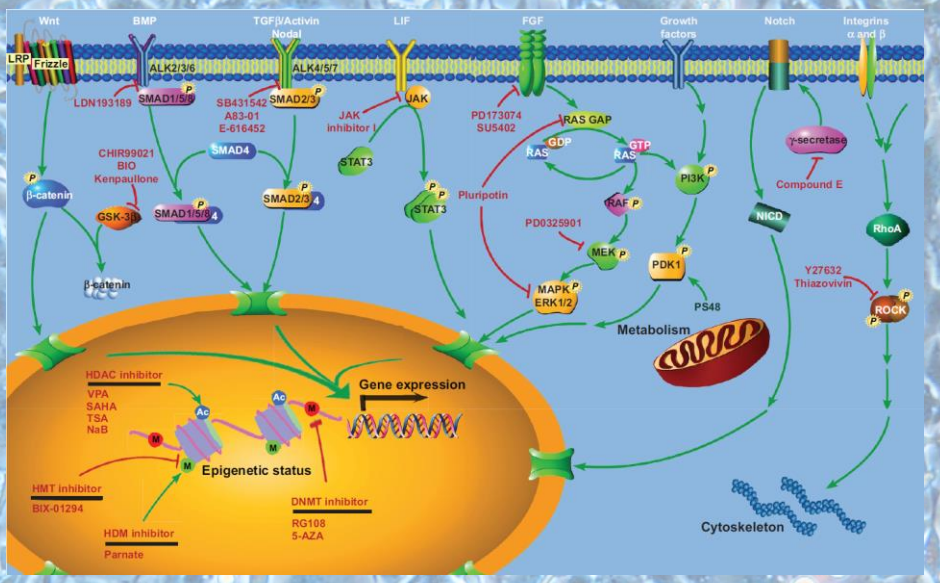
Conrad Hal Waddington (1905–1975)

Change of differentiation potential

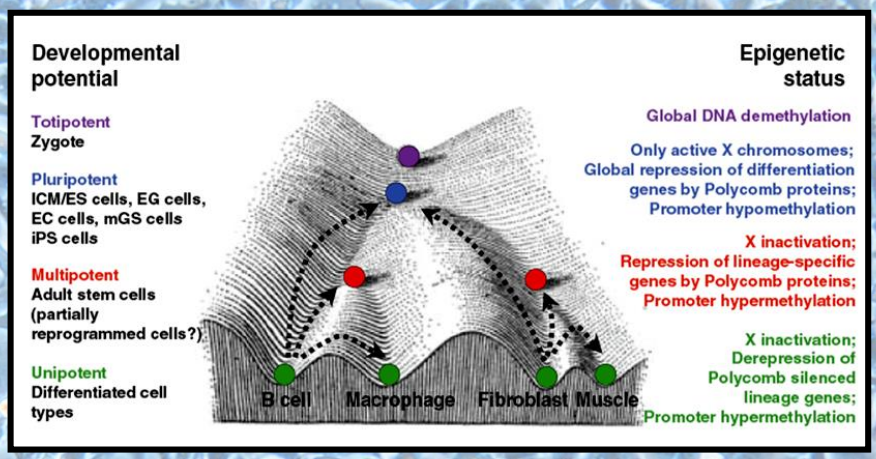


Zhang et al., *J Cell Sci*, 2012

Manipulation of stem cell fate and reprogramming

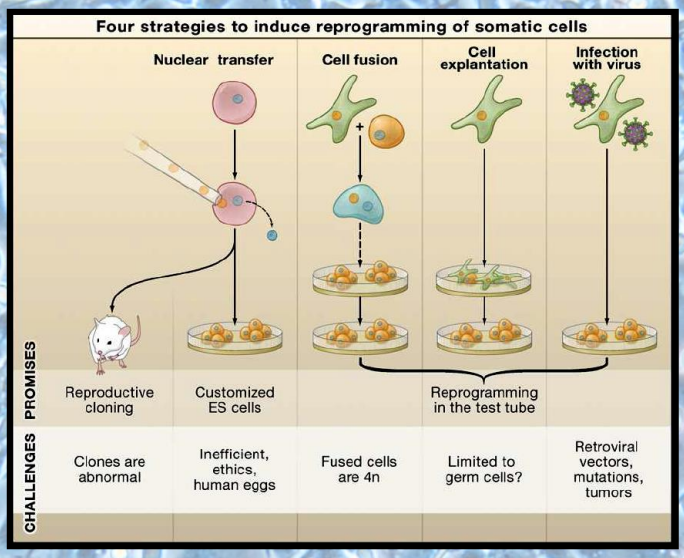


Development and epigenetic (re)programming

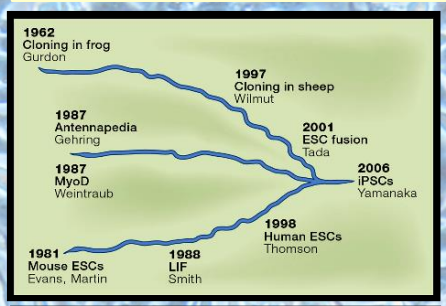


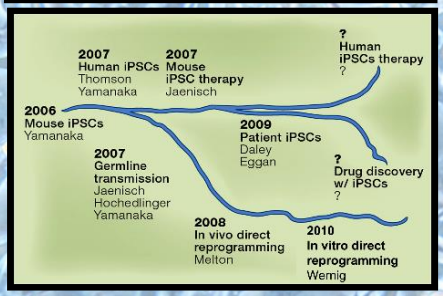
Hochedlinger, *Development*, *2009*

Reprogramming strategies



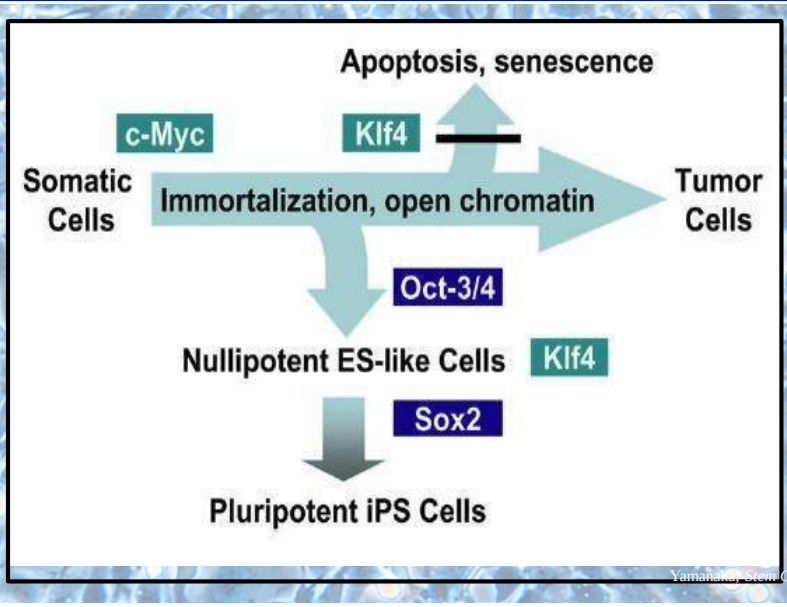
Induced pluripotent stem cells





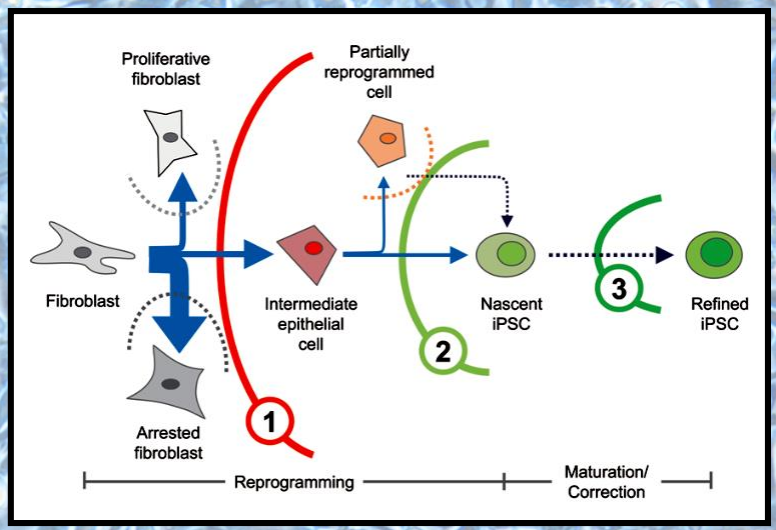
Shinya Yamanaka,
Nobel Prize: 2012

Induction of Pluripotent Stem Cells (iPS) from Somatic Stem Cells



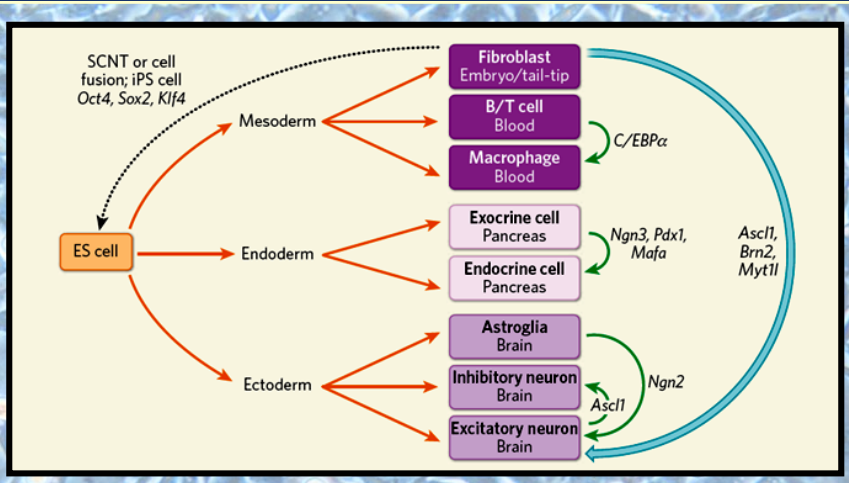
Yamanaka, *Stem Cell*, 2007

Induced pluripotent stem cells



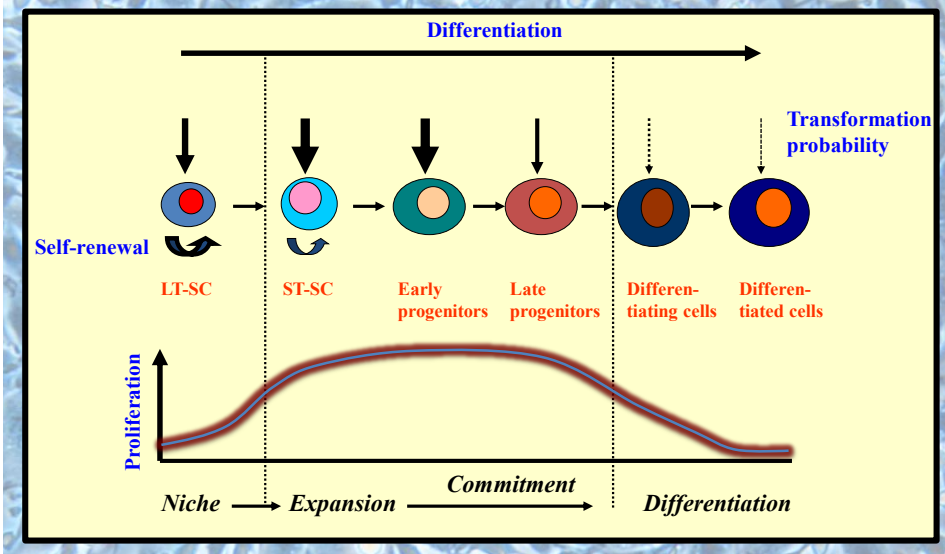
Liang and Zhang, *Nature Cell Res*, 2013

Direct Reprogramming and Lineage Conversion of Cells



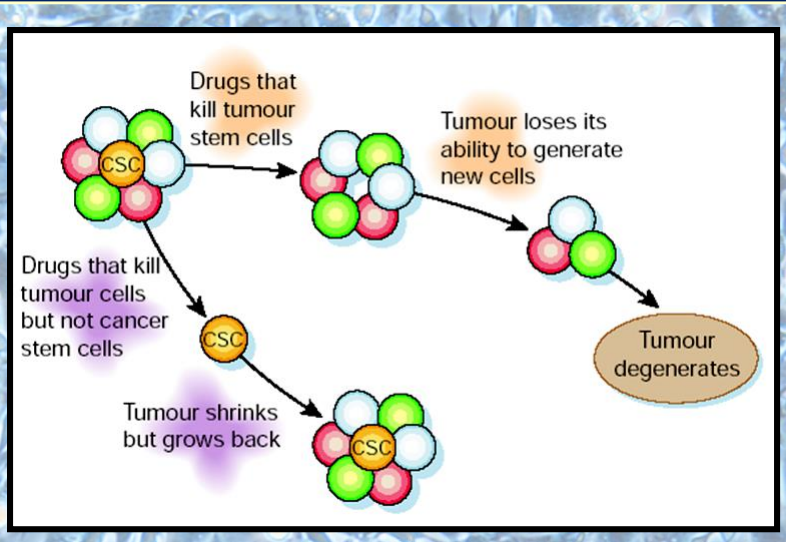
Cancer Stem Cells

Where did tumor cells come from?



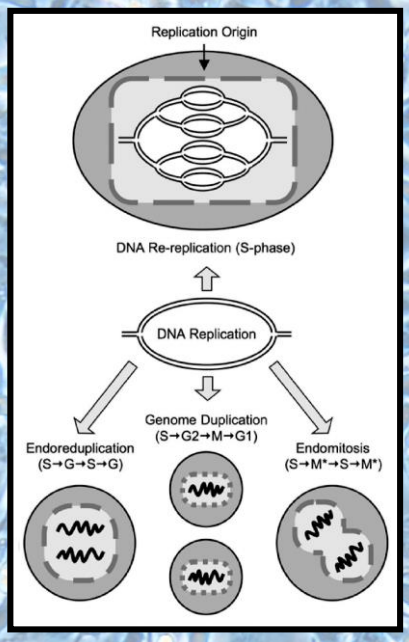
Tang, *Cell Res.* 2012

Cancer Stem Cells & Treatment



Weissman, *Nature*, 2001

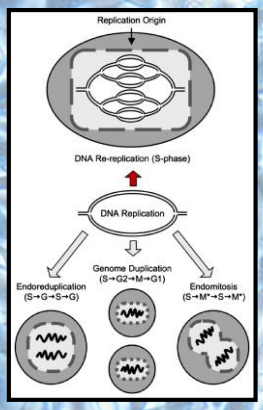
Potency and cell divisions



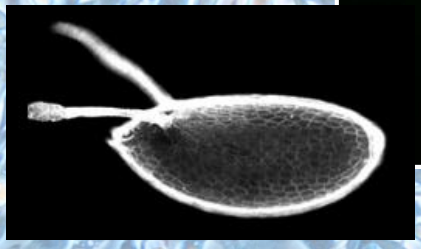
DNA replication and cell cycle: theme with variations

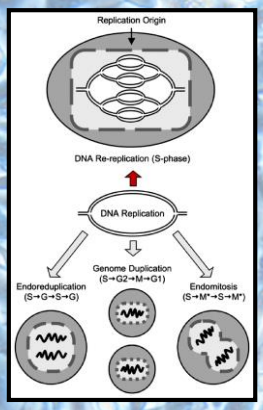
Re-replication

- DNA re-replication occurs when one or more of the normal controls that prevent reutilization of replication origins during S-phase is circumvented.
- Re-replicated DNA sequences: amplicons
- They are in: MA of Tetrahymena
  rRNAs in frog oocyte
  SG of Sciarid flies
  chorion genes on X in Drosophila
  Tumor cells



Chorion genes in the follicular cells are amplified





Re-replication of chorion genes

Despite of the follicular cells are Endoreduplicated, they amplify some of their chorion genes.

Minors: diploids, majors: amplified
Minor: 15 hours long expression,
Major: 2-3 hours long expression.

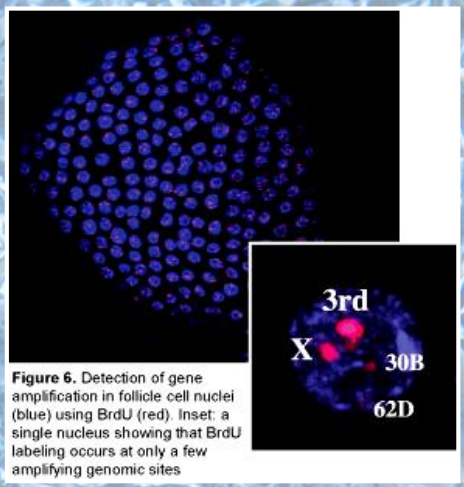
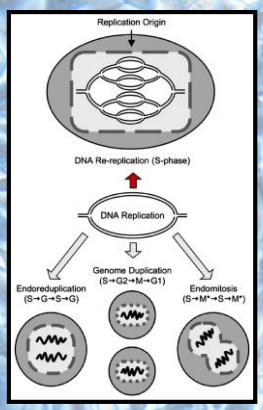
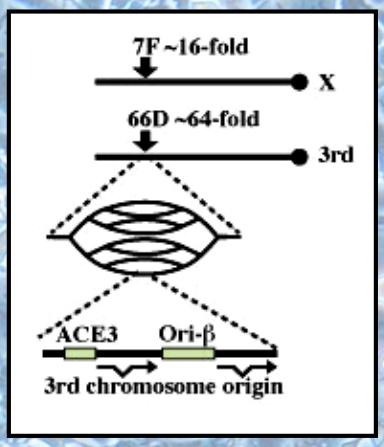


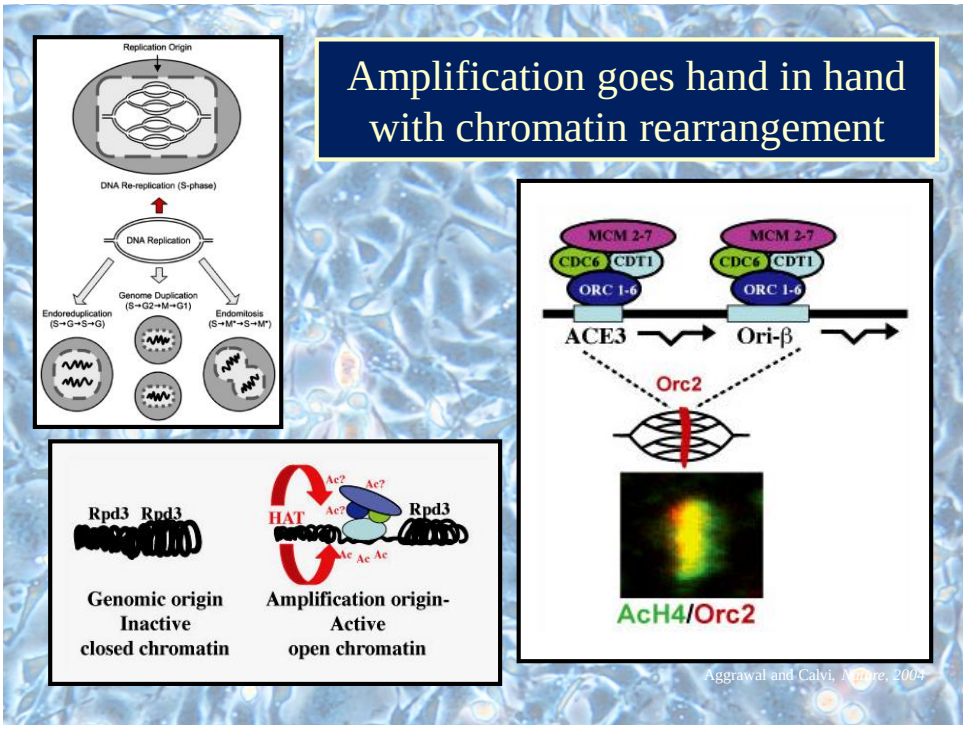
Figure 6. Detection of gene amplification in follicle cell nuclei (blue) using BrdU (red). Inset: a single nucleus showing that BrdU labeling occurs at only a few amplifying genomic sites

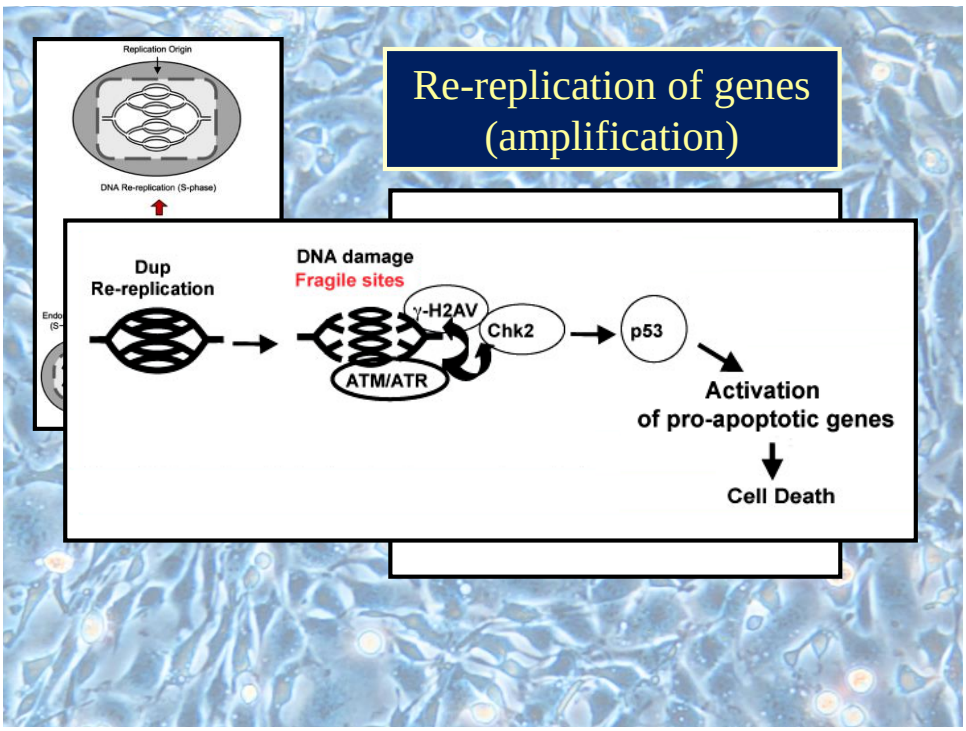


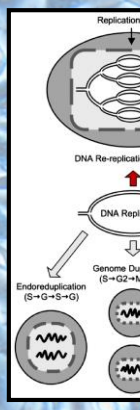
Regulation of amplification of the chorion genes

ACE3:
Amplification Central Elements on 3rd

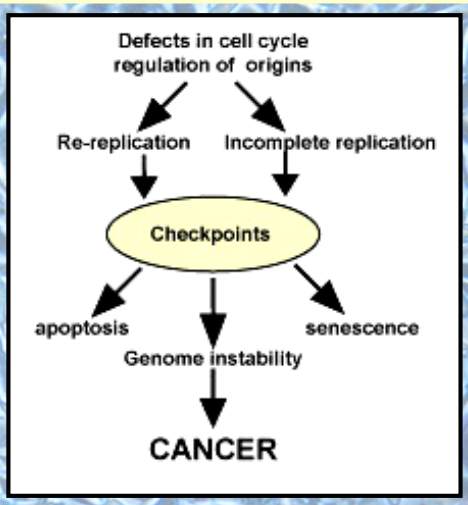



Amplification goes hand in hand with chromatin rearrangement
Replication Origin
DNA Re-replication (S-phase)
DNA Replication
Genome Duplication (S→G2→M→G1)
Endoreduplication (S→G→S→G)
Endomitosis (S→M*→S→M*)
Rpd3 Rpd3
Genomic origin
Inactive
closed chromatin
HAT
Ac?
Rpd3
Ac Ac Ac
Amplification origin-
Active
open chromatin
MCM 2-7
CDC6 CDT1
ORC 1-6
ACE3
Ori-β
Orc2
AcH4/Orc2
Aggrawal and Calvi, Nature, 2004

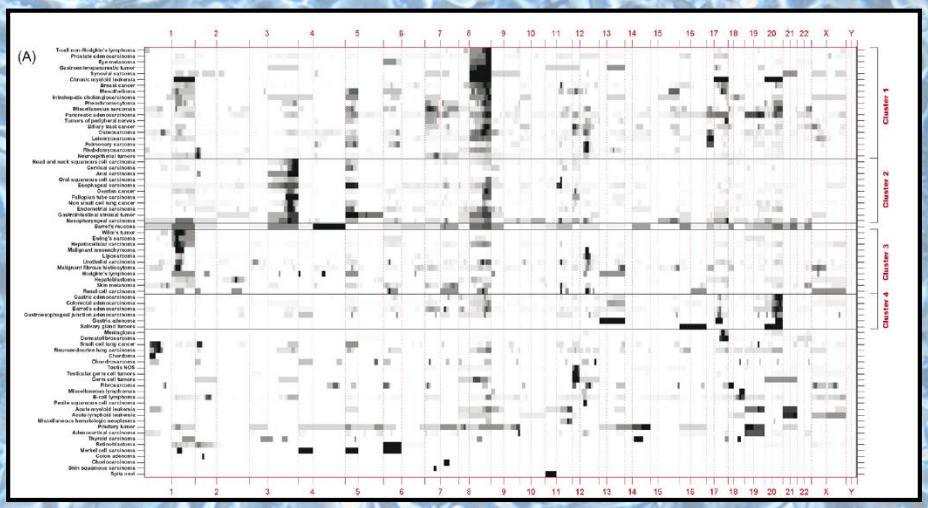

Re-replication of genes (amplification)
Replication Origin
DNA Re-replication (S-phase)
Dup
Re-replication
DNA damage
Fragile sites
γ-H2AV
Chk2
ATM/ATR
p53
Activation
of pro-apoptotic genes
Cell Death



Re-replication of genes (amplification)

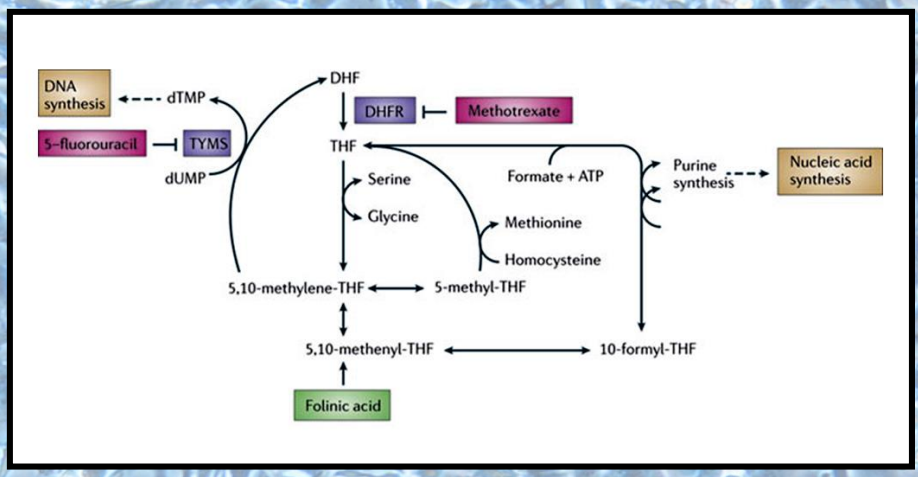


Amplification frequency in human neoplasms.



Myllykangas et al, *Sem. Cancer biol.*, 2007

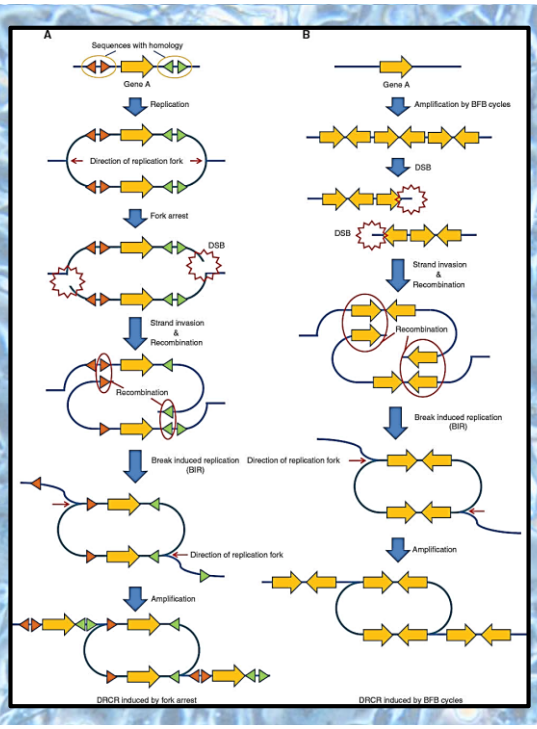
DHFR amplification in drug-resistent cancer cells



Heiden, *Nat. Rev. Drug Discovery, 2011*

TYM: thymidylate synthase, DHF: dihydrofolate, THR: tetrahydrofolate

Double rolling circle replication



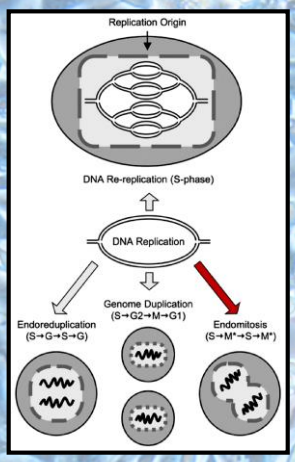
Watanabe et al, *Nucl Acid Res., 2011*

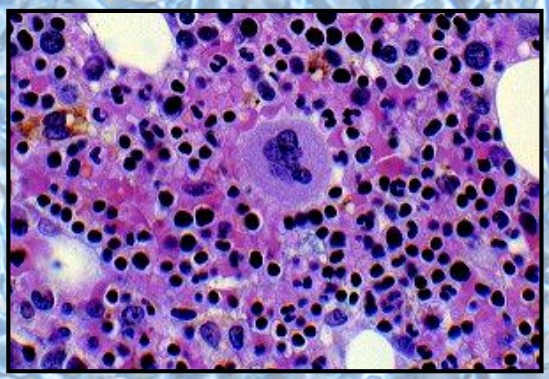
Endomitosis

- Endomitosis is a process in which successive S-phases are interrupted by a gap, during which the cells enter mitosis but do not complete anaphase and do not undergo cytokinesis.

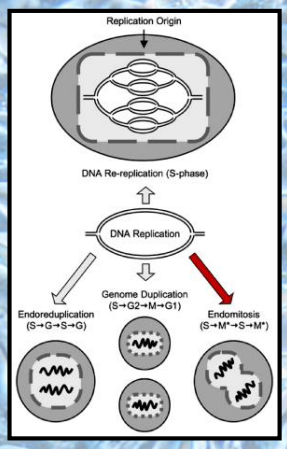
  Duplicated chromosomes produced by endomitosis exist as discrete units in a single polyploid nucleus or may be packaged into separate nuclei, depending on the phase at which mitosis is aborted.

Endomitosis in mammals

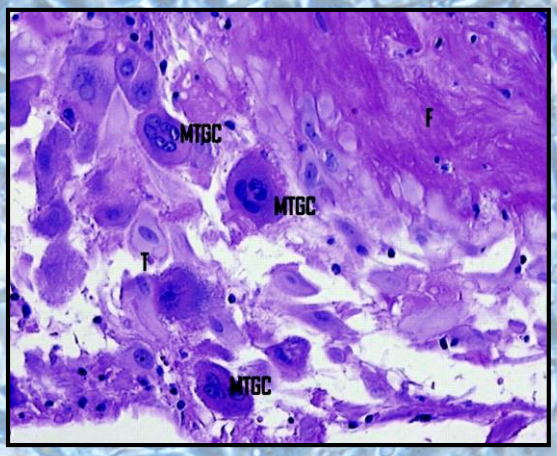




Megakaryocytes



Endomitosis in mammals 2

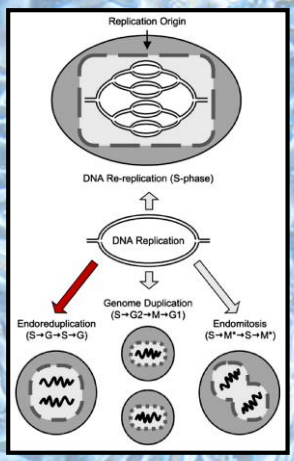


Multinucleated trophoblast giant cells

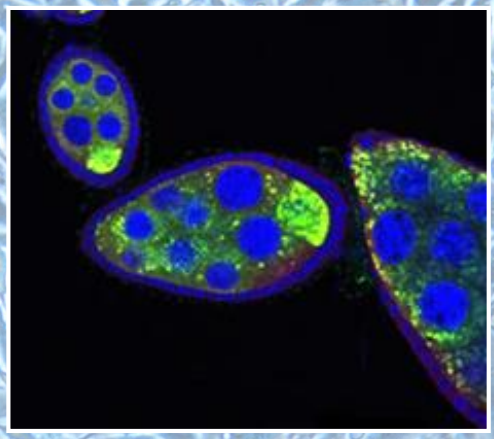
Endoreduplication

- Endoreduplication is the process by which a cell undergoes multiple S-phases without an intervening mitosis and its accompanying cytokinesis.

  Duplicated chromatids remain physically associated. Repeated rounds of endoreduplication can lead to the production of polytene chromosomes in which sister chromatids are tightly configured in parallel arrays.

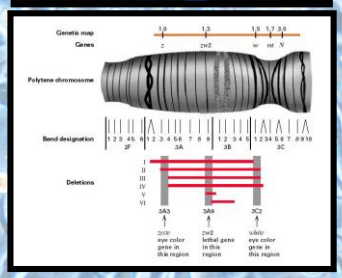


Endoreduplication in the ovary of Drosophila

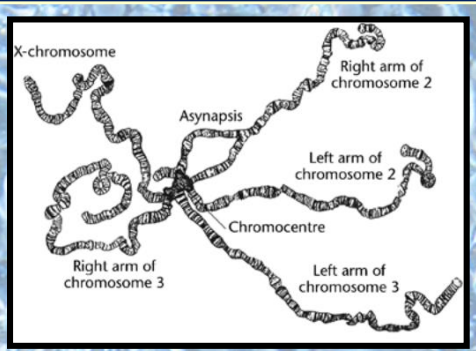


Follicular cells *and* nurse cells in developing follicles

Polytene chromosome



Calvin Bridges, 1935



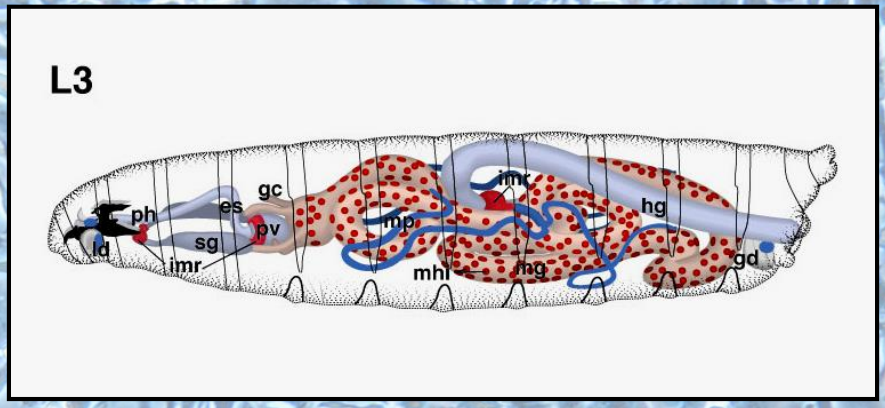
Balbiani rings (1881)

Grouping of tissues of *Drosophila* larvae

Cells/tissues in *Drosophila* larvae

- Imaginal discs (diploid)
- Larval tissues (polyploid)
- Histoblasts (diploid)

Histoblasts are embedded in the larval tissues



Various cell cycles are in the same organism

Embryo	Larval Instars	Pupa	Adult
	1st 2nd 3rd 		
Syncytial Divisions Postblastoderm Divisions Differentiating Larval Tissues Endo Cycles Nervous System Mitotic Divisions	Larval Tissues Endo Cycles/Cell Growth CNS/Imaginal Discs Archetypal Mitotic Cycles Abdominal Histoblasts G2 Arrest	Imaginal Discs and Abdominal Histoblasts Division and Differentiation	Gonads Mitosis (Stem Cells) Meiosis Endo Cycles (Ovary)

The End