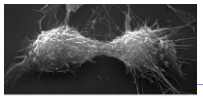
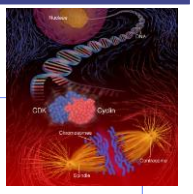
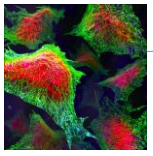




Regulation of Cell Division

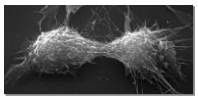


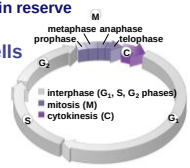
Coordination of cell division

- A multicellular organism needs to coordinate cell division across different tissues & organs
  - critical for normal growth, development & maintenance
    - coordinate timing of cell division
    - coordinate rates of cell division
    - not all cells can have the same cell cycle

Frequency of cell division

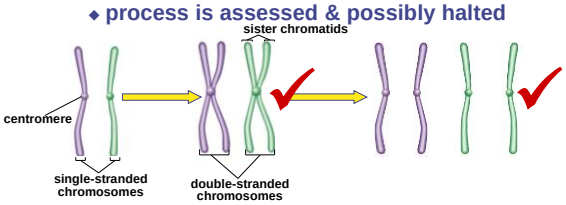
- Frequency of cell division varies by cell type
  - embryo
    - cell cycle < 20 minute
  - skin cells
    - divide frequently throughout life
    - 12-24 hours cycle
  - liver cells
    - retain ability to divide, but keep it in reserve
    - divide once every year or two
  - mature nerve cells & muscle cells
    - do not divide at all after maturity
    - permanently in G_0





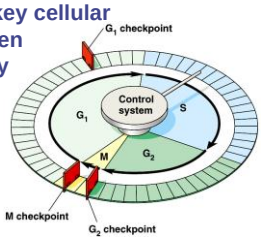
Overview of Cell Cycle Control

- Two irreversible points in cell cycle
  - replication of genetic material
  - separation of sister chromatids
- Checkpoints
  - process is assessed & possibly halted



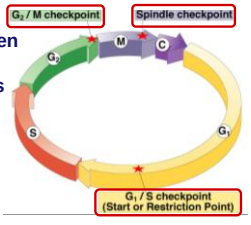
Checkpoint control system

- Checkpoints
  - cell cycle controlled by STOP & GO chemical signals at critical points
  - signals indicate if key cellular processes have been completed correctly



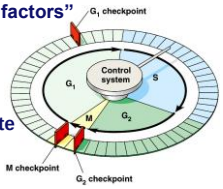
Checkpoint control system

- 3 major checkpoints:
  - G_1/S
    - can DNA synthesis begin?
  - G_2/M
    - has DNA synthesis been completed correctly?
    - commitment to mitosis
  - spindle checkpoint
    - are all chromosomes attached to spindle?
    - can sister chromatids separate correctly?



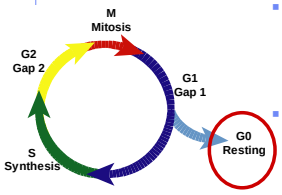
G_1/S checkpoint

- G_1/S checkpoint is most critical
  - primary decision point
    - "restriction point"
  - if cell receives "GO" signal, it divides
    - internal signals: cell growth (size), cell nutrition
    - external signals: "growth factors"
  - if cell does not receive signal, it exits cycle & switches to G_0 phase
    - non-dividing, working state



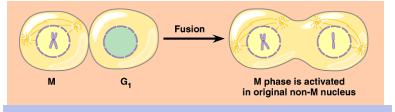
G_0 phase

- G_0 phase
  - non-dividing, differentiated state
  - most human cells in G_0 phase
    - liver cells
      - in G_0, but can be "called back" to cell cycle by external cues
    - nerve & muscle cells
      - highly specialized
      - arrested in G_0 & can never divide



Activation of cell division

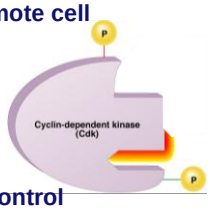
- How do cells know when to divide?
  - cell communication signals
    - chemical signals in cytoplasm give cue
    - signals usually mean proteins
      - activators
      - inhibitors



experimental evidence: Can you explain this?

"Go-ahead" signals

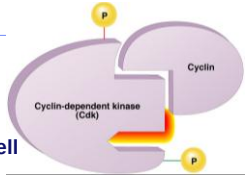
- Protein signals that promote cell growth & division
  - internal signals
    - "promoting factors"
  - external signals
    - "growth factors"
- Primary mechanism of control
  - phosphorylation
    - kinase enzymes
    - either activates or inactivates cell signals



Cell cycle signals

- Cell cycle controls
  - cyclins
    - regulatory proteins
    - levels cycle in the cell
  - Cdks
    - cyclin-dependent kinases
    - phosphorylates cellular proteins
      - activates or inactivates proteins
  - Cdk-cyclin complex
    - triggers passage through different stages of cell cycle

inactivated Cdk

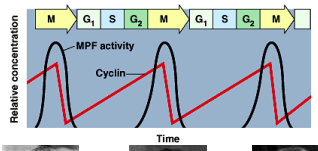


activated Cdk

1970s-80s | 2001

Cyclins & Cdks

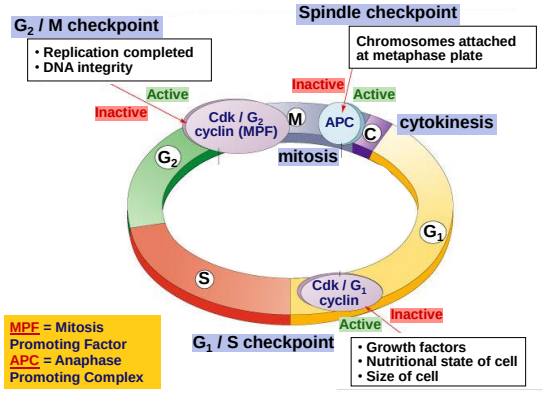
- Interaction of Cdk's & different cyclins triggers the stages of the cell cycle



Leland H. Hartwell checkpoints

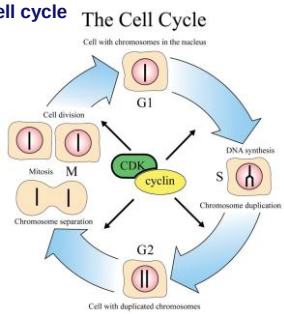
Tim Hunt Cdks

Sir Paul Nurse cyclins



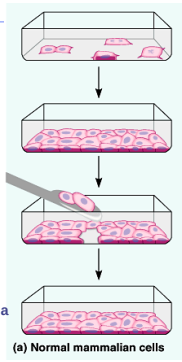
Cyclin & Cyclin-dependent kinases

- CDKs & cyclin drive cell from one phase to next in cell cycle
  - proper regulation of cell cycle is so key to life that the genes for these regulatory proteins have been highly conserved through evolution
  - the genes are basically the same in yeast, insects, plants & animals (including humans)

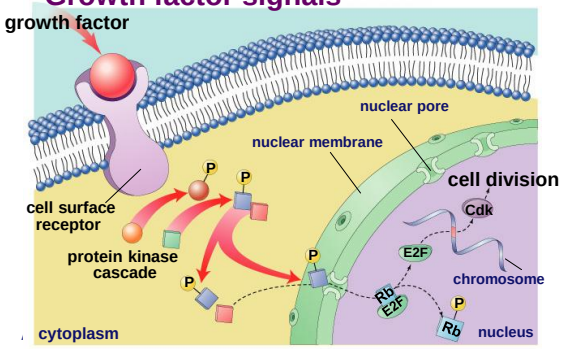


External signals

- Growth factors
  - coordination between cells
  - protein signals released by body cells that stimulate other cells to divide
    - density-dependent inhibition
      - crowded cells stop dividing
      - each cell binds a bit of growth factor
        - not enough activator left to trigger division in any one cell
    - anchorage dependence
      - to divide cells must be attached to a substrate
        - "touch sensor" receptors

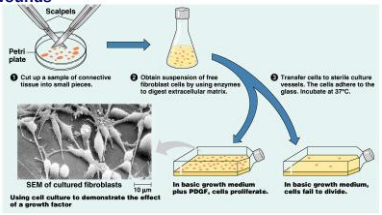


Growth factor signals



Example of a Growth Factor

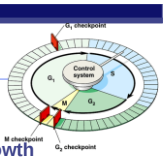
- Platelet Derived Growth Factor (PDGF)
  - made by platelets in blood clots
  - binding of PDGF to cell receptors stimulates cell division in connective tissue
    - heal wounds



Growth Factors and Cancer

- Growth factors can create cancers
  - proto-oncogenes
    - normally activates cell division
      - growth factor genes
      - become oncogenes (cancer-causing) when mutated
    - if switched "ON" can cause cancer
    - example: RAS (activates cyclins)
  - tumor-suppressor genes
    - normally inhibits cell division
    - if switched "OFF" can cause cancer
    - example: p53

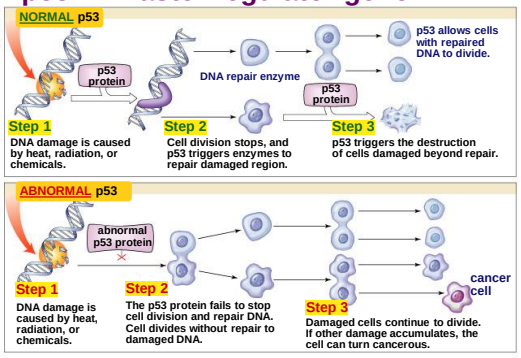
Cancer & Cell Growth



- Cancer is essentially a failure of cell division control
  - unrestrained, uncontrolled cell growth
- What control is lost?
  - lose checkpoint stops
  - gene p53 plays a key role in G_1/S restriction point
    - p53 protein halts cell division if it detects damaged DNA
      - options:
        - stimulates repair enzymes to fix DNA
        - forces cell into G_0 resting stage
        - keeps cell in G_1 arrest
        - causes apoptosis of damaged cell
    - ALL cancers have to shut down p53 activity

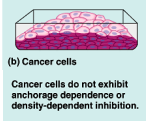
p53 discovered at Stony Brook by Dr. Arnold Levine

p53 — master regulator gene

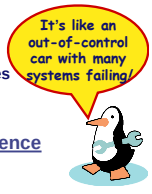


Development of Cancer

- Cancer develops only after a cell experiences ~6 key mutations ("hits")
  - unlimited growth
    - turn on growth promoter genes
  - ignore checkpoints
    - turn off tumor suppressor genes (p53)
  - escape apoptosis
    - turn off suicide genes
  - immortality = unlimited divisions
    - turn on chromosome maintenance genes
  - promotes blood vessel growth
    - turn on blood vessel growth genes
  - overcome anchor & density dependence
    - turn off touch-sensor gene

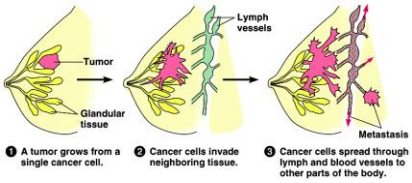

(b) Cancer cells

Cancer cells do not exhibit anchorage dependence or density-dependent inhibition.



What causes these "hits"?

- Mutations in cells can be triggered by
  - UV radiation
  - chemical exposure
  - radiation exposure
  - heat
  - cigarette smoke
  - pollution
  - age
  - genetics

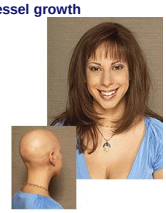


Tumors

- Mass of abnormal cells
  - Benign tumor
    - abnormal cells remain at original site as a lump
      - p53 has halted cell divisions
    - most do not cause serious problems & can be removed by surgery
  - Malignant tumor
    - cells leave original site
      - lose attachment to nearby cells
      - carried by blood & lymph system to other tissues
      - start more tumors = metastasis
    - impair functions of organs throughout body

Traditional treatments for cancers

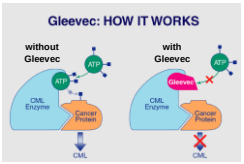
- Treatments target rapidly dividing cells
  - high-energy radiation
    - kills rapidly dividing cells
  - chemotherapy
    - stop DNA replication
    - stop mitosis & cytokinesis
    - stop blood vessel growth



New “miracle drugs”

- Drugs targeting proteins (enzymes) found only in cancer cells
  - Gleevec
    - treatment for adult leukemia (CML) & stomach cancer (GIST)
    - 1st successful drug targeting only cancer cells

Novartes



Any Questions??