Premedical - Biology

Mitosis and Cell cycle

Physiological modes of somatic cell

proliferation
cell cycle

resting cells
G0 phase

Proliferation in:

- ontogenesis
- physiological renewal of cells
- reparation and wound healing
- immune response

Aging (senescence)

- **limited number of cell division** (maximum 50) → **Hayflick's limit**

both in vivo and in vitro

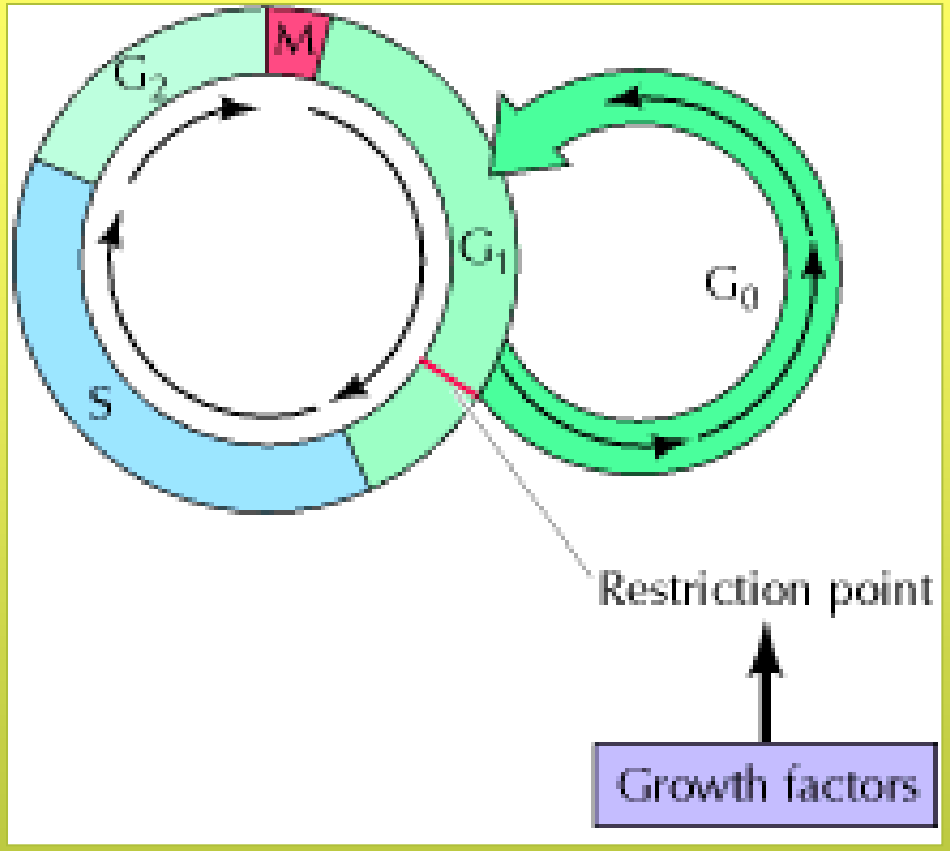
- accumulation of mutations
- decreased cytokines response, increased synthesis of inhibitory proteins
- shortening of telomere sequences at the ends of chromosomes

Resting (Quiescent) Cells: G0

G0 phase relates

to terminal stages of

differentiation



e.g. hepatocytes divide

1x a year;

neurons, myocytes

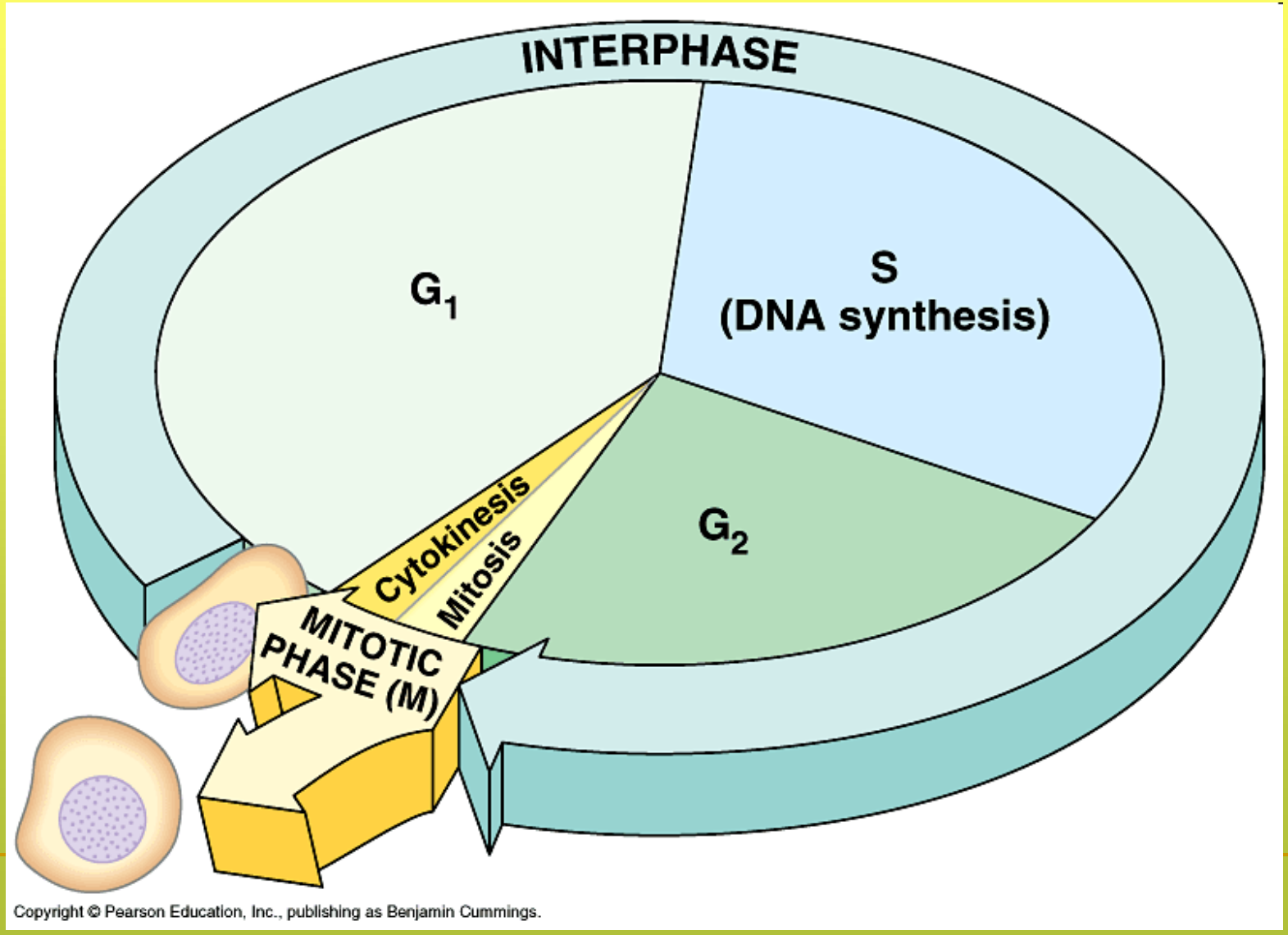
do not divide;

epithelial cells divide 1-2x a day

Cell cycle

G ~ Gap/Growth

S ~ DNA sythesis



The cell cycle

- **M phase and interphase**
- **M phase: Mitosis and cytokinesis**
- Interphase : G1, S, G2 phase
- 46 chromosomes, 23 chromosomes from each parent
- mitosis – **distribution of identical sets of 46 chromosomes to daughter cells**

2n → **2n**

2n

Cell Cycle

- **G1** phase – the longest and the most variable part of the cell cycle
  - growth of the cell
  - completion of organelles (ribosomes, mitochondria, endoplasmic reticulum etc.)
  - RNA and protein synthesis
  - synthesis of nucleotides, preparation for replication

- **S phase –** replication of nuclear DNA (extranuclear DNA replicates during the whole interphase)
- **G2 phase –** cell growth, protein and RNA synthesis, origin of cell structures
- **M phase:**

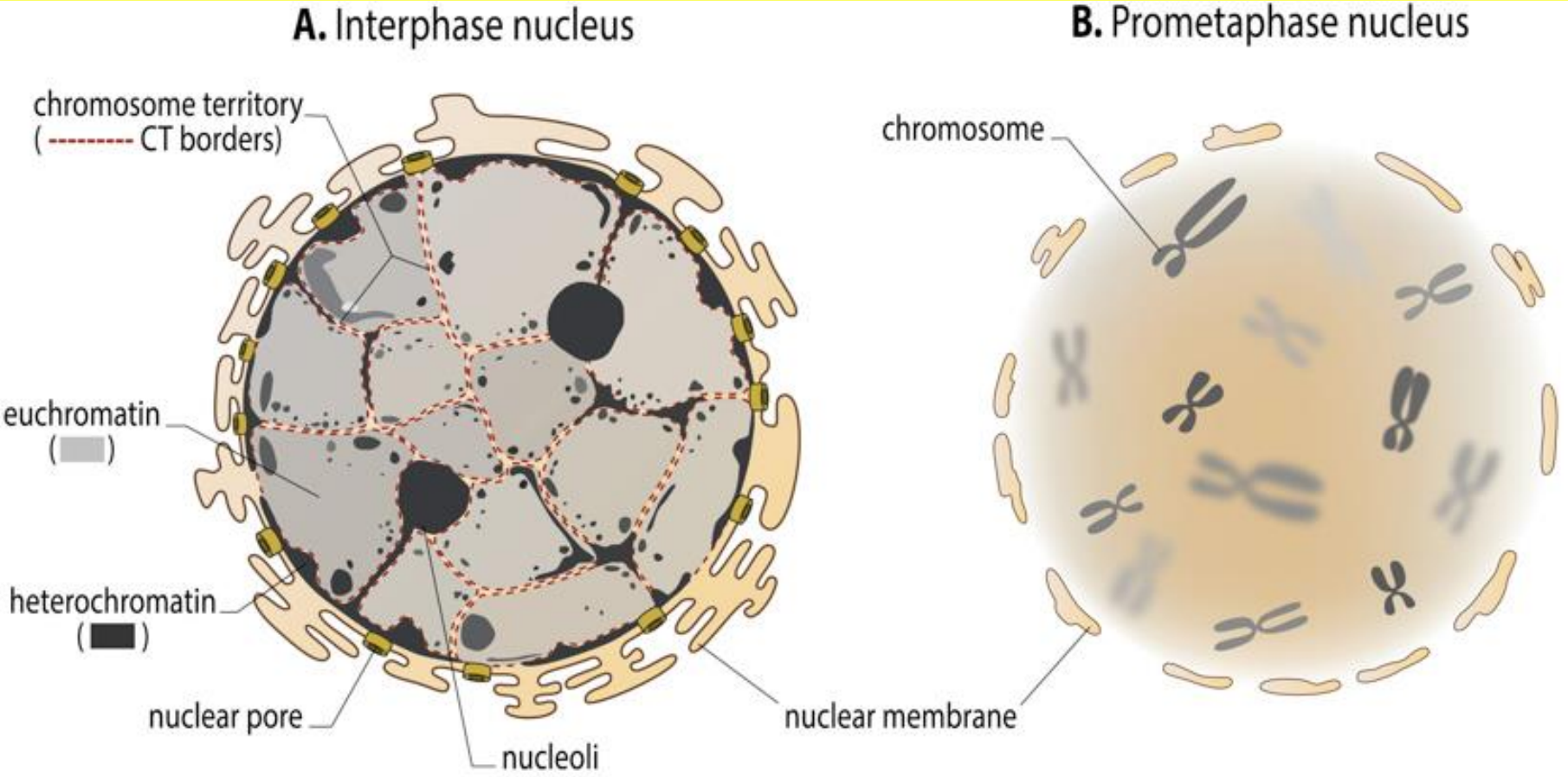
Mitosis - division of the nucleus

Cytokinesis – division of the cell

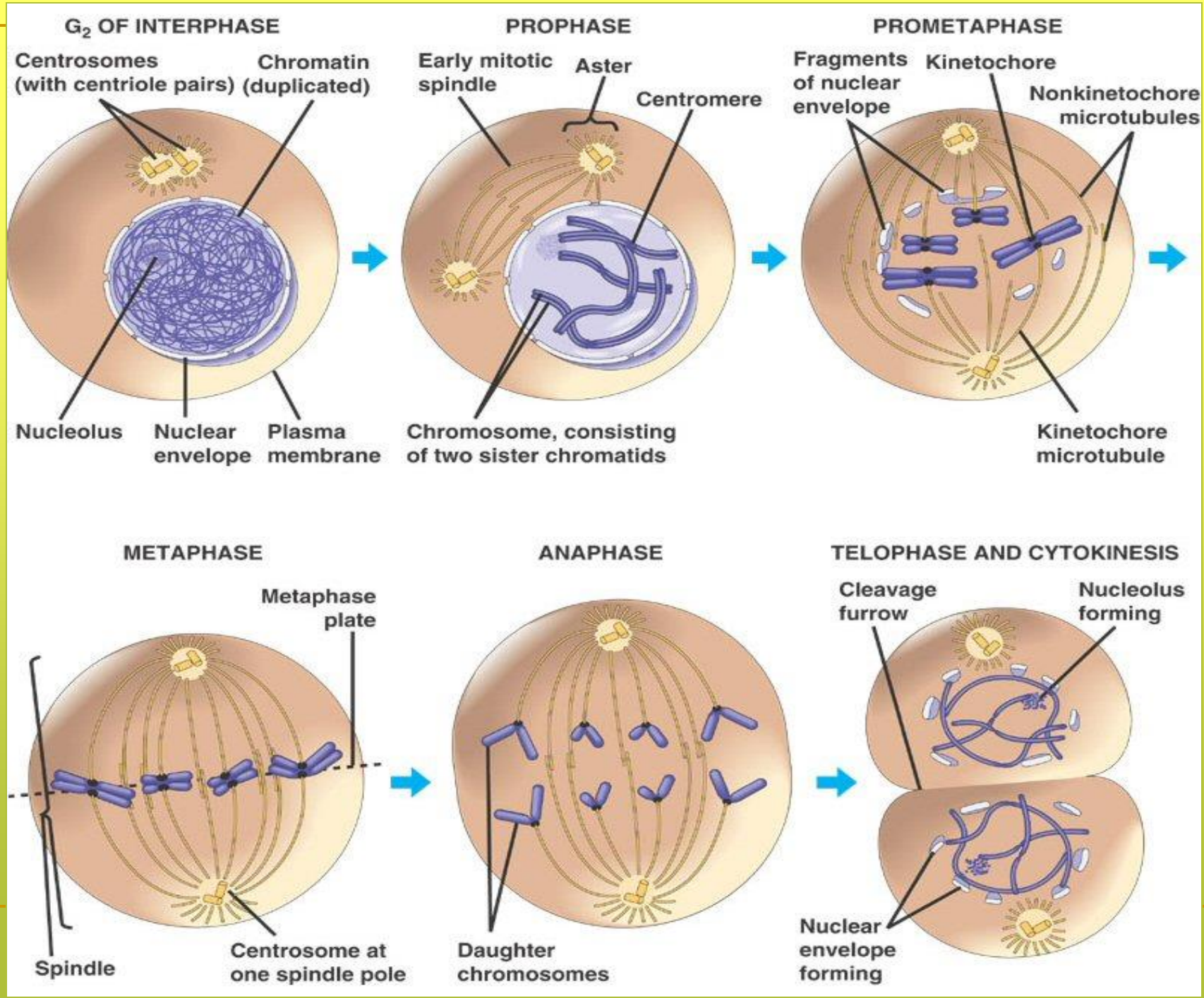
Mitosis – animal cells

Prophase: Chromatin fibers are getting coiled, spiralized. Nucleoli disappear and microtubuli begin to form mitotic spindle

Prometaphase: Nuclear envelope fragments. Mitotic spindle interacts with chromosomes. Chromosomes are getting more condensed.



https://www.mechanobio.info/genome-regulation/what-is-chromatin-heterochromatin-and-euchromatin/


G2 OF INTERPHASE
Centrosomes (with centriole pairs)
Chromatin (duplicated)
Nucleolus
Nuclear envelope
Plasma membrane
PROPHASE
Early mitotic spindle
Aster
Centromere
Chromosome, consisting of two sister chromatids
PROMETAPHASE
Fragments of nuclear envelope
Kinetochore
Nonkinetochore microtubules
Kinetochore microtubule
METAPHASE
Metaphase plate
Spindle
Centrosome at one spindle pole
ANAPHASE
Daughter chromosomes
TELOPHASE AND CYTOKINESIS
Cleavage furrow
Nucleolus forming
Nuclear envelope forming

Mitotic spindle

• Fibers made of microtubules, spindle starts from centrioles - 9 sets of triplets of microtubules from subunits tubulin α, β

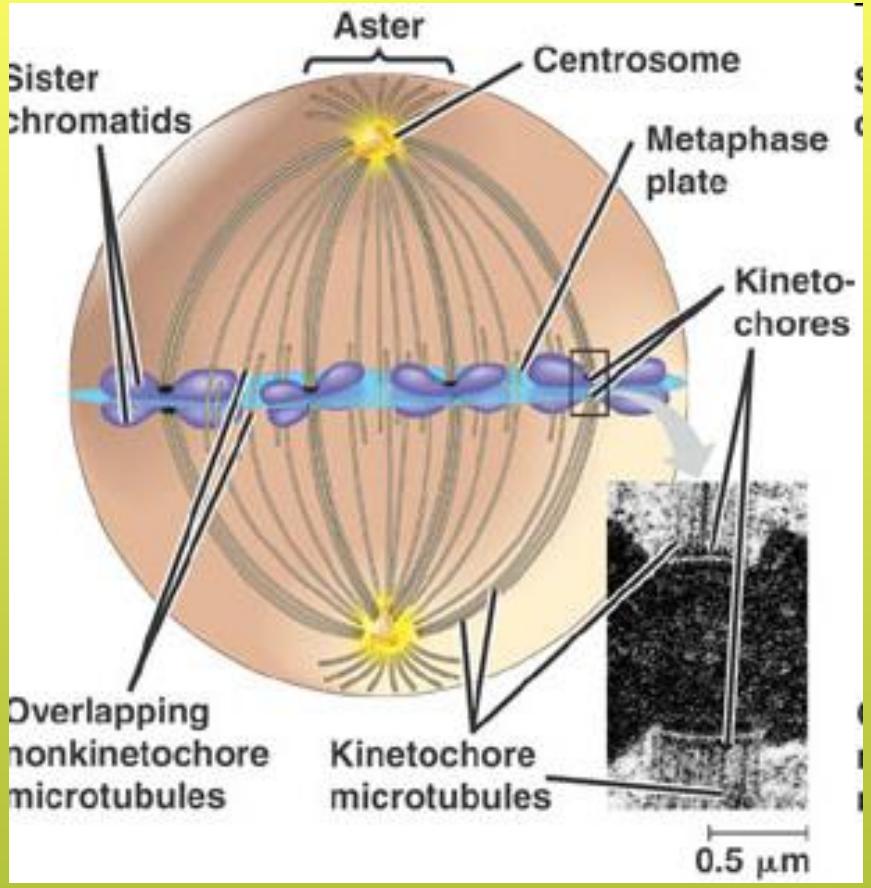
- **Microtubule organizing center**

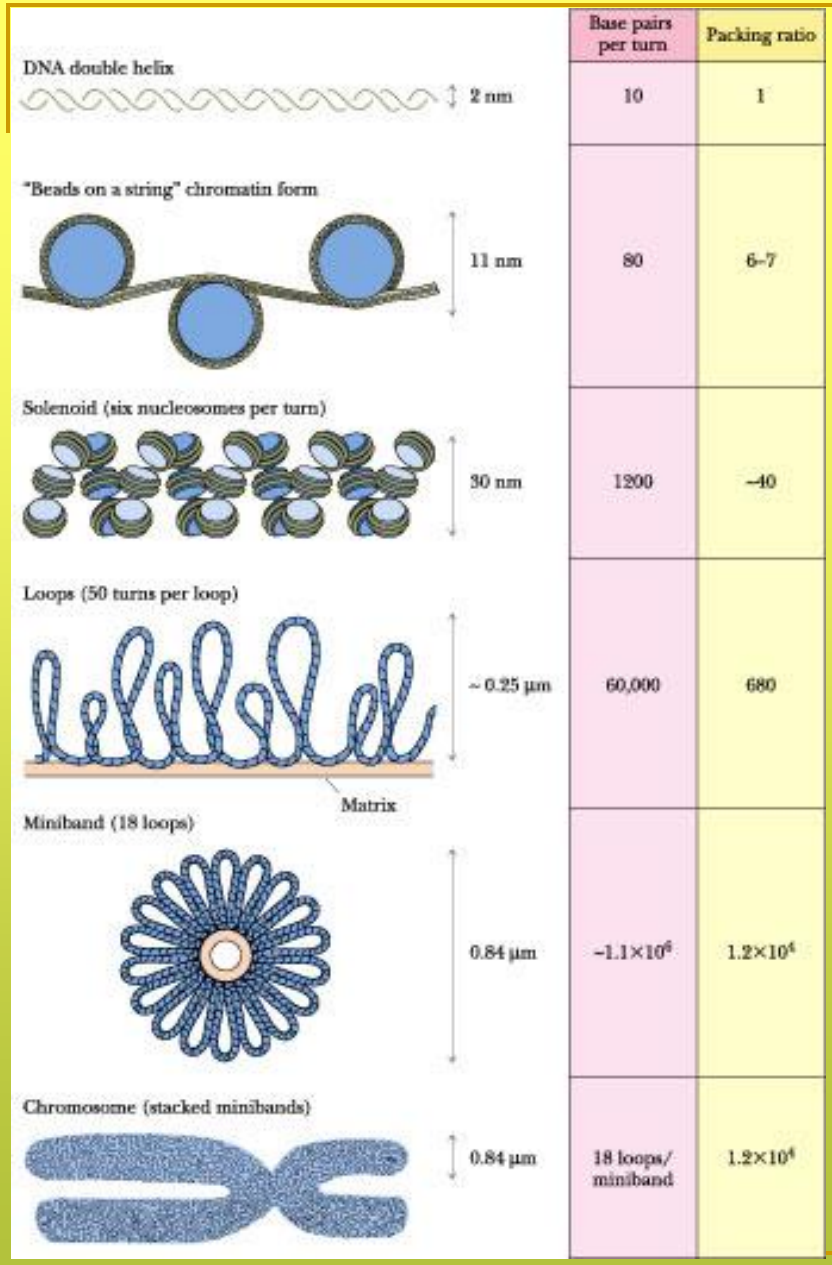
• Mitotic spindle elongates by incorporating subunits of protein tubulin

• Microtubule polarity

- Kinetochore microtubules
- Non-kinetochor m. (polar)
- Astral microtubules

kinetochor – proteins and chromosomal DNA at the centromere





Base pairs per turn	Packing ratio
10	1
80	6–7
1200	~40
60,000	680
~1.1×10⁶	1.2×10⁴
18 loops/ miniband	1.2×10⁴

Nucleosome:

DNA double helix + histone core

Histone core = octamer of two copies of H2A, H2B, H3, H4 histons

Spacer segment between two nucleosomes is free or associated with H1 histone

String of nucleosomes is coiled into **solenoid** (6 nucleosomes in each turn)

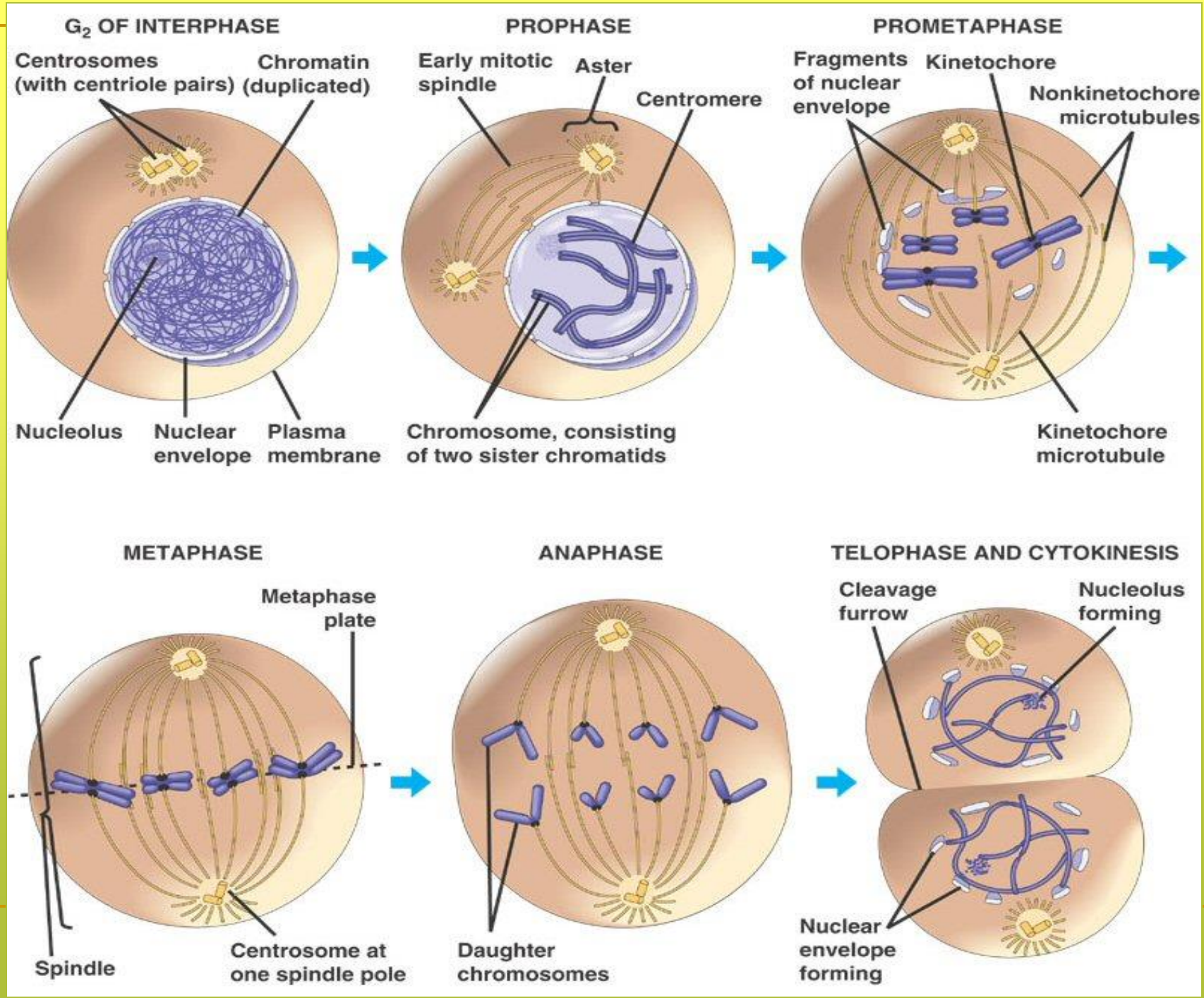
Solenoid is packed into loops, attached to **non-histone protein scaffold** (Laemli loops). Non-histone protein scaffold with loops is coiled into spiral structure of **chromatids**

https://youngbloodbiology.wikispaces.com/Components+of+the+Genome+and+Interphase

Metaphase: Spindle poles are at opposite positions. Chromosome are located on the metaphase plate (in equatorial plane). Each chromosome is attached by kinetochore to the mitotic spindle.

Anaphase: Chromatids move to opposite poles of the cell. Kinetochore mictotubules are getting shorter, the poles move further apart. There are at the end two collection of chromosomes.

Telophase: Non-kinetochore microtubules elongate. Nuclear envelope generates. Cytokinesis starts to run.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TELOPHASE AND CYTOKINESIS
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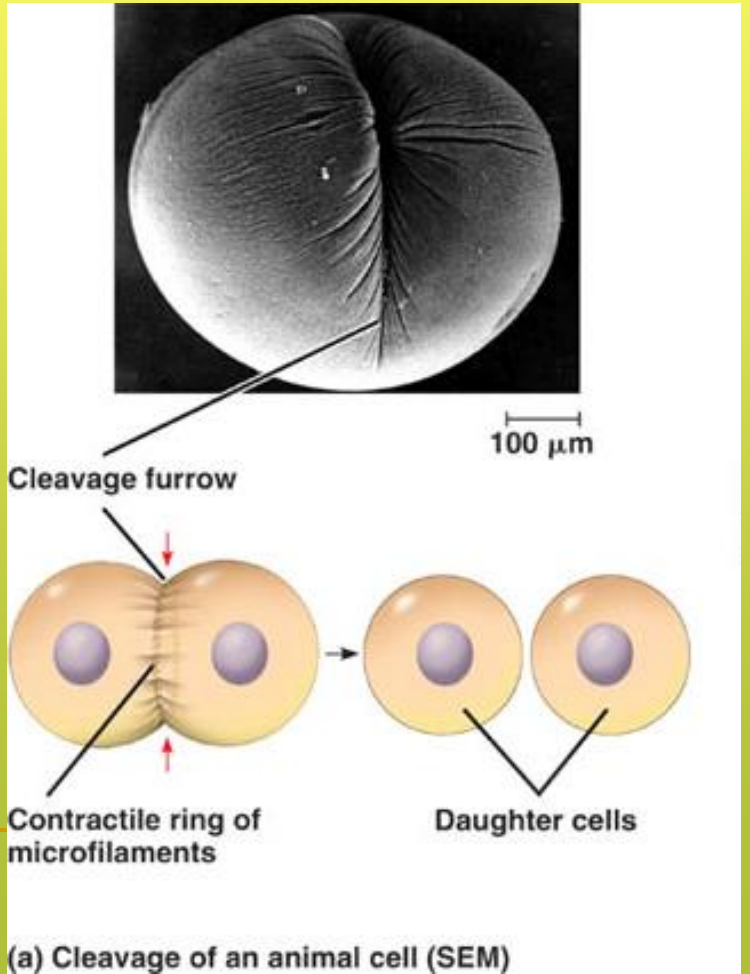
Nucleolus forming
Nuclear envelope forming

Cytokinesis

Cleavage

- contractile ring of actin microfilaments
- cell plate in plant cells



(a) Cleavage of an animal cell (SEM)

Cell cycle

- External signals and internal network of interactions – signalling transduction pathways regulate the cell cycle
- **Cancer cells have escaped from cells cycle controls**

Check points

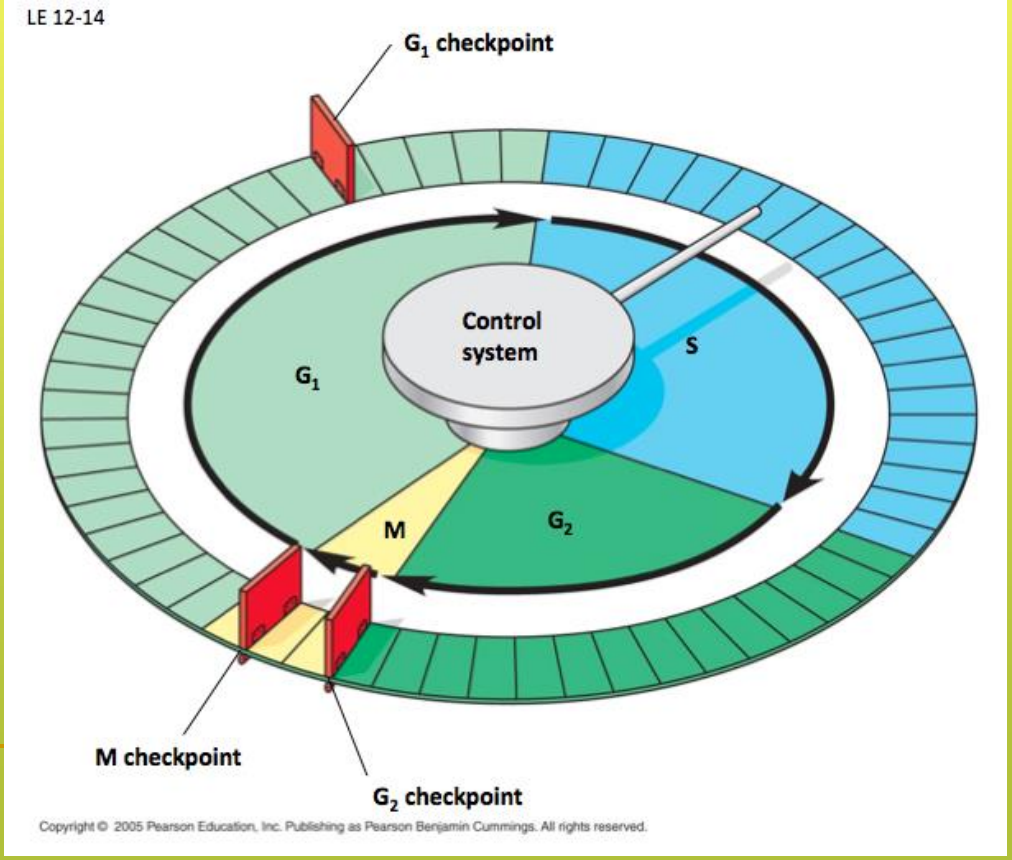
trigger and coordination of key events

Checkpoints are critical points, where signals can stop or go-ahead to the next phase of cell cycle:

G1 checkpoint

G2 checkpoint

M checkpoint



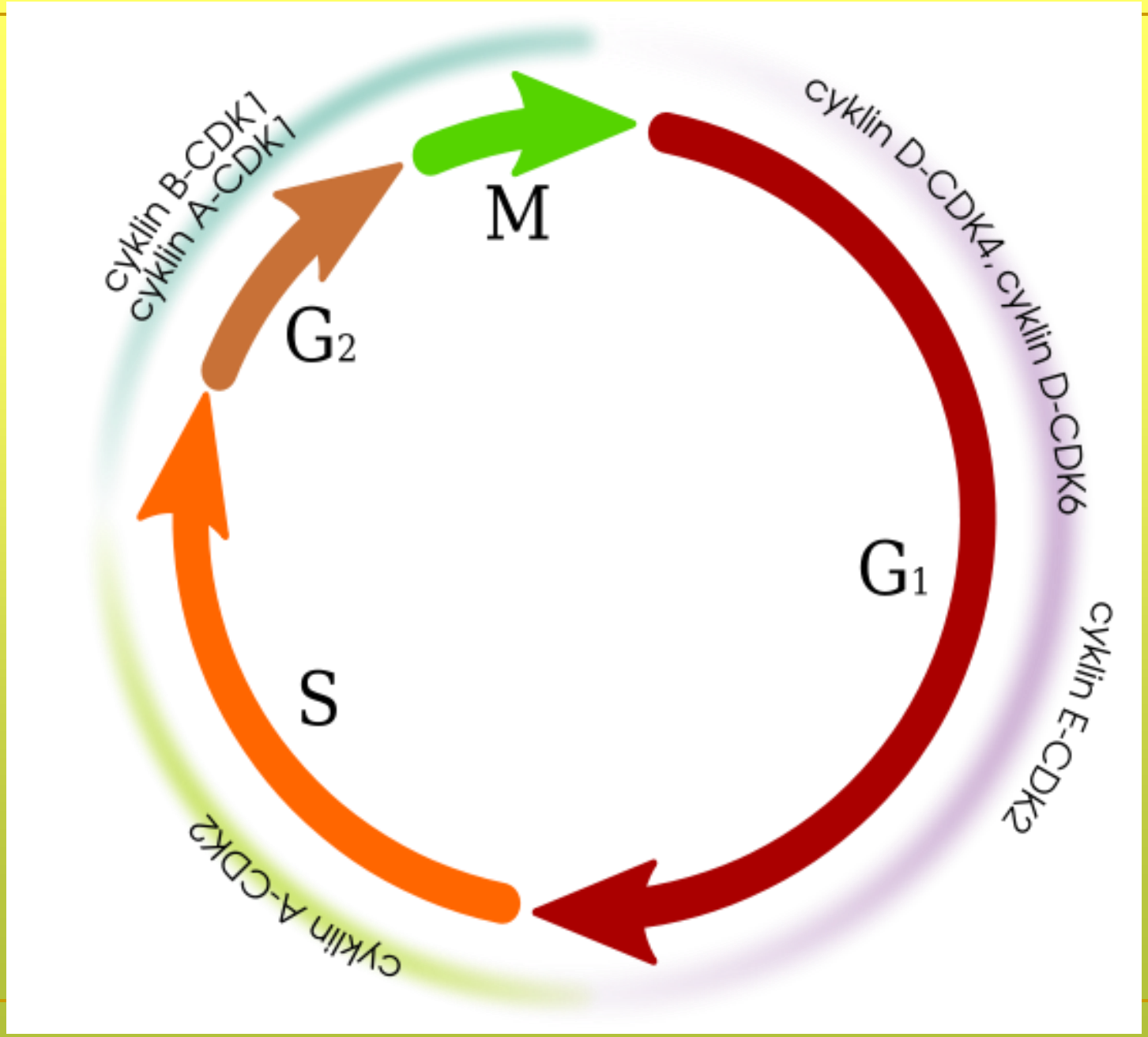
Control system of cell cycle

- **Cyclin –** cyclic accumulation and degradation of proteins during the cell cycle
- **Cdk – cyclin dependent kinases (CDK)**

  = enzymes that phosphorylate other proteins in active states

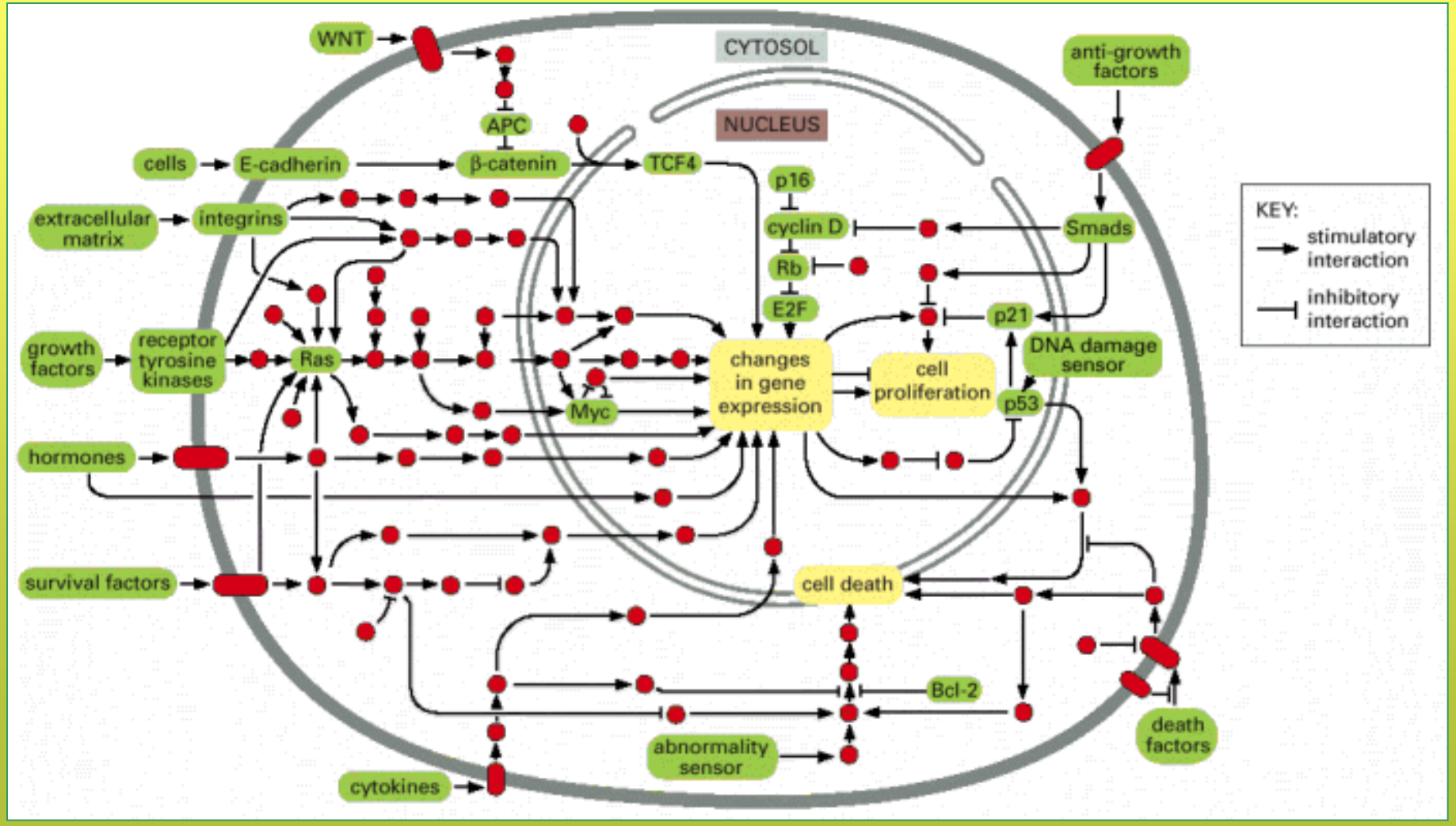
  = **activation by cyclin**

complex cyclin / kinase => protein phosphorylation => triggers cell cycle phases



http://cs.wikipedia.org/wiki/Soubor:Bun%C4%9B%C4%8Dn%C3%BD_cyklus_CDK.svg

Signal transduction pathways – proliferation, apoptosis



Genes regulating cell cycle:

Protooncogenes

- products **stimulate** cell division
- Genes for **growth factors, receptors, regulatory proteins**, **Ras proteins**
- mutated forms **= oncogenes** => permanent or increased mitotic activity

  (effect of one allele mutated)

Tumor suppressor genes (TSG) „antioncogenes“

- products **inhibit** mitotic division
- effect of both alleles mutated

- **Rb1** gene, product RB protein
  - Mutations in retinoblastom and other tumors
- **TP 53** gene, **p53** product – induction of DNA repair or apoptosis = programmed cell death
- mutations in many tumors

Carcinogenesis

Mutator genes – genes for reparation enzymes

Proteins encoded by proto-oncogenes and tumor-suppressor genes are components of cell-signalling pathways.

Multistep model of cancer development

Apoptosis = programmed cell death

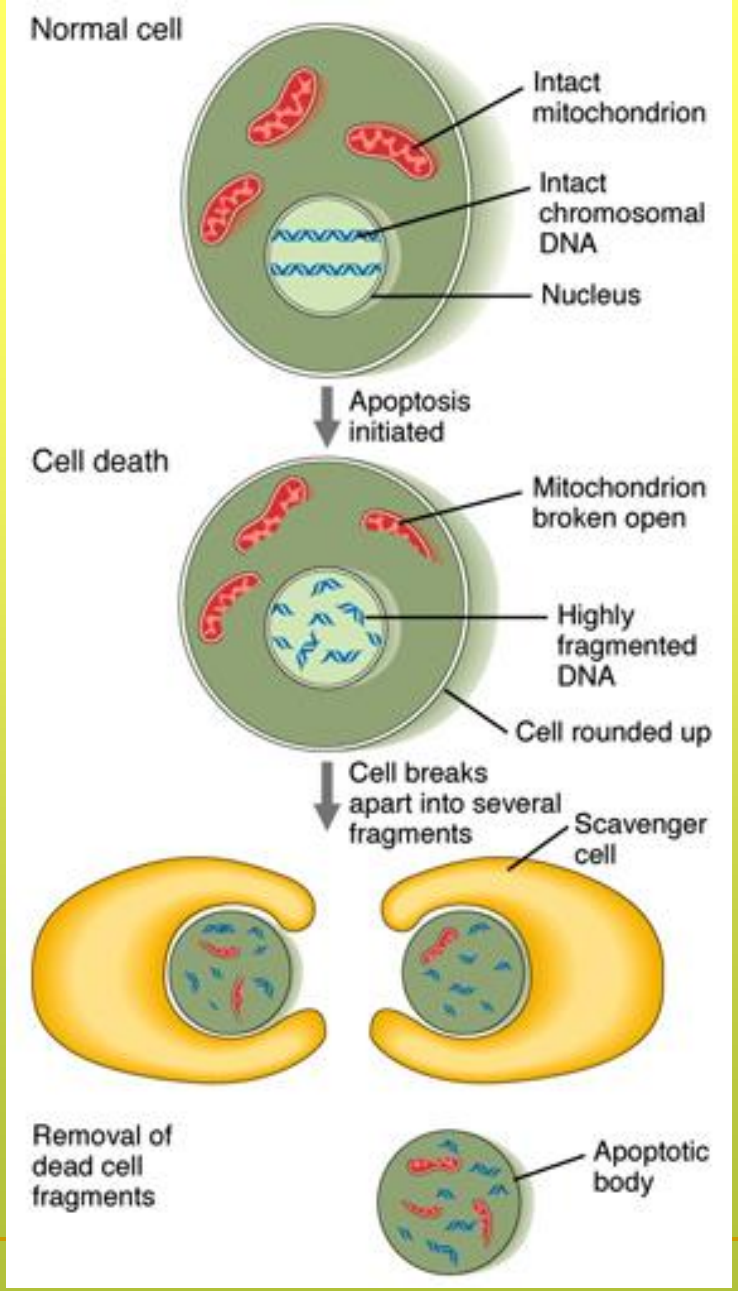
- final stage of aging process in the cell
- elimination of cells, which can not be repaired
- during embryogenesis - reduction of redundant parts
- some diseases
- Purpose: elimination of cells, that accomplished their fate and could become destructive for the organism

Apoptosis:

- without disintegration of both plasma membrane and organelles
- chromatin condensation, surface blebbing, cell fragmentation → **apoptotic bodies**
- phagocytosis without inflammation

Necrosis:

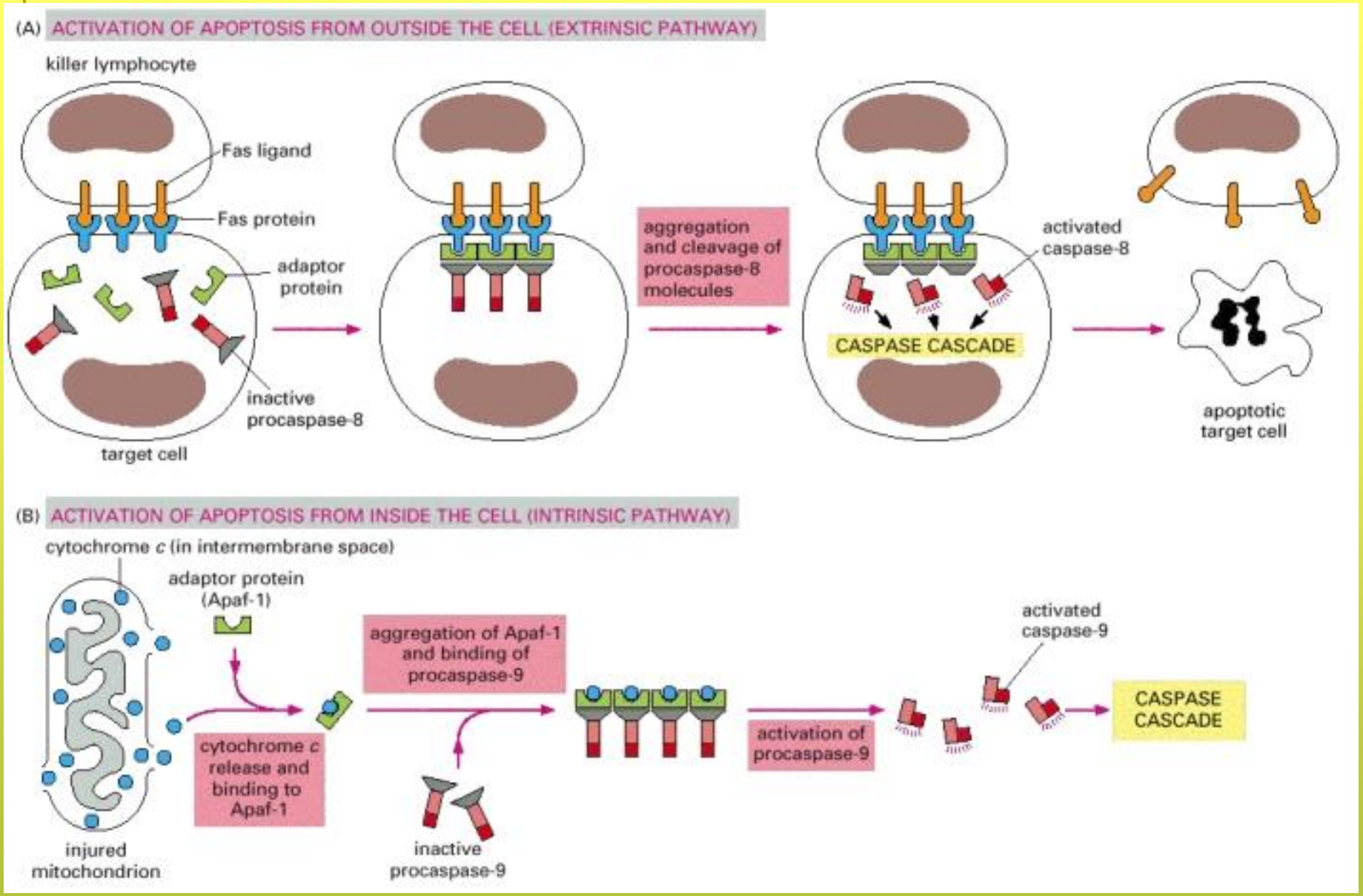
disruption of plasma membrane and organelles, release of the cell content into extracellular space → **inflammation**



Caspases

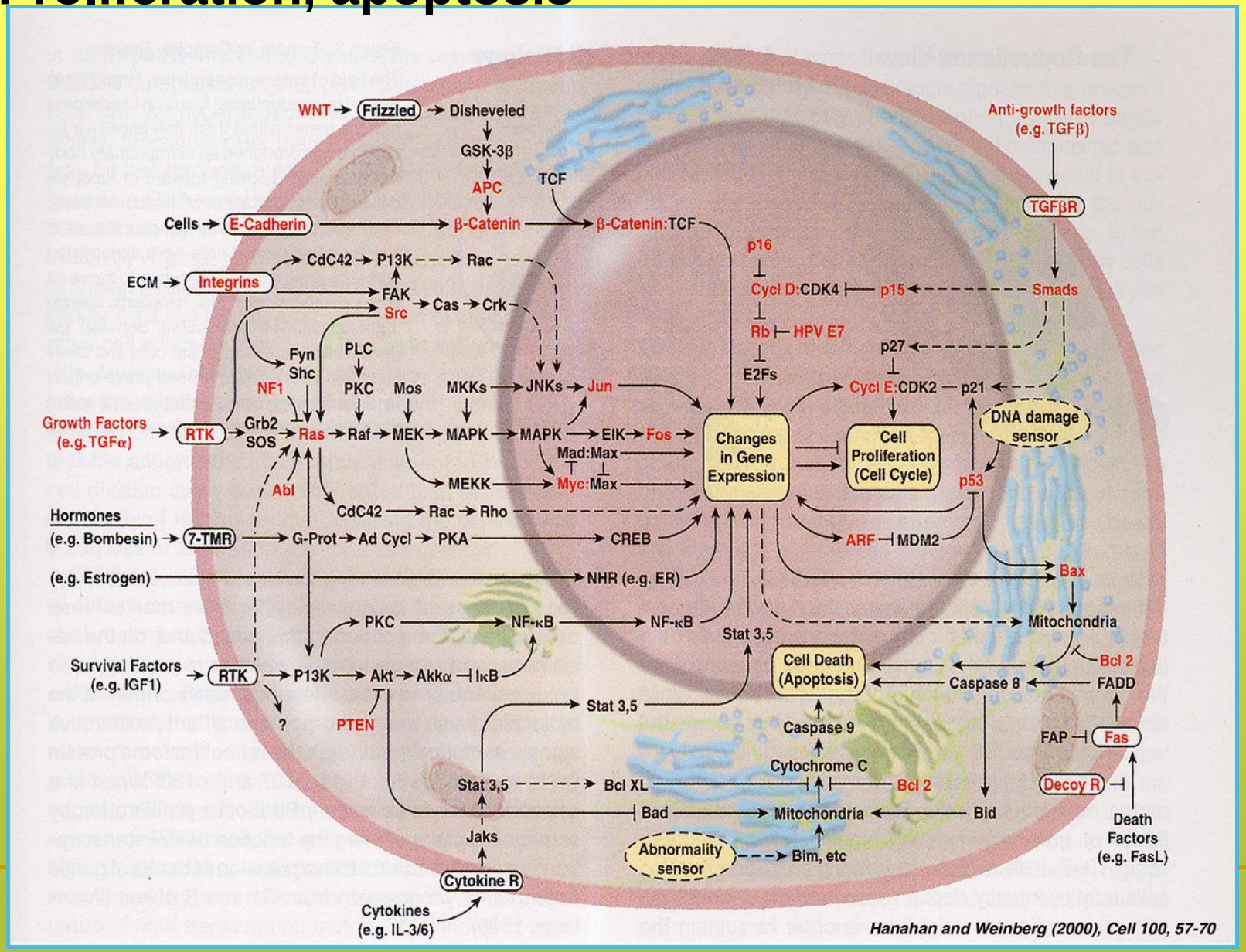
are a family of cysteine proteases that play essential roles in apoptosis (programmed cell death), necrosis, and inflammation

http://www.bio.miami.edu/dana/250/250S12_15.html



Molecular Biology of the Cell. 4th edition.
Alberts B, Johnson A, Lewis J, et al.
New York: Garland Science; 2002

Signal transduction pathways – Proliferation, apoptosis

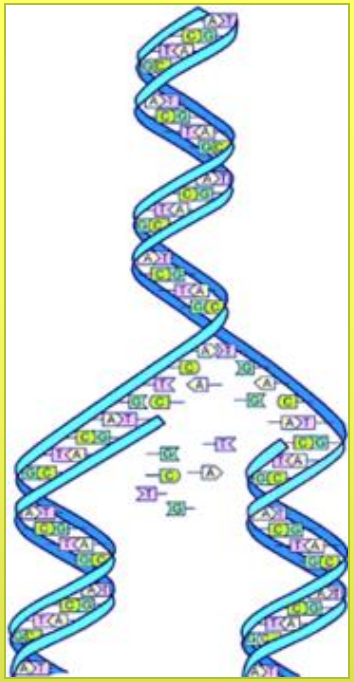


Hanahan and Weinberg (2000), Cell 100, 57-70

Thank you for your attention

Campbell, Neil A., Reece, Jane B., Cain Michael L., Jackson, Robert B., Minorsky, Peter V.**,** **Biology**, Benjamin-Cummings Publishing Company, 1996 – 2010.

DNA replication



- Semiconservative =

synthesis of the new strand
to the old one

- Replication begins

simultaneously at multiple sites
(in Eukaryotes)

at the beginning of S phase – single fragments
at the end of S phase – accumulation of double fragments

- **Asynchronous replication**: some parts are replicated

earlier: constitutional genes (permanently active), euchromatin,
other later: heterochromatin

- Antiparalel strand is replicated in the form of fragments (Okazaki fragments)
- **Initiation** of replication: **RNA primer** – DNA polymerase can not start synthesis from free nucleotides; it can only add nucleotides to the 3' end of a preexisting polynucleotide

Enzymes required for replication :

- **DNA polymerase** (DNA-dependent DNA-polymerase) - **polymerization**
- **primase** (DNA-dependent RNA-polymerase) – **primer** synthesis
- **helicase** – unwinding of the DNA double helix
- **gyrase** – unfolding and folding of high order spiralizations of chromatine fibre
- **ligase** – connecting fragments