Cell cycle and apoptosis

Cell cycle

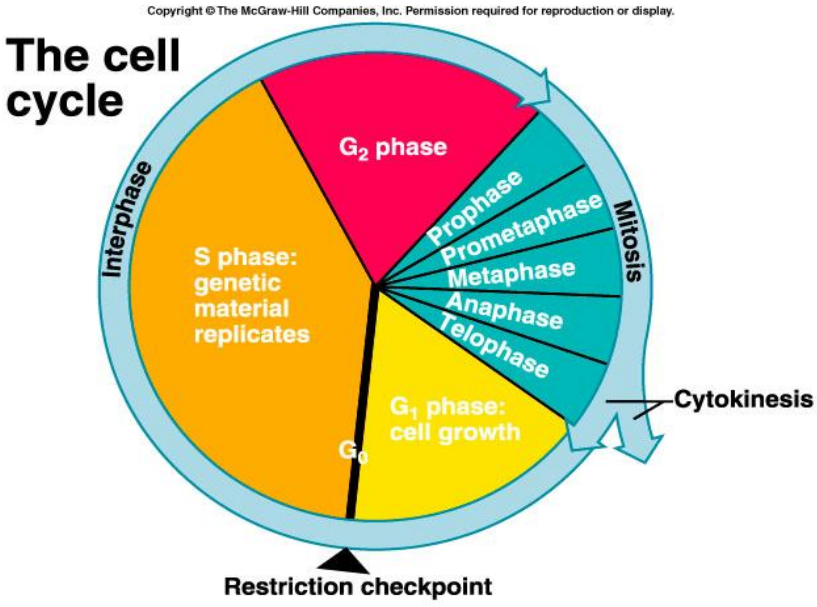
- Cell cycle
  - —Definition
  - —Stages and steps
    - Interphase (G1/G0, S, and G2)
    - Mitosis (prophase, metaphase, anaphase, telophase, karyokinesis, cytokinesis)
  - —Control checkpoints
- Apoptosis
  - — Definition
  - — Types of cell death
  - — Apoptotic pathways

Cell cycle

- The time a cell spent between birth and the end of cell division

- Why cells divide?
  - To keep an organism healthy and running
- Why cells die?
  - To keep an organism healthy and running

Who decides?



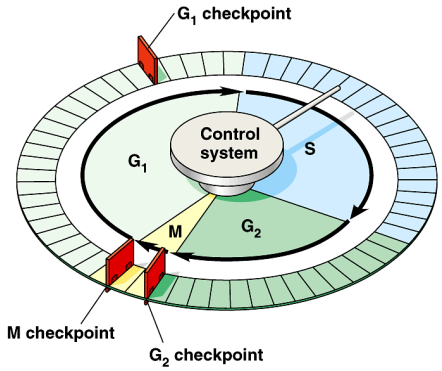
http://www.cellsalive.com/mitosis.htm

Cell cycle

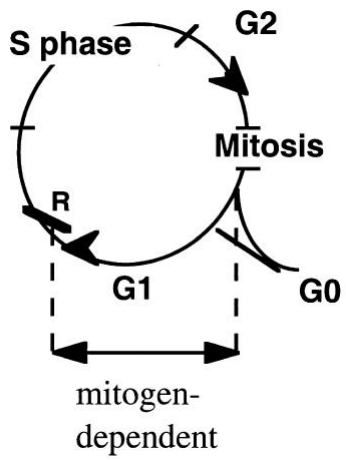
- ***2 phases: interphase – division***

INTERPHASE- 90% of the time

- **G1:** newly formed cells absorb nutrients and protein mass doubles along with the number of organelles (G1-restriction point control before DNA replication)



Cell cycle



From: The Restriction Point of the Cell Cycle
Madame Curie Bioscience Database [Internet].
Austin (TX): Landes Bioscience; 2000-.

Cell cycle – G1 phase

- From G1, cells may stop the cell cycle and enter the G0 phase - resting in the absence of extracellular signals division; G0 cells do not grow in size
- Stopping in G0 can be :
  - Final - terminally differentiated cells - neurons, skeletal muscle cells
  - Temporary: liver cells

Cell cycle

- MAPK signaling pathway initiates cell cycle progression

Cell cycle

- Progression from one phase to another is controlled by checkpoints
  - G1
  - G2
  - M

"A checkpoint is one of several points in the eukaryotic cell cycle at which the progression of a cell to the next stage in the cycle can be halted until conditions are favorable."

Source: Boundless. www.boundless.com/biology/textbooks/boundless-biology-textbook/cell-reproduction-10/control-of-the-cell-cycle-89/regulation-of-the-cell-cycle-at-internal-checkpoints-398-11625/

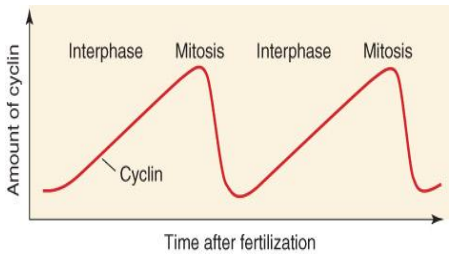
G1 checkpoint

- The G1 point at which commitment occurs and the cell no longer requires growth factors to complete the cell cycle
- Also known as "restriction point" or "the point of no return"
- What is different between the "before" and "after" of G1?

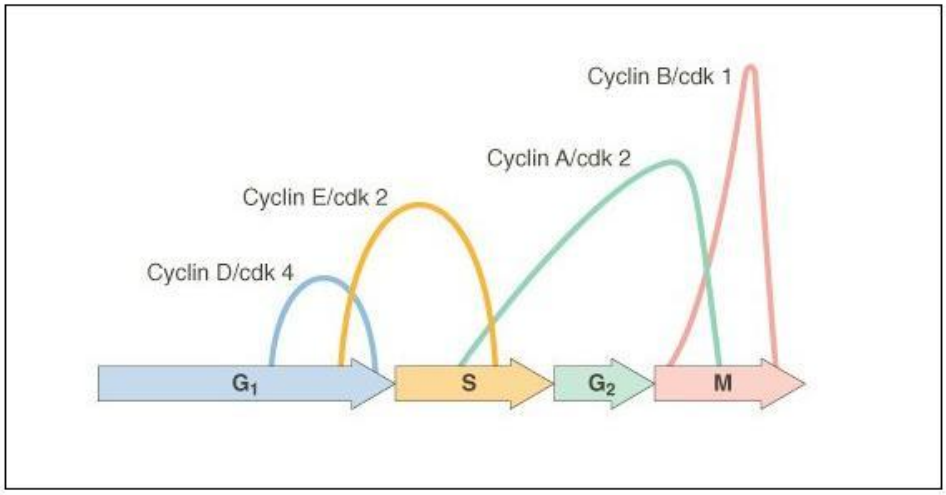
Cell cycle

- MAPK signaling pathway initiates cell cycle progression, by synthesis of G1 specific cyclins
- Cyclin – an unstable protein which is induced, stabilized and accumulates in a specific phase of the cell cycle

The cycle of a cyclin

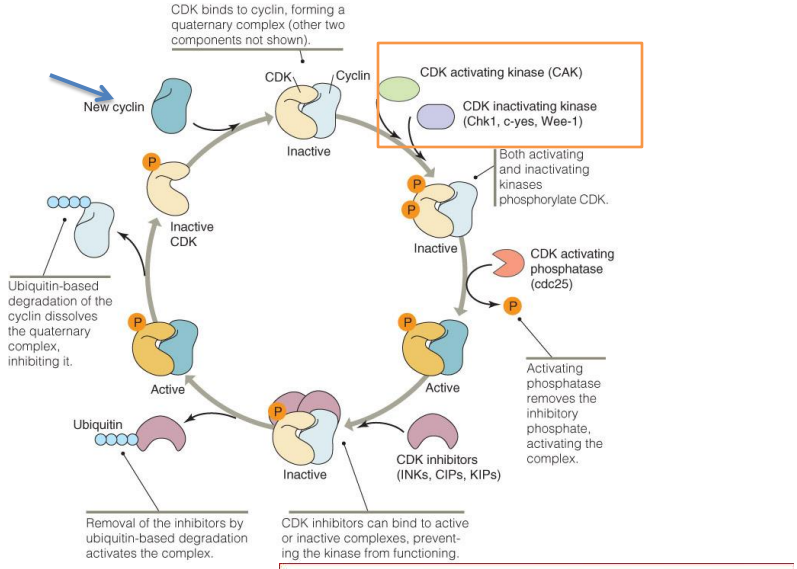


Cyclins

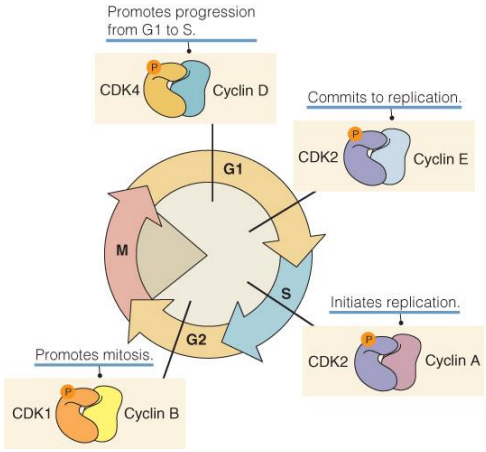


http://facweb.furman.edu/~wworthen/bio111/mitosis.htm

Cyclin-CDK complex – life cycle



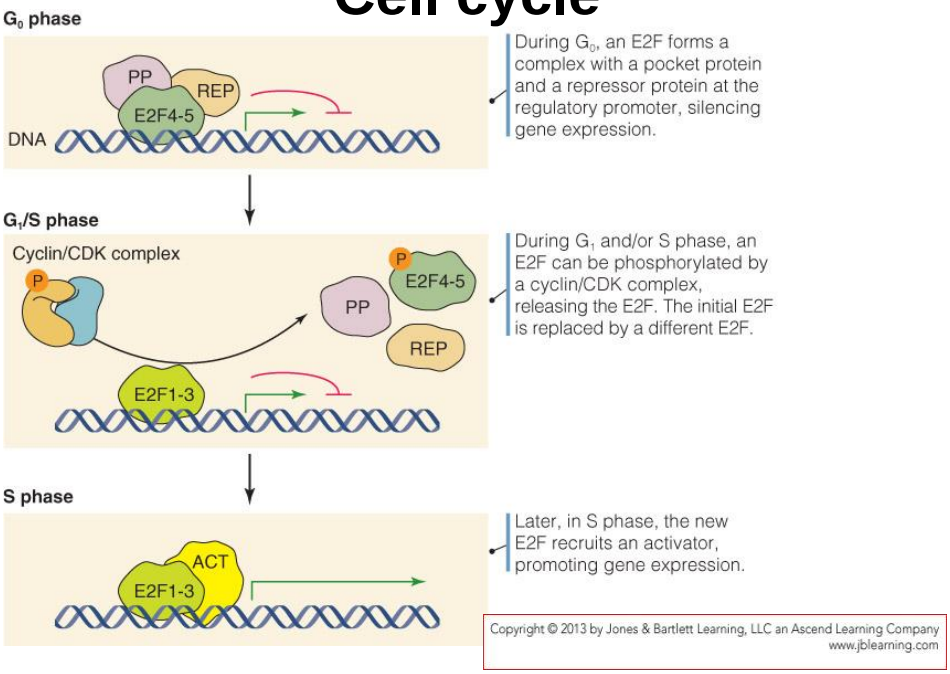
Cyclin/CDK complexes



Cell cycle

- The drive behind G1 to M progression is E2F transcription factor family

Cell cycle



Cell cycle – S phase

• **S**: DNA replication, for mitosis; at the end of this phase, each chromosome is composed of two sister chromatids - cell has two sets of chromosomes (4n)

•Growth factor – independent!

•Arrest in S phase can occur, if unrepairable DNA damage or shortage of nucleotides

Cell cycle – G2 phase

- **G2**: cells continue to grow, preparing for mitosis (G2-restriction point control before mitosis)

- G2 kinases prevent DNA re-replication
- Cell checks for DNA damage

G2/M checkpoint

- Cell checks for:
  - DNA damage
  - Presence of proteins required for cell division

- DNA damage checkpoint genes (p53) are activated by breaks in the double strand of DNA

MITOSIS:

- takes place in somatic cells of all eukaryotic organisms (containing the restriction point M)

- equal distribution of the 2 sets of chromosomes between the two daughter cells (a cell diploid parent creates two diploid daughter cells)

- division of the nucleus (karyokinesis) precedes division cytoplasm (cytokinesis)

-phases: 1. Prophase
2. Metaphase
3. Anaphase
4. Telophase

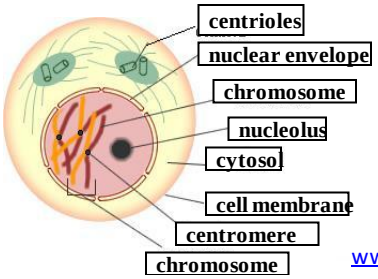
- Cytokinesis – separation of cytoplasm

MITOSIS – Organelles rearrangement

- Organelles still exist, although not in their "classical" (interphase) ultrastructure:
  - Nucleus – disorganizes
  - RE, Golgi – fragment in many vesicles
  - Specific organelle: mitotic spindle – organized by microtubules

Prophase

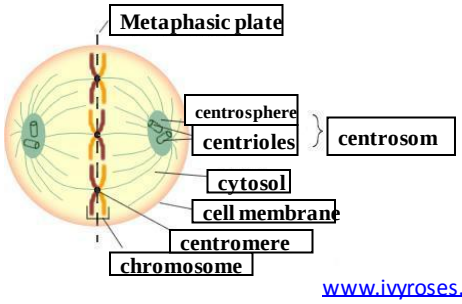
- chromatin condenses to form *chromosomes.*
- sister chromatids are joined at the centromere
- cyclin B/cdc2 phosphorylates lamins
- progressive disorganization of nucleoli
-centrosome doubles and moves to opposite poles of the cell, forming between them spindle fibers



www.ivyroses.com

Metaphase

- each chromatid is attached to microtubules belonging to one of the centrosomes
- line up in the equatorial area, forming metaphase plate



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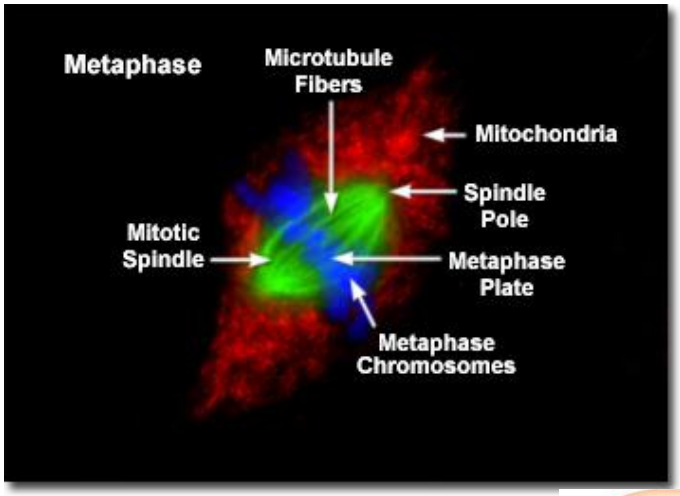
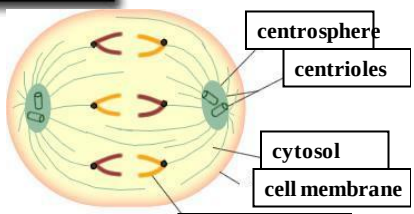


www.micro.magnet.fsu.edu

•the longitudinal cleavage of the two chromatids of each chromosome



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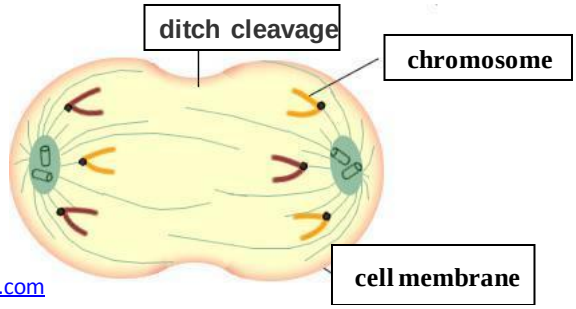
M checkpoint

- Cell checks for attachment of all sister chromatids to mitotic spindle
- Mitotic spindle fibers attach with their plus end to the kinetochore of each chromatid

Anaphase

• sister chromatids separate and migrate to the cell poles using dynein



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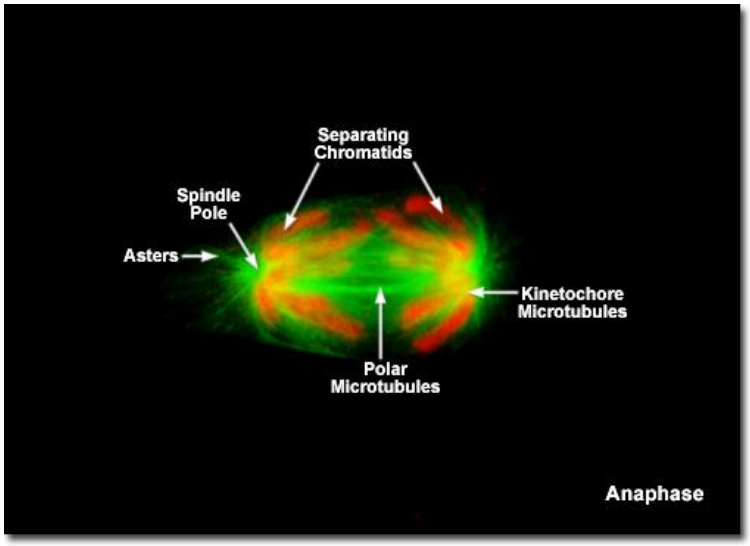
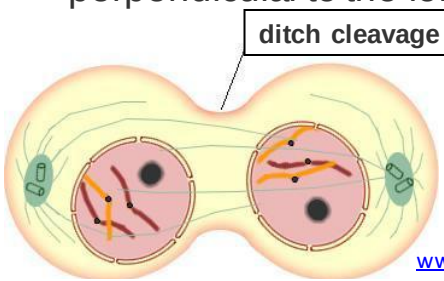
Anaphase



meiosis-and-mitosis.pbworks.com

Telophase

- chromosomes – reach division spindle poles, and decondenses
- division spindle disorganization
- reorganization of the nuclear envelope (around the two nuclei)
- contractile ring formation in the equatorial plane perpendicular to the long axis of the spindle



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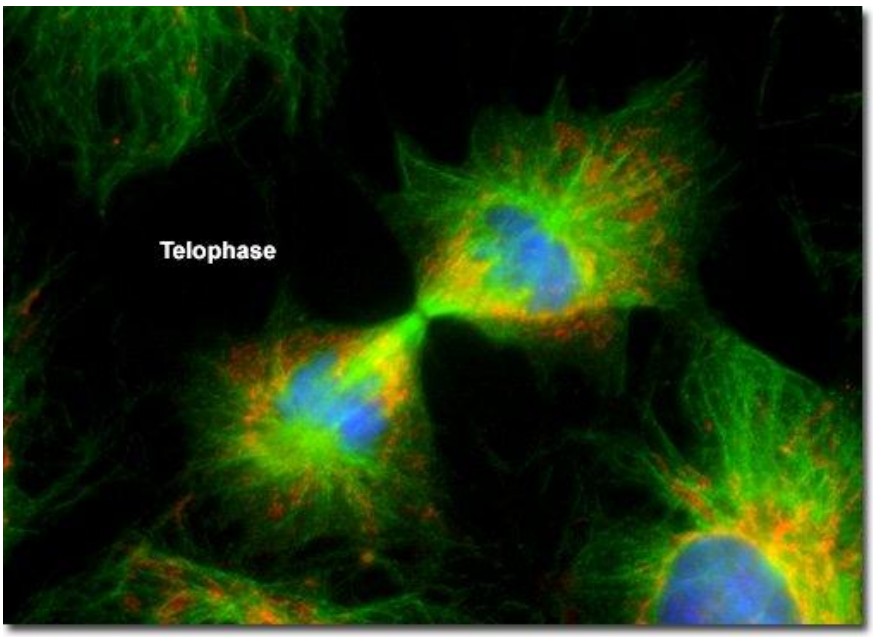

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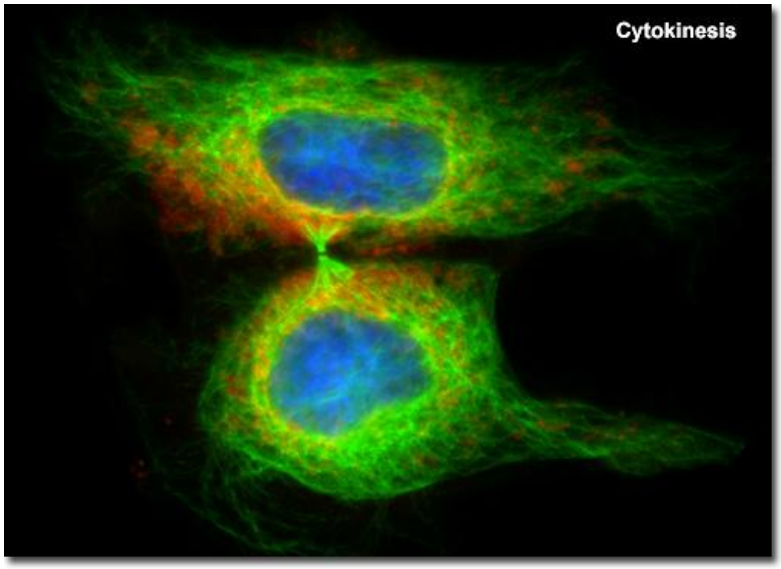
Cytokinesis

- cytoplasm division and organelles separation between the two daughter cells
- result: 2 daughter cells



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MEIOSIS

- reduce the number of chromosomes, so that each daughter cell has a haploid number of chromosomes
- specific to the gametes

- Roles:
  1. ensure diploid number of chromosomes in the egg cell (fecundated oocyte)
  2. provide a combination of particular features to the descendants

MEIOSIS

-2 stages: the first meiotic division and the second meiotic division

• before the first meiotic division, DNA replication is achieved with double the number of chromosomes
• each chromosome consists of two chromatids
• in meiosis occur 2 nuclear divisions and result 4 haploid nuclei
• between meiosis I and II, there has been no multiplication of genetic material

Essentials on chromosomes' status

Meiosis I separates the chromosomes of a pair

daughter cells are haploid

• chromosomes have two chromatids identical or recombinant

Meiosis II separates sister chromatids

• resulting cells undergoes maturation giving rise to *gametes*

• *fertilization* restores the diploid number of chromosomes

Forms of cell death

- Criteria
  - Morphological (apoptotic, necrotic, autophagic or associated with mitosis)
  - Enzymological (with or without involvement of caspases or other lytic enzymes, such as nucleases)
  - Functional aspects (programmed or accidental, physiological or pathological)
  - Immunological characteristics (immunogenic or non-immunogenic)

Forms of cell death

Apoptosis – the physiological type of cell death

-Gene-controlled program

-Is characterized morphologically by cell shrinkage, plasma membrane blebbing, nuclear condensation, and DNA fragmentation. The dead cell is packaged into membrane-bound apoptotic bodies, which are engulfed and removed by neighboring cells or tissue phagocytes. Apoptosis is usually associated with minimal inflammation

Forms of cell death

- **Necrosis** is characterized by loss of plasma membrane integrity, organelle and cell swelling, and ultimately, cell lysis

- **Necroptosis** shares some critical inductive-phase features with apoptosis but possesses many of the morphological characteristics of necrosis.
- - swelling of the cell and its organelles, particularly the mitochondria, and by consequent cell implosion.

Apoptosis Pathways

(*a*) the intrinsic pathway, gated by proteins encoded by the *BCL-2* gene family, which control the release of specific caspase-activating factors from mitochondria

(*b*) the extrinsic pathway – specialized death receptors, which transmit signals from extracellular death ligands across the plasma membrane to engage the intracellular caspase machinery.

In both cases, executants of apoptosis are caspases!

Apoptosis

- Caspases are members of a protein family with protease activity
  - Synthesized in inactive form
- Some members have regulatory function (8, 9), also called initiator caspases
  - activate effector caspases (3, 6, 7) by proteolysis
- Effector caspases
  - drive the execution phase of the apoptotic death program by cleaving hundreds or even thousands of structurally and functionally critical proteins within the cell.

Intrinsic apoptosis

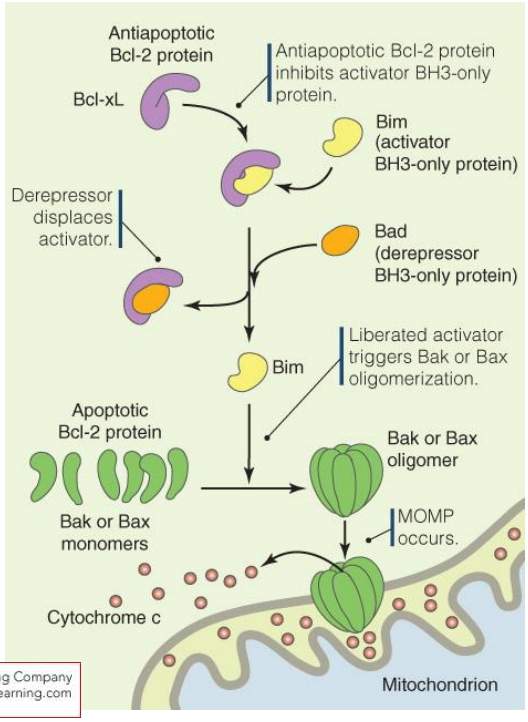
- Controlled by Bcl2 proteins
- Executed by caspases
- Specific molecular complex: apoptosome

Apoptosis control

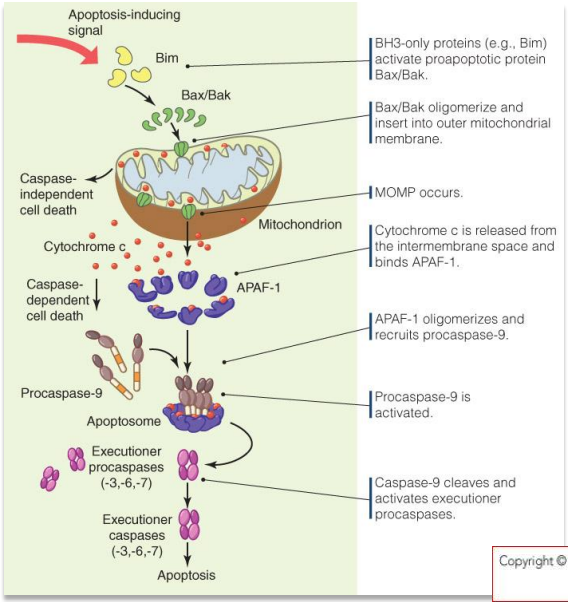
- Anti-apoptotic Bcls prevent caspases activation
- Pro-apoptotic Bcls lead to activation of caspases

Intrinsic apoptosis pathway

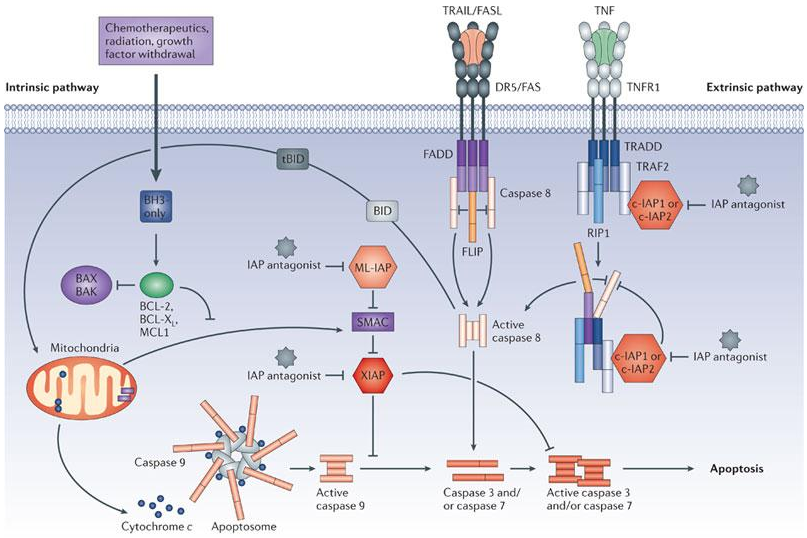
DNA damage activates p53 protein



Mitochondrial Outer Membrane Permeabilization (MOMP)



Review on apoptosis pathways



Nature Reviews | Drug Discovery

Fulda & Vucic; Nature Reviews Drug Discovery 11, 109-124 (February 2012) doi:10.1038/nrd3627

Summary

- Cell life can be divided into interphase and mitosis/meiosis
- The cell cycle is only partially dependant on extrinsic signals
- Advancement through cell cycle depends on/is controlled by cyclins-cyclin-dependant kinases and has several checkpoints
- Further reading at http://www.ncbi.nlm.nih.gov/books/NBK26824/

Summary

- There are many ways for a cell to die
- Apoptosis is the genetically-determined type of cell death
- Apoptosis can be intrinsic or extrinsic
- The effectors of apoptosis are the caspases
- Further reading at http://www.ncbi.nlm.nih.gov/books/NBK26873/