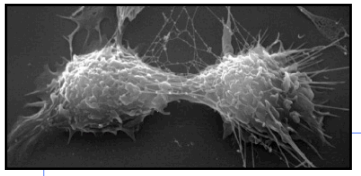
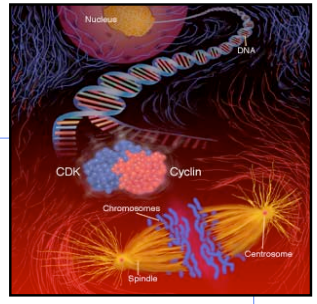
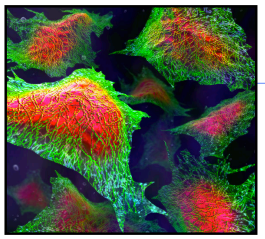
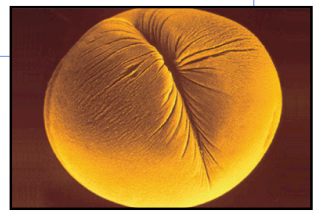




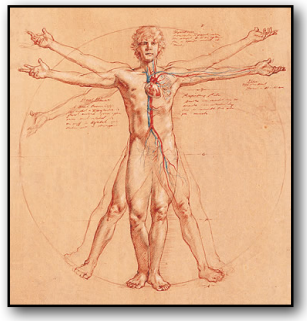
Regulation of Cell Division





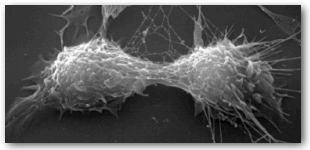
Coordination of cell division

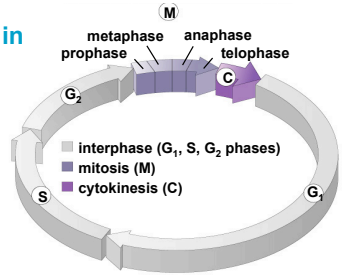
- A multicellular organism needs to coordinate cell division across different tissues & organs.
  - critical for normal growth, development & maintenance
    - Cells must coordinate timing of cell division
    - Cells must coordinate rates of cell division
      - Because specialized cells have different functions, not all cells can have the same cell cycle
        - Cells regulate the rate of their cycle through signal molecules present in the cytoplasm



Frequency of cell division

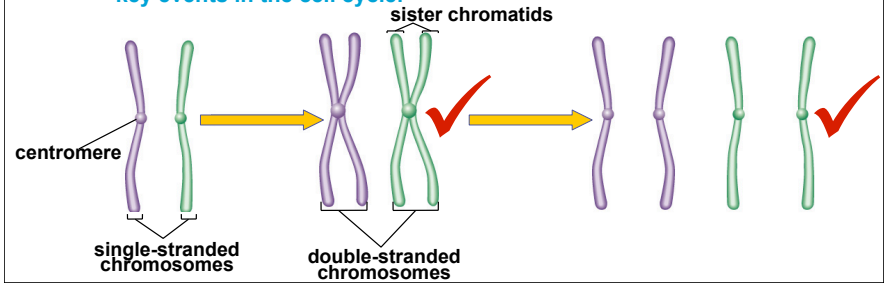
- Frequency of cell division varies by cell type
  - embryo
    - cell cycle < 20 minute
  - skin cells
    - divide frequently throughout life
    - 12-24 hours cycle
  - liver cells
    - retain ability to divide, but keep it in reserve
    - divide once every year or two
  - mature nerve cells & muscle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





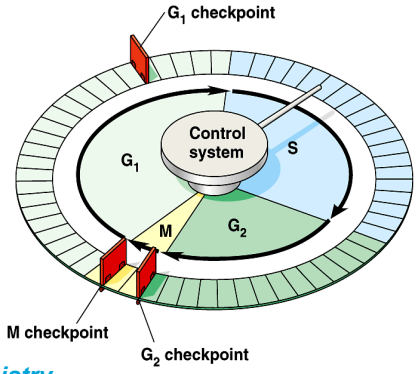
Overview of Cell Cycle Control

- Two irreversible points in cell cycle
  1. replication of genetic material
  2. separation of sister chromatids
- The cell is regulated at certain CHECK POINTS.
  - Here, stop and go signals regulate the cycle.
    - A process is assessed & possibly halted
- Cells have a Cell Cycle Control System:
  - A cyclically working group of molecules that trigger and coordinate key events in the cell cycle.



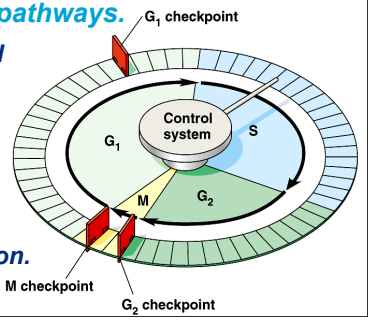
Checkpoint control system

- Cells Have Multiple Important Checkpoints:
  - The cell cycle is controlled by STOP & GO chemical signals at critical points in the life of a cell. Three main ones are:
    1. G1 Checkpoint
    2. G2 Checkpoint
    3. M Checkpoint
  - At checkpoint times, the cell turns off the activity of certain proteins and turns on the activity of other proteins or synthesizes newly needed proteins.
    - *This way the cell stops certain behaviors & chemistry and starts other behaviors & chemistry.*



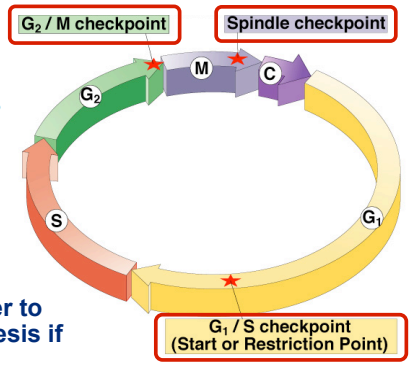
Checkpoint control system

- At Checkpoints, the cell is able to change activities IF & WHEN the right messages have been received
  - The molecular signals that tell the cell to divide originate both from inside and outside the cell
    - *External signals are translated into internal signals through signal transduction pathways.*
      - *Checkpoints can be "moved through" if key processes have been completed correctly so the cell can continue and complete the next step of activities in preparation for cell division.*

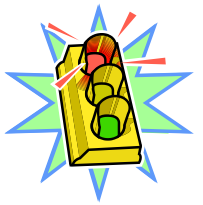


Checkpoint control system

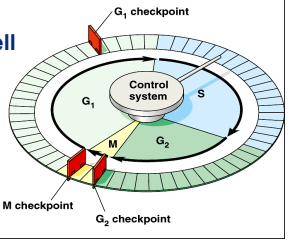
- Three major checkpoints:
  - G_1/S (G_1) checkpoint
    - Start or "restriction point" - the point at which the cell decides it will divide
      - Can DNA synthesis begin?
  - G_2/M (G_2) checkpoint
    - Commits cell to starting mitosis
      - has DNA synthesis been completed correctly?
  - Spindle (M) checkpoint
    - Cell starts anaphase in order to complete mitosis & cytokinesis if everything is in order.
      - Are all chromosomes attached to spindle?
      - Can sister chromatids separate correctly to deliver DNA properly to each daughter cell?



G_1/S checkpoint

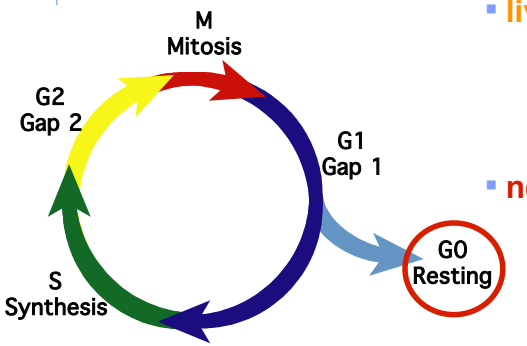


- The G_1/S checkpoint is MOST critical
  - primary decision point
    - "restriction point"
  - Cells have built in stop signals that halt the cell cycle at checkpoints, but if cell receives "GO" signals, it divides
    - internal signals:
      - cell size *(large enough?)*
      - cell nutrition *(receiving enough nutrients & energy?)*
      - have crucial cellular processes been competed correctly?
    - external signals: "growth factors"
      - ligands secreted from elsewhere that tell cells with the right receptor proteins that they need to divide
  - if a mature cell does not receive signal, it exits cycle & switches to G_0 phase
    - non-dividing, normal working state



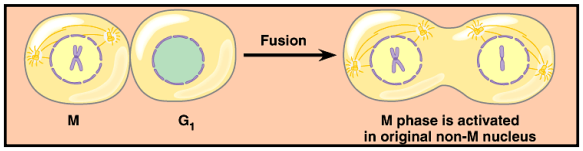
G_0 phase

- G_0 phase
  - non-dividing, differentiated state of cell
  - most human cells are 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 coordinate cell division activities?
  - cell communication involves molecular signals
    - These chemical signals in cytoplasm are usually proteins
      - *Act as activators or as inhibitors of cell division*

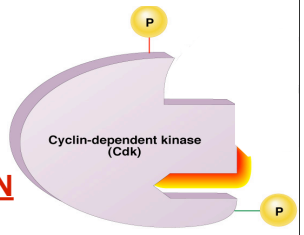


Experimental evidence: Can you explain this?
When researchers fused a cell in M phase with a cell in G1 phase, the G1 nucleus immediately began mitosis, skipping its own S and G2 phases.

Molecules present in the cytoplasm during the M phase control the progression to that phase

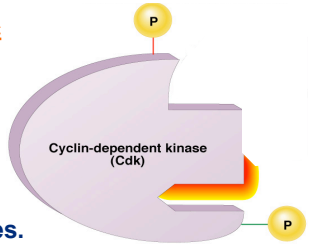
"Go-ahead" signals

- Certain protein signals promote cell growth & division:
  - internal signals: "promoting factors"
  - external signals: "growth factors"
- Primary mechanism of Cell Cycle control involves PHOSPHORYLATION
  - Involves key kinase enzymes
    - They give 'go' signal at at G1 & G2 checkpoints
      - Phosphorylation either activates or inactivates specific proteins thus changing cell behavior:
        - S phase is activated after G1
        - M phase is activated after G2



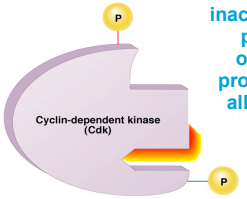
"Go-ahead" signals

- Many of the kinases that phosphorylate other proteins (activating or deactivating them) are called cyclin-dependent kinases or Cdks
  - Cdks are always present in the growing cell but are normally switched off (inactive) so the cell doesn't proceed past G_1 and doesn't divide.
    - Cdks become active when bound to a protein called Cyclin
      - Cyclin fluctuates in cytoplasmic concentration & is not always present in the cell
      - Cyclin protein is only made by the cell when the cell needs to pass through the G1 or the G2 checkpoint in order to activate certain Cyclin-dependent kinases.

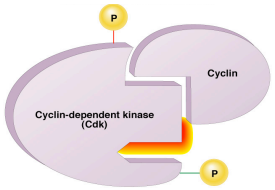


Cell cycle controls

- **cyclins**
  - regulatory proteins
  - levels cycle in the cell
    - Cyclins are made when needed & then break down again & disappear.
- **Cdks**
  - cyclin-dependent kinases
  - phosphorylates cellular proteins
    - activates or inactivates proteins that will affect a cell proceeding through G1 to S phase or through G2 checkpoints to M phase.
- **Cdk-cyclin complex**
  - triggers passage through to a different stages (checkpoints) of the cell cycle



inactivated Cdk
(no cycline attached)
Cell does not proceed through checkpoint because kinase is inactive & not able to phosphorylate other necessary proteins that would allow for the start of new cell behaviors.



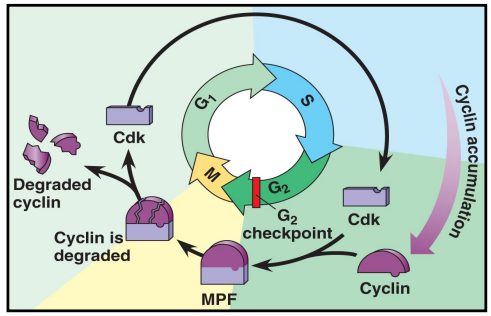
activated Cdk
(bound to cyclin)
Cell proceeds through checkpoint

Molecular Control of Cell Cycle

Cyclins production:

- There are multiple types of cyclins, each activating a specific cdk.
- Cyclins are unstable & synthesized discontinuously during the cell cycle.
  - ➡ Oscillations in the activities of cyclin-dependent kinases (CDKs) dictate orderly progression through the cell division cycle.

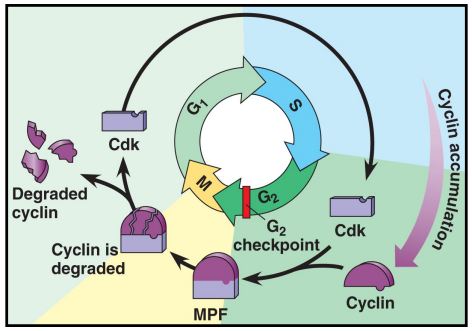
Ex: MPF or "maturation promoting factor" = a cyclin-cdk complex that triggers the cell to pass the G_2 checkpoint and go into the M phase.



Molecular Control of Cell Cycle

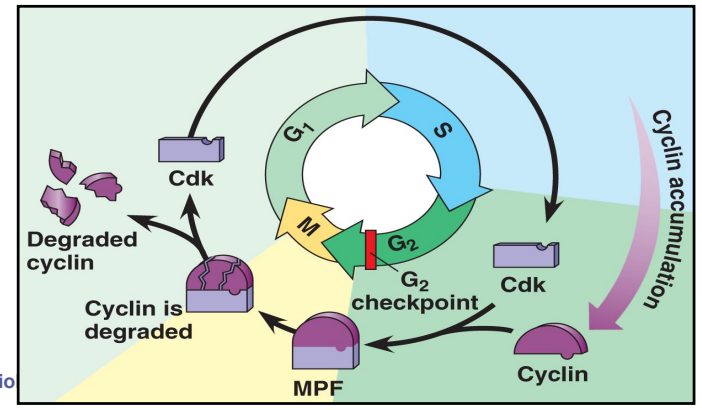
1. MPF's Cyclin (M Cyclin) levels RISE during S and G2 phase
   M Cyclins start binding with their specific Cdks:
   - Forms active cyclin-cdk complexes (called MPF).
   - The kinases in the complexes are now switched ON.
   - Kinases phosphorylates key proteins involved in starting mitosis.

Ex: activates proteins involved in condensing chromosomes and helping with spindle formation and nuclear membrane break down.



Molecular Control of Cell Cycle

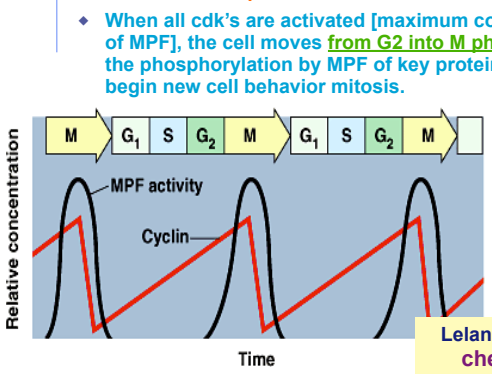
2. Cyclin levels FALL abruptly during M phase
   With no cyclin attached, the kinase changes shape, switching back off.

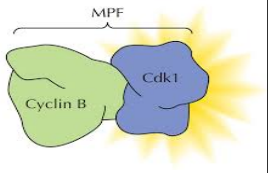


Cyclins & Cdks

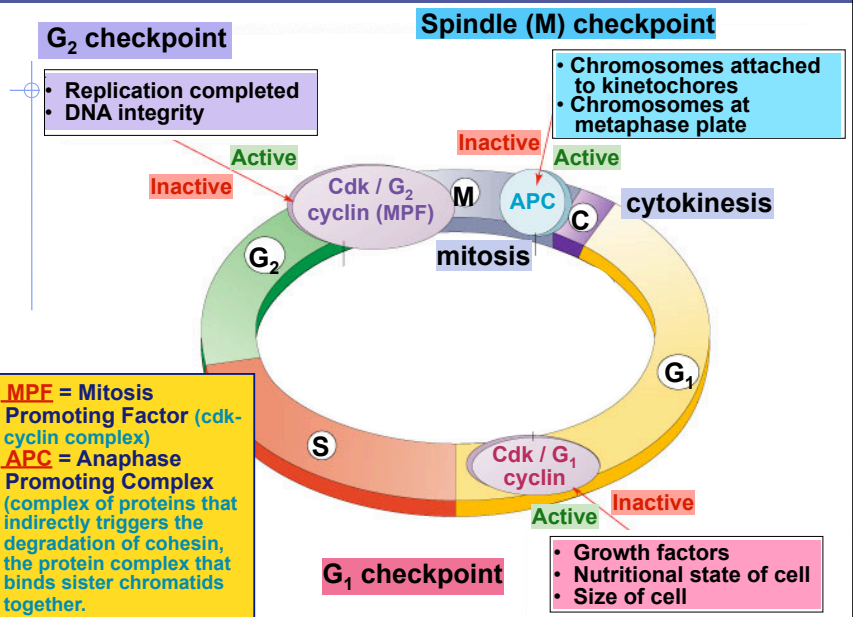
1970s-80s | 2001

- **Interactions of Cdks & specific cyclins trigger the movement of a cell through certain stages of the cell cycle**
  - **For the G2 Checkpoint, as you can see in the graph below, cyclin concentrations increase in the cell throughout the S and G2 phases.**
  - **Cyclins start binding to their cdk's that are always present leading to a sharp increase in the presence/concentration of MPF [cyclin-cdk complexes].**
  - **When all cdk's are activated [maximum concentration of MPF], the cell moves from G2 into M phase due to the phosphorylation by MPF of key proteins needed begin new cell behavior mitosis.**

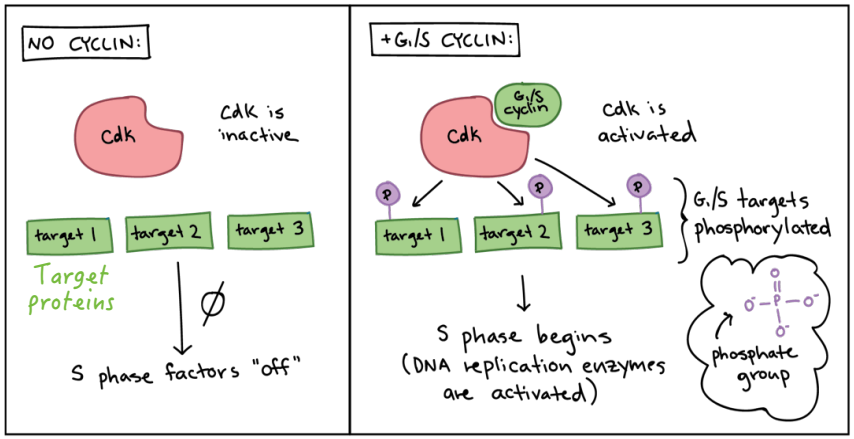




Leland H. Hartwell checkpoints | **Tim Hunt Cdks** | **Sir Paul Nurse cyclins**

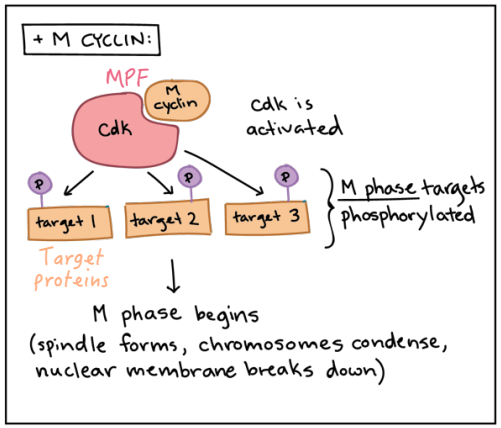


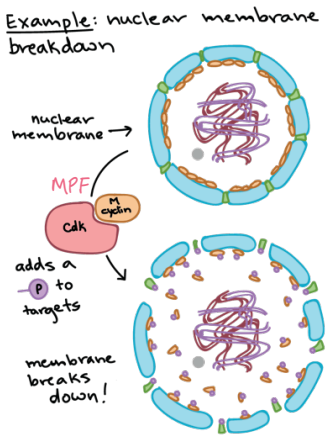
Activation of certain Cdks by certain cyclins results in cell stoping G_1 & starting S phase activities.



Activation of the right Cdk allows the cell to pass through the G_1 (Start or Restriction) Checkpoint

Activation of certain Cdks by certain cyclins results in cell stoping G_2 & starting M phase activities.

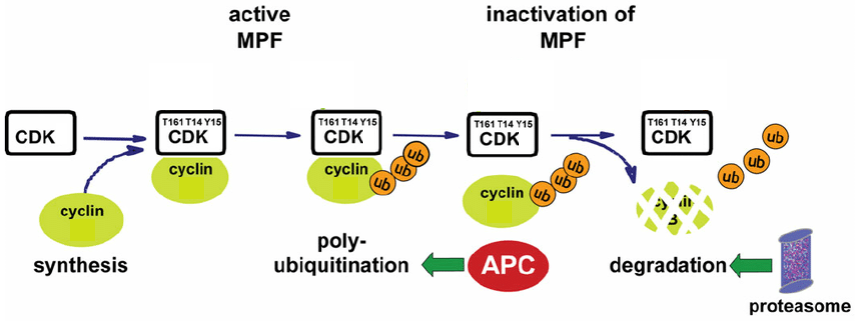




Activation of the right Cdk allows the cell to pass through the G_2 (M) Checkpoint

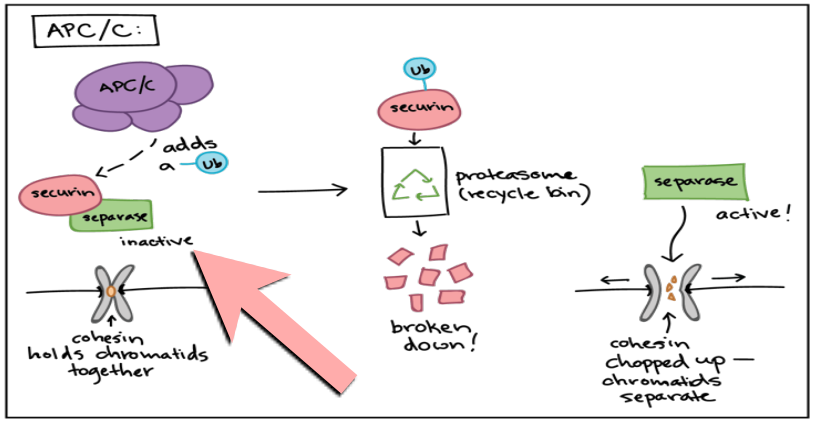
MPF (a Cdk bound to M Cyclin) triggers the start of M phase (cell division) as well as its own destruction.

- In addition to initiating M phase (mitosis), MPF activates the anaphase-promoting complex/cyclosome (APC/C)
  - APC/C causes M cyclins to be destroyed starting in anaphase.
    - APC is an enzyme (though NOT a kinase) which adds small protein tags called ubiquitin (Ub) to Cyclin.
      - Proteins tagged with ubiquitin are hydrolyzed into amino acids by a protein structure called the proteasome
    - Destruction of M cyclins turns off the Cdk of the MPF and pushes the cell out of mitosis, allowing the new daughter cells to enter G1.



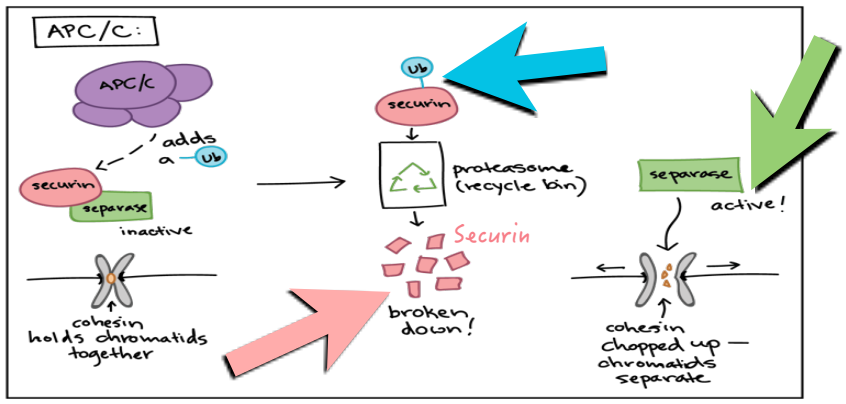
Anaphase Promoting Complex (APC) is not a Cdk (kinase), but it controls the cell starting Anaphase & ending Mitosis

- The APC/C also indirectly destroys the cohesin proteins that hold the sister chromatids together, allowing them to separate in anaphase and move to opposite poles of the cell.
  - Securin normally binds to a protein called separase, inactivating it.

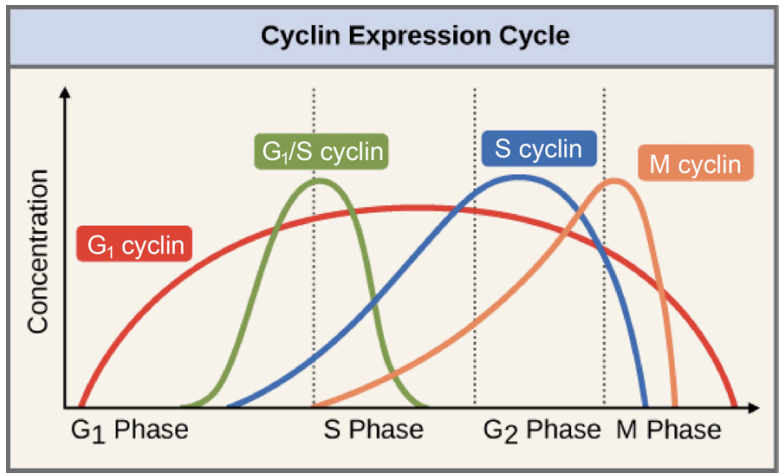


Anaphase Promoting Complex (APC) is not a Cdk (kinase), but it controls the cell starting Anaphase & ending Mitosis

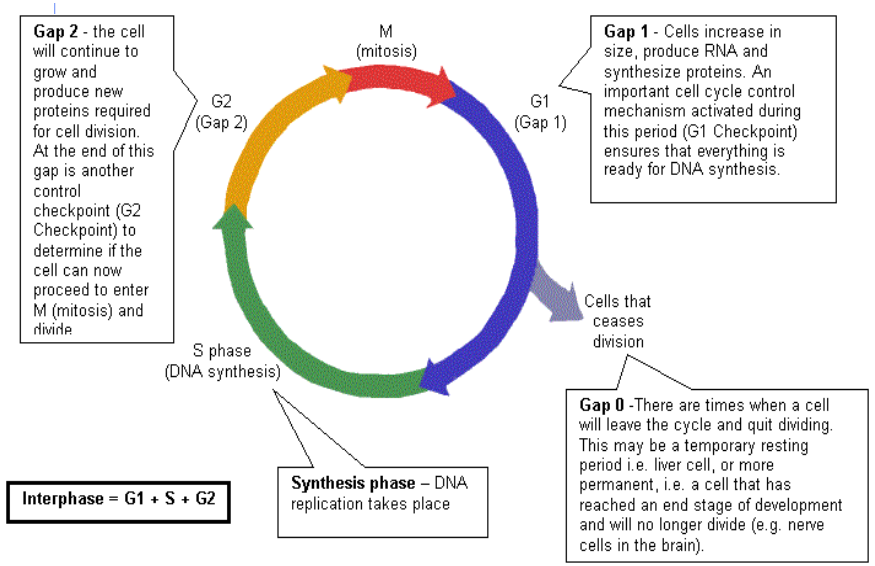
- APC/C adds a ubiquitin tag to the protein securin, sending it for recycling.
  - Without its inhibitor, separase enzyme activates.
    - Separase breaks down the cohesins holding sister chromatids together



Cyclin concentrations fluctuate *(genes are turned on to make cyclin based on the signals the cell receives).*

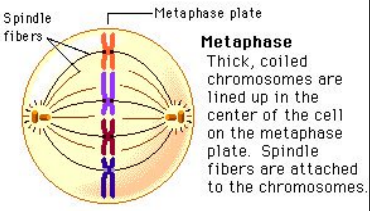


Review: Control of Cell Cycle



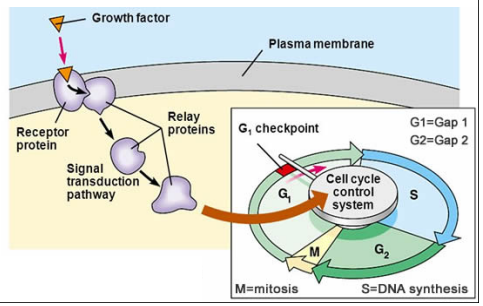
Remember, Internal & External signals control the cell cycle

- **Internal Signals control movement through checkpoints:**
  - Example: M Phase checkpoint
    - **Separation of sister chromatids does not begin until all chromosomes are properly attached to the spindle at the metaphase plate**
      - When all sister chromatics are attached to a kinetochore microtubule, proteins are activated (not Cdks in this case), which activate separase, which cleaves the cohesions holding the sister chromatids together.
  - Example of other checkpoints: S phase checkpoint has been found
    - Stops cells with DNA damage from proceeding the cell cycle
  - Example of other checkpoints: A new checkpoints between anaphase and telophase has been discovered in 2014
    - Ensures anaphase is completed and the chromosomes are well separated before cytokinesis begins, avoiding chromosomal damage



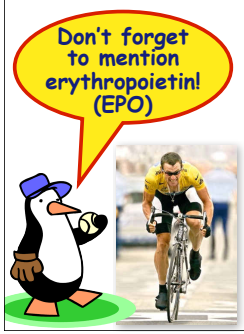
Remember, Internal & External signals control the cell cycle

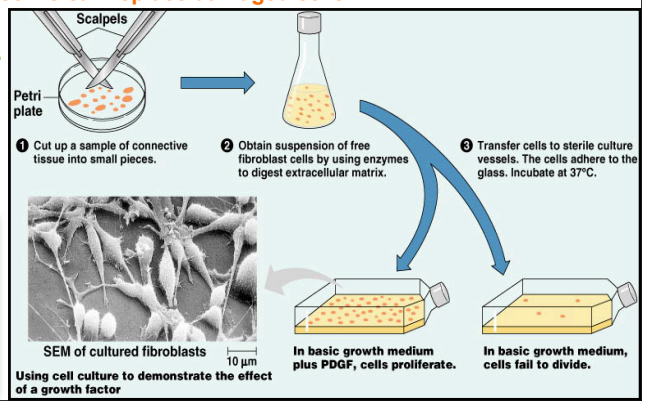
- **External Signals can be both Chemical & Physical:**
  - If necessary nutrient is lacking *[like glucose for Cellular Respiration or enough amino acids for additional protein synthesis]*, division does not occur
  - Most cells also need certain growth factors to divide
    - Growth factors: protein signals released by body cells that stimulate other cells to divide
      - The secretion of these signal molecules help cells coordinate activities
      - Different cell types respond specifically to different growth factor or combinations of growth factors



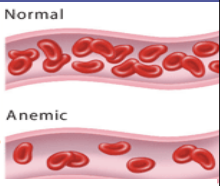
Example of a Growth Factor

- **Platelet Derived Growth Factor (PDGF)**
  - made by platelets that accumulate in plugs/blood "clots" used to plug areas where cells were damaged and are missing
    - Secreted when body is injured, causes proliferation (multiplication) of fibroblast cells that help heal wounds
    - binding of PDGF to cell receptors stimulates cell division in connective tissue cells so we can replace damaged cells
      - helps heals wounds

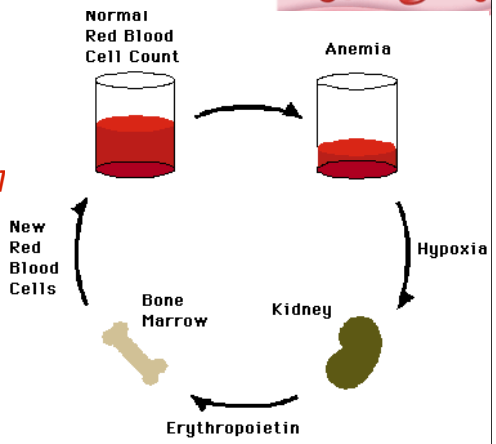




EPO - Just some interesting facts

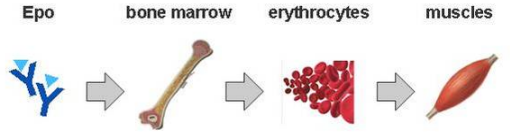


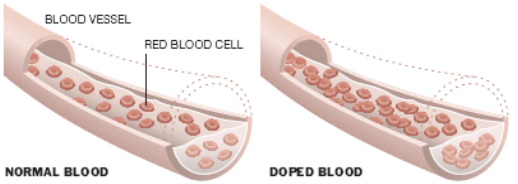
- **Erythropoietin (EPO):** A hormone produced by the kidney that promotes the formation of red blood cells in the bone marrow.
  - EPO is a glycoprotein (a protein with a sugar attached to it).
  - The kidney cells that make EPO are sensitive to low O_2 levels in the blood *[hypoxia]*
    - These cells release EPO when the oxygen level is low in the kidney [and, thus, body].
    - EPO then stimulates the bone marrow to produce more red cells via mitosis & thereby increase the oxygen-carrying capacity of the blood.



EPO & Illegal Blood Doping

- EPO has been much misused as a performance-enhancing drug (one form of "blood doping") in endurance athletes including some cyclists (in the Tour de France), long-distance runners, speed skaters, and Nordic (cross-country) skiers.
  - Extra Red Blood Cells [erythrocytes] allows an athlete to carry more O_2 to their muscle cells
  - When misused, EPO is thought to be especially dangerous
    - Perhaps because dehydration can further increase the viscosity of the blood, increasing the risk for heart attacks & strokes.
    - EPO has been banned by the Tour de France, the Olympics, and other sports organizations.

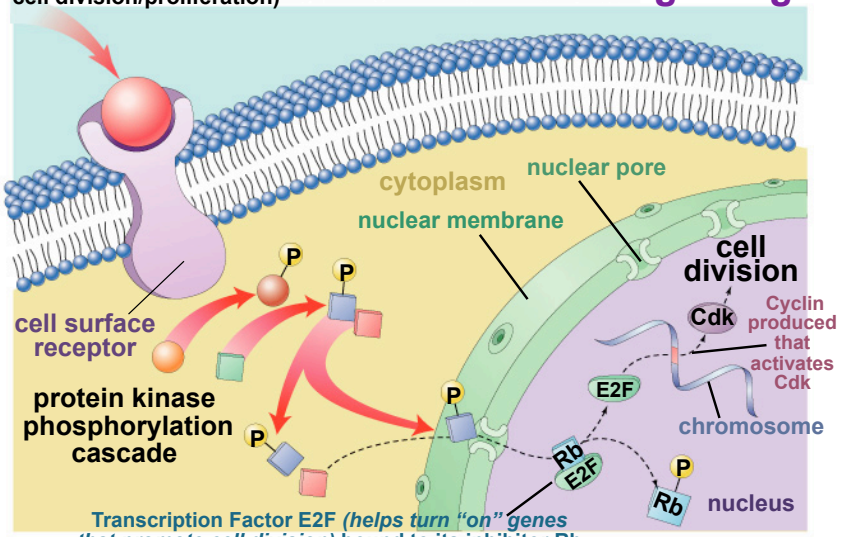




growth factor

(a ligand that stimulates cell division/proliferation)

Example of Growth Factor Signaling

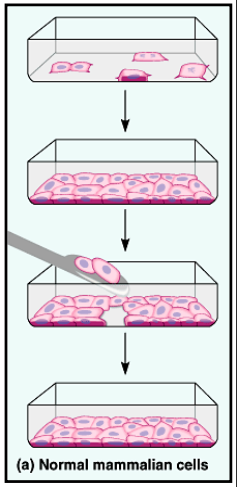


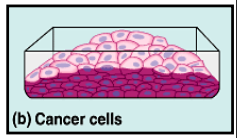
Transcription Factor E2F *(helps turn "on" genes that promote cell division)* bound to its inhibitor Rb

External Signals help coordinate cells

All normal cells exhibit:

1. density-dependent inhibition
   - normally, crowded cells stop dividing
     - cell-surface membrane proteins in one cell bind to cell-surface membrane proteins in a neighboring cell
       - plasma membrane protein interactions cause signal transduction cascades in both cell cytoplasms, preventing passage through the cell cycle in both cells
         - In cell cultures, cells divide normally till a single layer has form
         - If some cells are removed, the cells surrounding the space divide to fill the hole.
2. anchorage dependence
   - normally, cells must be attached to a substrate in order to divide
     - "touch sensor" receptors work



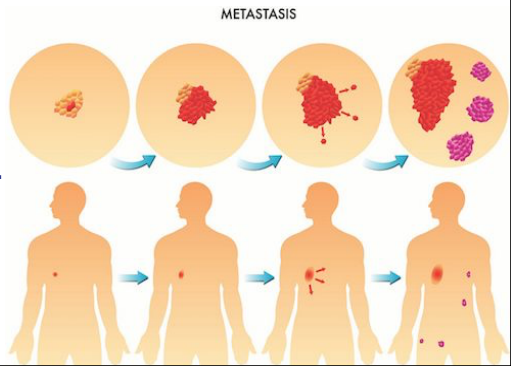


Cancer cells FAIL TO EXHIBIT these two properties!!! (Cells that can divide indefinitely - that have become cancer cells - are said to have undergone transformation)

Cancer Cells Move Through the Cell Cycle Even When They Should not

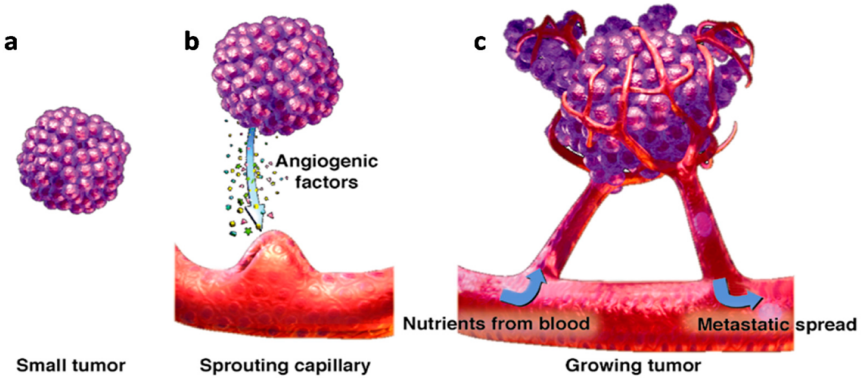
- Cancer cells also exhibit "replicative immortality."
  - They divide many more times than a normal cell of the body.
    - Unlike many cancer cells, human cells can go through only about 40-60 rounds of division before they lose the capacity to divide, "grow old," and eventually die.

- Due to the accumulation of key DNA mutations, cancer cells engage in activities that allow them to grow, divide, & spread.
  1. Cancer cells gain the ability to migrate to other parts of the body, a process called metastasis



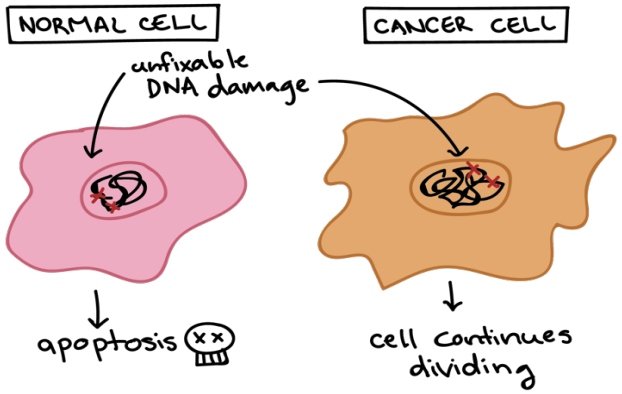
Due to the accumulation of key DNA mutations, cancer cells engage in activities that allow them to grow, divide, and spread.

2. Cancer cells secrete chemicals that promote growth of new blood vessels, a process called angiogenesis.
   - Cancer cells this way are provided with higher rates of oxygen and nutrients to maintain a faster metabolism



Due to the accumulation of key DNA mutations, cancer cells engage in activities that allow them to grow, divide, and spread.

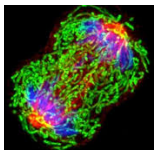
3. Cancer cells also fail to undergo apoptosis, programmed cell death, under conditions when normal cells would (e.g., due to certain types of DNA damage).



Growth/Promoting Factors & Cancer

- Cancers *(a disease of uncontrolled cell division)* occur when cell proceed through the cell cycle when they should not be.
  - Its development and progression are usually linked to a series of changes in the activity of cell cycle regulators.
    - These changes are often caused by DNA mutations in the genes that encode cell cycle regulator proteins.

- Failures occur in two areas:
  - Positive regulators may be activated inappropriately or overactive (become oncogenic).
  - Negative regulators (tumor suppressors) may be inactivated or not reactive enough.
    - Failures of "stop" signals/responses lead cells to divide uncontrollably if they are also simultaneously getting several "go" signals.



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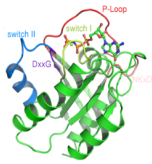
Growth/Promoting Factors & Cancer

- Various genes are involved in regulating division
  - Proto-oncogenes: Types of growth and promoter factor genes
    - Normally activate cell division by producing proteins that promote activities that relate to moving cells through the cell cycle
      - These proto-oncogenes get turned on, and thus certain proteins products are made, when the cell should divide.
    - When mutated, proto-oncogenes can become oncogenes (cancer-causing)!
      - If the gene is mutated or switched permanently "ON" (even in the absence of a signal to do so) cancer can result.



1. The cell may always produce mRNA and, thus, too much of certain protein growth or promoting factors
2. The cell may always produce defective receptors, internal relay proteins, or enzymes that keep promoting cell division in the absence of any signal to do so.

Example: When a proto-oncogene turns into an oncogene

- Proto-oncogenes encode...
  1. the EGFR receptor *(Epidermal Growth Factor Receptor)*
     - a category of receptor tyrosine kinase
  2. the Ras protein
     - a type of G protein - a guanosine-nucleotide-binding protein
  3. the signaling enzyme Raf
     - a type of kinase
- Together these proteins are part of a particular signal transduction cascade, that, when activated, causes certain genes to be expressed and the cell to undergo cell division.
  - The RAS protein is thus involved in signal transduction
    - Ras helps get a signal from outside the cell communicated to the nucleus.

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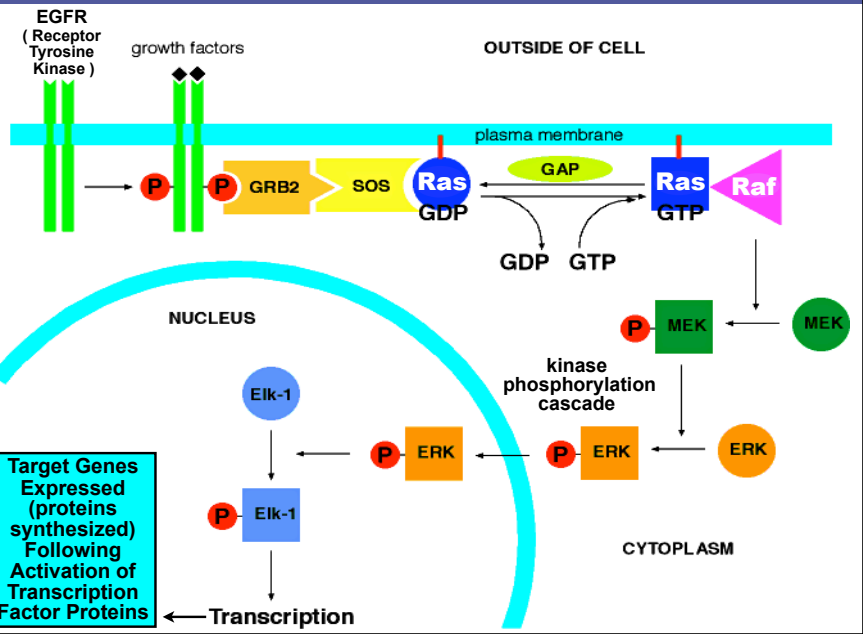
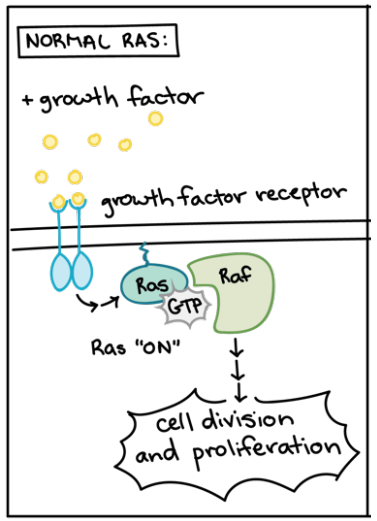


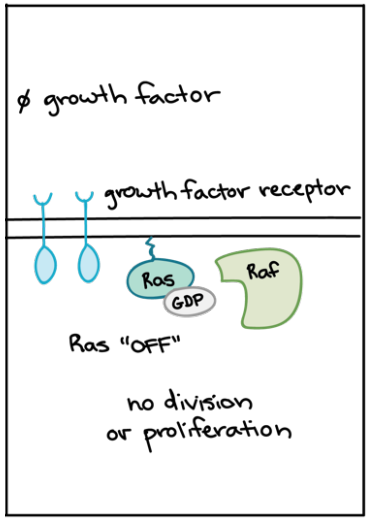
Example: When a proto-oncogene turns into an oncogene

- The Ras protein is thus involved in signal transduction
  - Ras is a G protein, meaning that it switches back and forth between an inactive form (bound to the small molecule GDP) and an active form (bound to the similar molecule GTP).
    - When growth factor (no ligand) is bound to the receptor, Ras protein should change into its active form.



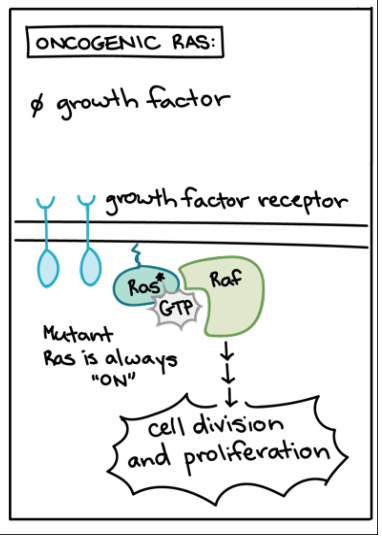
Example: When a proto-oncogene turns into an oncogene

- When no growth factor (no ligand) is bound to the receptor, Ras protein should be in the inactive form.
  - When inactive, Ras does not activate the Raf enzyme and the Raf enzyme does not activate a phosphorylation cascade
    - No signal is sent to the cell to begin activities related to preparing for or engaging in division.
      - The cell did not get the message to proceed through the cell cycle.

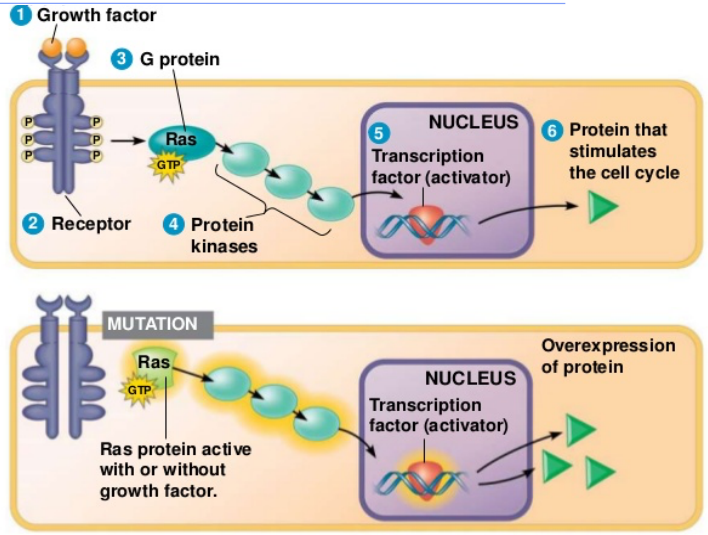


Example: When a proto-oncogene turns into an oncogene

- Ras should be produced in a controlled fashion in normal cells and/or should be able to activate signal transduction only when and if enough external growth factor has docked onto the cell receptor.
  - Mutations in the ras gene cause production of a defective version of Ras protein that is overactive, always in the "on" state or which takes much longer to switch off.
  - Mutations in the ras gene can permanently activate the gene, keeping it always "on," causing too much Ras protein to be produced.
    - Such changes can cause transmission of the message for the cell to divide even in the absence of extracellular signal (growth factor)



One Version of an Abnormal Ras Protein



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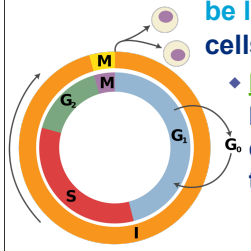
Positive & Negative Regulators Control the Cell Cycle

- Cdks, and their cyclins, and the APC/C are direct regulators of cell cycle transitions.
  - They get activated, moving the cell through the cell cycle, based on the consequences of signals from inside and outside the cell.
    - Positive signals, like Growth Factors, activate the production of cyclins and increase activity of Cdks, helping the cell move through the cell cycle
    - Negative signals, like DNA damage, by activating certain proteins, can decrease or block activities that cause a cell to move through the cell cycle.
  - The cell must also be able to halt progress through the cell cycle when the cell should not divide yet
    - Ex: DNA damage can occur in body cells due to UV rays from the sun.
      - Cells must be able to deal with this damage, fixing it if possible and preventing cell division if not.

Negative Regulator Errors & Cancer

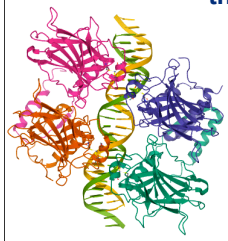
- Various genes are involved in regulating cell division
  - Failures in cell cycle regulation may lead to cancer
    - Just like positive regulators (proteins that help the cell move through the cell cycle) may be too active, negative regulators (proteins that stop the cell from moving through the cell cycle) of the cell cycle may be less active (or even nonfunctional) in cancer cells.



  - Ex. of Negative Regulator Failure: A protein that halts cell cycle progression in response to DNA damage may no longer sense damage or trigger the normal DNA repair or apoptosis response.
    - The cell may continue to move through the cell cycle and divide, passing these DNA errors on to daughter cells

Negative Regulator Errors & Cancer

- Tumor-Suppressor Genes: Genes that proteins that normally inhibits cell division by halting the cell from moving through the cell cycle
  - if switched "OFF" cancer can result
    - The cell would no longer produce a needed inhibitor to stop cell division or the cell from moving through the cell cycle.



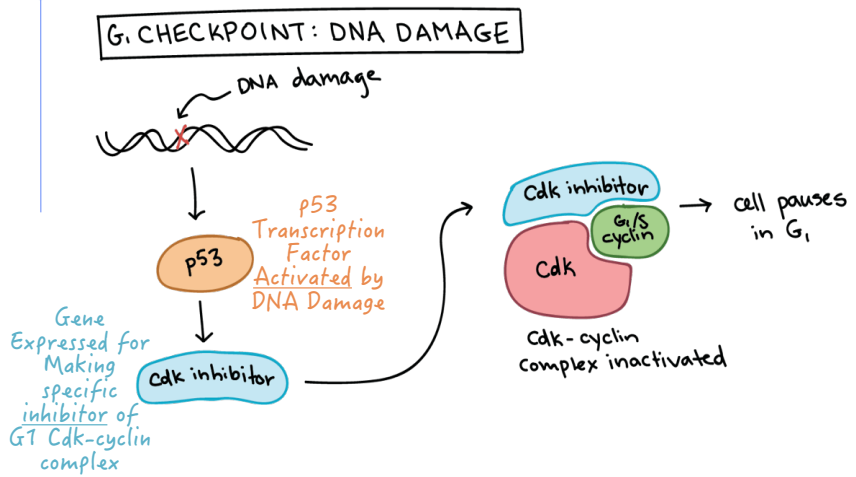
  - One of the most important tumor suppressors is protein p53, which plays a key role in the cellular response to DNA damage.
    - p53 acts primarily at the G1 checkpoint (controlling the G1 to S transition)
      - p 53 blocks cell cycle progression in response to damaged DNA and other unfavorable conditions

Example of Tumor Suppressor Gene: p53

- Gene p53 codes for a transcription factor, p53 protein *(a protein that helps turn on other genes)*
  - p53 protein activates three main anti-cancer mechanisms
    - Knows as the "Guardian Angel of the Cell"

1. When a cell's DNA is damaged, a sensor protein activates p53 protein, which will halt cell cycle progress
   - Activated p53 protein activates a gene that produces a Cdk inhibitor protein (CKI)
     - This inhibitor deactivates the G1 Cdk-Cyclin Complex, preventing progress of cell from G1 into S phase.
       - The cell, paused in G1, has time to repair the DNA damage the cell experienced in G1

P53 Protein Can Arrest Cell Cycle Progression

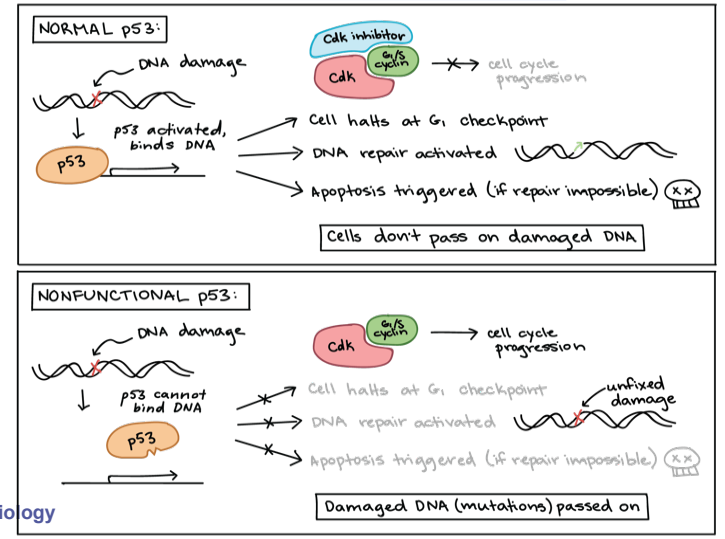


Example of Tumor Suppressor Gene: p53

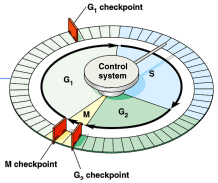
2. Activated p53 also activates DNA repair enzymes while the DNA is in G1, before the DNA is copied in S phase.
   - If DNA damage is fixed, p53 deactivates and the G1 Cdk-Cyclin will reactivate (once its inhibitor is released) and the cell will proceed through the cell cycle to S phase

3. If the DNA damage is not fixable, p53 remains active and helps activate the genes for making the caspase proteins needed to perform apoptosis (*programmed cell death*)
   - If cell dies, it cannot pass on the damaged DNA to daughter cells.
     - Daughter cells don't inherit potentially damaging DNA mutations
       - Mutations in oncogenes and tumor suppressor genes could result in a cell that is cancerous

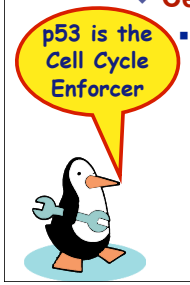
P53 Protein Can Activate DNA Repair & Apoptosis Too



Cancer & Cell Growth



- Cancer is essentially a failure of cell division control
  - unrestrained, uncontrolled cell growth
- What control is lost in cancerous cells?
  - Cells are getting checkpoint "go" signals
  - Cells have lost checkpoint "stop" signals



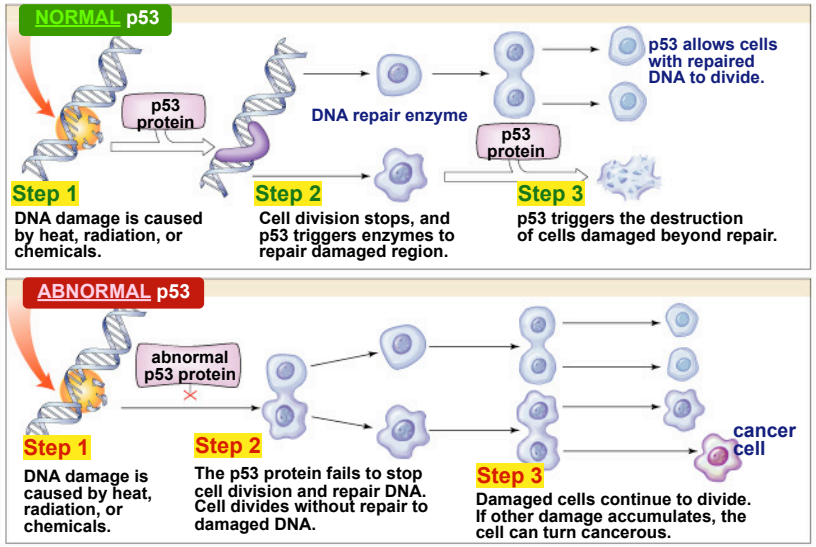
- In cancer cells, p53 is often missing, nonfunctional, or less active than normal!
  - For example, many cancerous tumors have a mutant form of p53 that can no longer bind DNA.
  - Since p53 acts by binding to target genes and activating their transcription, the non-binding mutant protein is unable to do its job

p53 discovered at Stony Brook by Dr. Arnold Levine

Cancer & Cell Growth

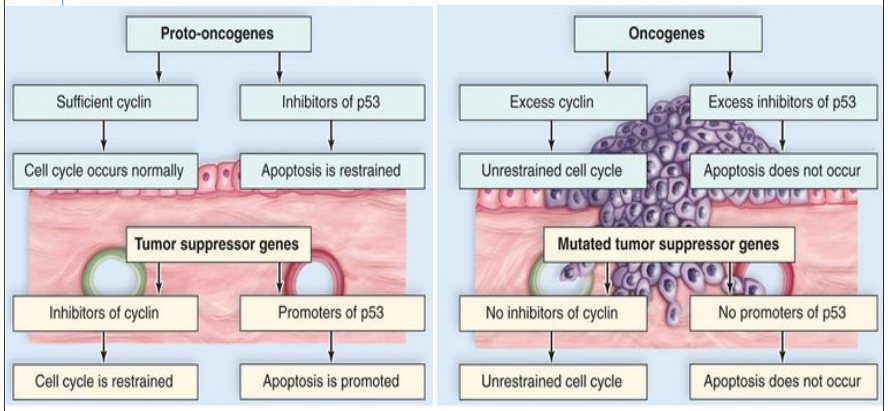
- Gene p53 plays a key role in G_1/S restriction point
  - p53 protein halts cell division if it detects damaged DNA
    - keeps cell in G_1 arrest - forces cell into G_0 resting stage
    - stimulates repair enzymes to fix DNA
    - causes apoptosis of damaged cell
- When p53 is defective, a cell with damaged DNA may proceed with cell division.
  - The daughter cells are likely to inherit mutations due to the un-repaired DNA of the mother cell.
    - Over generations, cells with faulty p53 tend to accumulate mutations, some of which may turn proto-oncogenes to oncogenes or inactivate other tumor suppressors.
      - p53 is the gene most commonly mutated in human cancers, and cancer cells without p53 mutations likely inactivate p53 through other mechanisms
        - Almost all cancer cells shut down p53 activity

p53 — master regulator gene



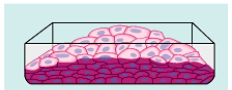
Examples of Failures of Cell Cycle Control

- Normal vs. Abnormal After Gene Mutation



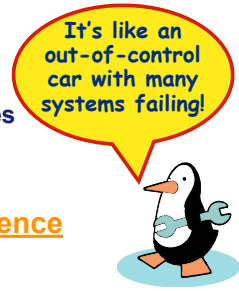
Development of Cancer

- 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



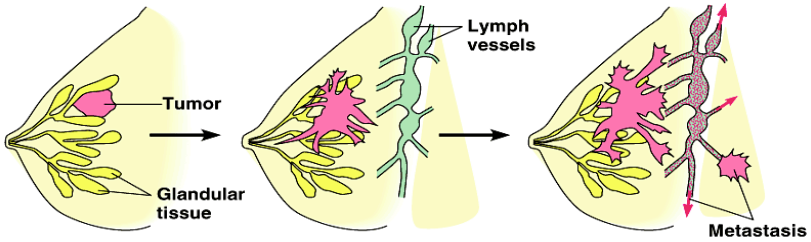
(b) Cancer cells

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

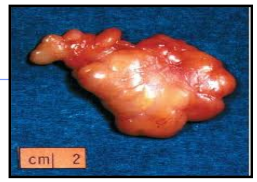


What causes these "hits"?

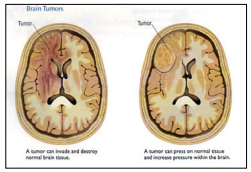
- Mutations in a cell's DNA can be caused by
  - UV radiation
  - chemical exposure *(mutagens or carcinogens)*
    - chemicals in cigarette smoke (vaping liquids?)
    - pollution
    - alcohol
  - viruses that damage DNA
  - radiation exposure
  - genetic inheritance
  - age *(some damage to DNA or errors when copying DNA will accumulate over time)*



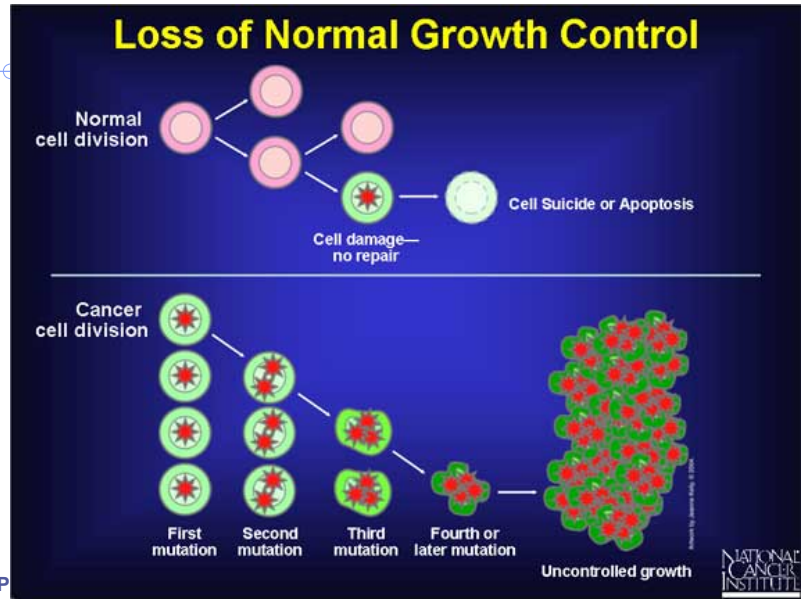
Tumors *(abnormal growth of body tissue)*



- **Benign tumor (Not Cancer)**
  - abnormal cells remain at original site as initial clump of cells
    - p53 still halts some cell division
      - Cell may still exhibits characteristics like anchorage dependence
  - most do not cause serious problems & can be removed by surgery



- **Malignant tumor (Cancer)**
  - cells leave original site
    - cells lose attachment to nearby cells
      - Cells no longer exhibit anchorage dependence
    - cells carried by blood & lymph system to other tissues
      - Cells can start creating tumors elsewhere in body = metastasis
  - tumors impair functions of organs throughout body
  - tumor cells with higher metabolisms use up the nutrients of healthy cells



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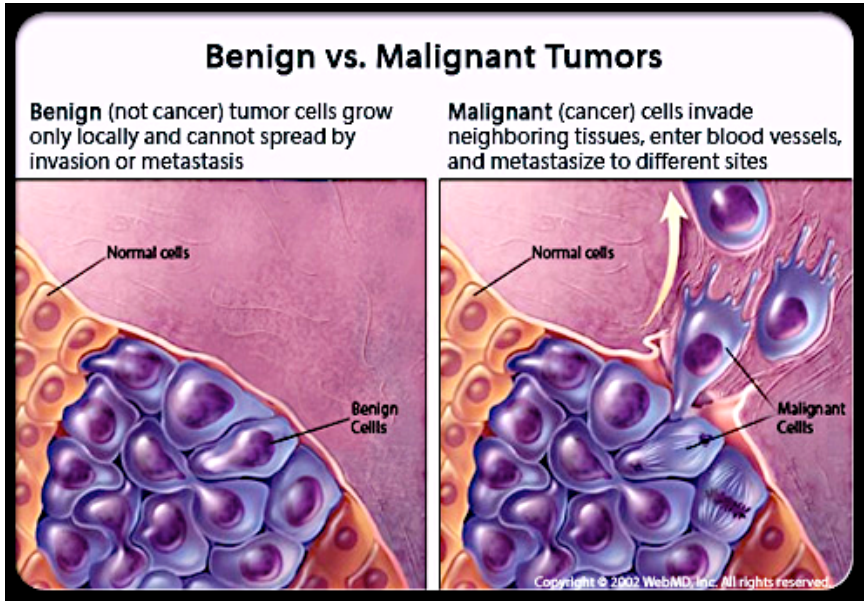
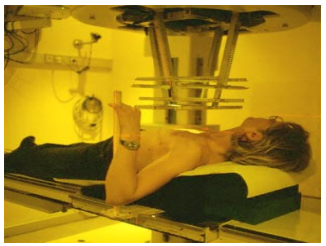


Traditional treatments for cancers

- **Treatments targets rapidly dividing cells**
  - high-energy radiation (to damage even further cell DNA)
    - kills rapidly dividing cells (when other necessary proteins can no longer be made)
  - chemotherapy
    - to damage DNA further
    - stop DNA replication
    - stop mitosis & cytokinesis
    - stop blood vessel growth *(angiogenesis)*



- Cell division may temporarily be halted in healthy cells too
- Some DNA damage may occur in healthy cells too

Newer "miracle drugs" Being Created

- **Goal: Design drugs that target malfunctioning proteins found only in cancer cells due to DNA mutations**
- **Gleevec (2001)**
  - **treatment for adult leukemia (CML) & stomach cancer (GIST)**
    - **In CML, the tyrosine kinase enzyme in white blood cells is locked in its activated form *[it has a distinct shape that is different from healthy tyrosine kinases in other cells due to cancer-causing DNA mutations].* This causes the excessive proliferation and high white blood cell count which is characteristic of CML.**
    - **Imatinib (Gleevec) binds to the site of tyrosine kinase activity and prevents its activity, eventually causing tumor cell death (apoptosis).**
  - **1st successful drug targeting cancer cells and not other healthy cells of the body**