02.17.10
Lecture 14 - The cell cycle and cell death
The cell cycle: cells duplicate their contents and divide
The cell cycle may be divided into 4 phases

- **G1 PHASE**
- **G2 PHASE**
- **S PHASE** (DNA replication)
- **INTERPHASE**
- **M PHASE**
  - mitosis (nuclear division)
  - cytokinesis (cytoplasmic division)
The cell cycle triggers essential processes (DNA replication, mitosis)
Progression of the cell cycle is regulated by feedback from intracellular events.
Cyclin-dependent protein kinases drive progression through the cell cycle

- Cyclin-dependent kinases (Cdks) are inactive unless bound to cyclins
- Active complex phosphorylates downstream targets
- Cyclin helps to direct Cdks to the target proteins
Cellular levels of (mitotic) M-cyclin rises and falls during the cell cycle

- M-cyclin levels are low during interphase but gradually increases to a peak level during mitosis
- M-cdk activity is, likewise, low in interphase but increases in mitosis
The abundance of cyclins (and the activity of Cdks) is regulated by protein degradation

- M-cyclin becomes covalently modified by addition of multiple copies of ubiquitin at the end of mitosis
- Ubiquitination is mediated by the anaphase promoting complex (APC)
- Ubiquitination marks cyclins for destruction by large proteolytic machines called proteasome
Cdns are also regulated by cycles of phosphorylation and dephosphorylation.
Cdk activates itself indirectly via a positive feedback loop
Distinct cyclins partner with distinct Cdns to trigger different events of the cell cycle.
S-Cdk triggers DNA replication - its destruction ensures this happens once per cell cycle
Checkpoints ensure the cell cycle proceeds without errors
Checkpoint: DNA damage arrests the cell cycle in $G_1$
Checkpoint: spindle assembly

- Mitosis must not complete unless all the chromosomes are attached to the mitotic spindle
- Mitotic checkpoint delays metaphase to anaphase transition until all chromosomes are attached
- Prolonged activation of the checkpoint --> cell death
- Mechanism of many anti-cancer drugs
Cells can withdraw from the cell cycle and dismantle the regulatory machinery

- $G_0$ is a quiescent state
- Cdns and cyclins disappear
- Some cells enter $G_0$ temporarily and divide infrequently (i.e. hepatocytes)
- Other differentiated cell types (neurons) spend their life in $G_0$
Apoptosis: the necessity for cell death in multicellular organisms

- Embryonic morphogenesis
- Killing by immune effector cells
- Wiring of the developing nervous system
- Regulation of cell viability by hormones and growth factors (most cells die if they fail to receive survival signals from other cells)
Developmentally-regulated apoptosis

A
Epithelial cells must die to allow fusion of palate
Mammary epithelium cells die when deprived of hormones at end of lactation
Cells of Müllerian ducts die in males
Prostate cells die when deprived of hormone

Up to 80% of neurons die in some ganglia
Over 99% of immature T cells die in thymus
Cells of interdigital webbing die

Apoptosis vs. necrosis

(A) Necrotic cell

(B) Apoptotic cells

(C) Phagocytic cell

engulfed dead cell
Necrosis
Apoptosis

- Microrvilli contract
- Junctions break
- Chromatin condenses around the nucleus

- Cell blebs form
- Chromatin condensation continues
- Apoptotic bodies are phagocytosed by neighboring cells and macrophages
Apoptosis occurs very quickly and precisely
Apoptotic cells are phagocytosed by macrophages

A. Attraction of phagocytes via soluble "find me" signals

B. Recognition and phagocytosis via displayed "eat me" signals and lack of "don’t eat me" signals

C. Production of anti-inflammatory cytokines

Caspases are specialized proteases that mediate apoptosis

Figure 10 from Molecular Biology of the Cell by Garwood Science (1998)
Apoptosis is mediated by an intracellular proteolytic cascade
Cell-surface death receptors regulate the extrinsic pathway of apoptosis
The intrinsic pathway of apoptosis depends on mitochondria.
The Bcl-2 family of proteins regulate the intrinsic pathway of apoptosis.
Animal cells require extracellular signals to divide, grow, and survive

- **Mitogens** - stimulate cell division by overcoming cell cycle “brake” that leads to G\(_0\)

- **Growth factors** - stimulate growth (increased cell size) by promoting synthesis and inhibiting degradation of macromolecules

- **Survival factors** - suppress apoptosis
Mitogens stimulate proliferation by inhibiting the Rb protein
Growth factors increase synthesis & decrease degradation of macromolecules
Survival factors mediate essential cell death during formation of the nervous system.
Survival factors suppress apoptosis by regulating Bcl-2 proteins
Malfunction of apoptosis leads to disease

- Cancer (TNF produced by macrophages activates extrinsic pathway)
- Neurodegenerative diseases
- AIDS (HIV deactivates Bcl-2)
- Ischemic stroke
- Autoimmune disease (lupus)