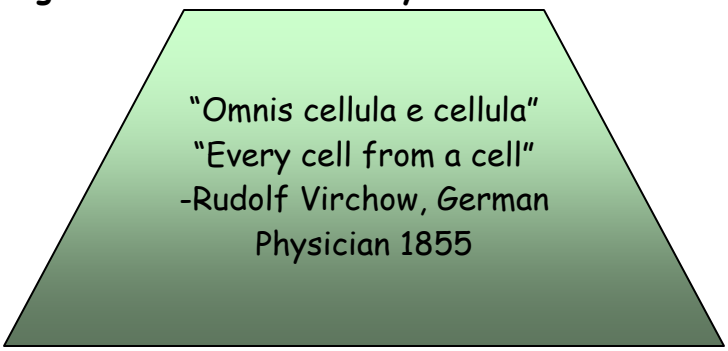
Lesson 2 Reading Material: "The Cell Cycle and Cancer"



MULTI-CELLULAR ORGANISMS

Living things are different from non-living things because they have the ability to reproduce their own kind. Plants can produce more plants. Birds can produce more birds. Humans can produce more humans. All of these organisms are multi-cellular organisms meaning that they are made up of more than one cell. Every cell in an organism contains the exact same genetic material called DNA that makes up an organism's genome. How does this genetic material get copied and distributed to daughter cells from one initial cell? A complex cycle, called the cell cycle is responsible for

1. using existing DNA to synthesis new DNA
2. checking the cell at various points called checkpoints to make sure that all process are being done without errors
3. dividing the cell once it has two copies of identical DNA into two daughter cells

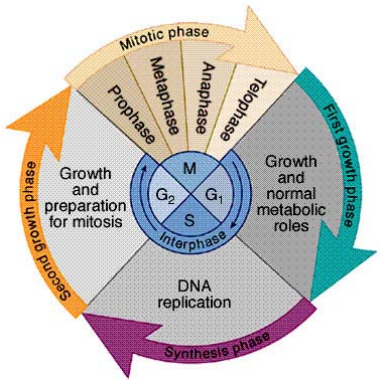
DNA AND CHROMOSOMES

DNA, your genetic material, codes for proteins that carry out a lot of functions in your cell. DNA has many nitrogenous bases linked in certain sequences, or genes, that code for specific proteins. Genes are units that specify and organism's inherited traits. How much DNA is in one human cell? Each human cell contains about 3 meters of DNA. That is a lot of genetic material that needs to be copied every time a cell divides. Luckily, our DNA is packaged into chromosomes. Chromosomes are threadlike, gene-carrying

structures that are found in the nucleus. Think of them as one very long string of DNA all packaged up with proteins that help stabilize their structure and carry out certain functions associated with replication. Human somatic cells contain 46 chromosomes. Somatic cells are all cells in the body except reproductive cells. Once a chromosome is duplicated, it contains two sister chromatids. Each chromatid is identical to each other and attached in the middle by their centromeres. During a process called mitosis, the sister chromatids are pulled apart and end up in two identical daughter cells.

THE CELL CYCLE:

The timing and rate of cell division in different parts of a plant or animal are crucial to normal growth, development and maintenance of an organism. The number of times a cell divides is dependent on the cell. For example, your skin cells divide frequently, whereas the cells in your liver only divide if they need to repair a wound. The decision of a cell to cycle or not to cycle is dependent upon molecular regulation. This regulation is often disrupted in cancer cells allowing them to grow out of control. It is important to understand how the cell cycle functions normally, in order for us to determine how cancer cells escape this controlled division.



http://www.bmb.psu.edu/courses/biotc489/notes/cycle.jpg

The cell cycle is divided into four different phases:

Interphase
- G1: Gap 1 phase where the cell increases in size and prepares to synthesize DNA
- S: Synthesis phase where DNA is synthesized
- G2: Gap 2 phase where the cells prepares for mitosis

M: Mitosis phase where the enlarged parent cell finally divides in half to produce its two daughter cells, each of which contains identical and complete set of chromosomes.

The passage of a cell through the cell cycle is controlled by proteins in the cytoplasm. Among the main players in animal cells are:

Cyclins

G_1 cyclin (cyclin D)
S-phase cyclins (cyclins E and A)
Mitotic cyclins (cyclins B and A)

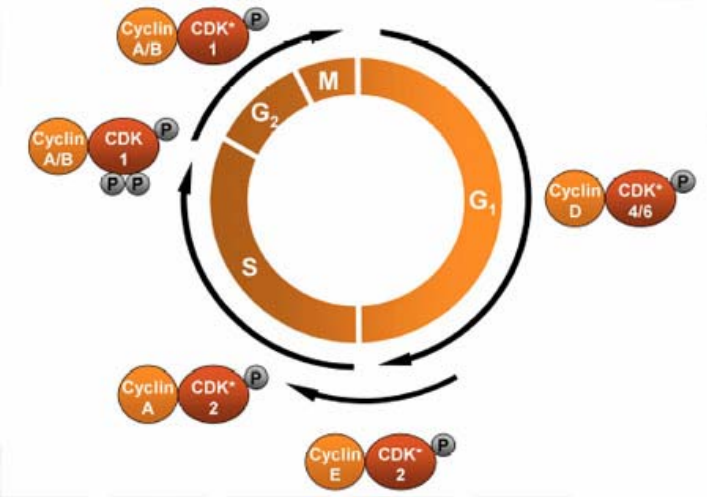
Their levels in the cell rise and fall with the stages of the cell cycle.

Cyclin-dependent kinases (Cdks)

G_1 Cdk (Cdk4)
S-phase Cdk (Cdk2)
M-phase Cdk (Cdk1)

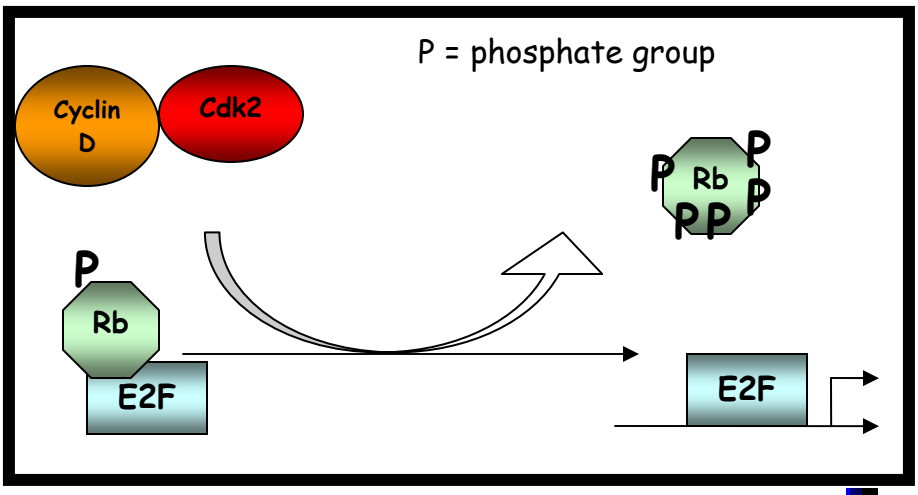
-Their levels in the cell remain fairly stable, but each must bind the appropriate cyclin (whose levels fluctuate) in order to be activated.

-They add phosphate groups to a variety of protein substrates that control processes in the cell cycle.



http://www.chemie.unikl.de/fachrichtungen/lmctox/eisenbra/forschung/cyclin.jpg

STEPS IN THE CELL CYCLE:



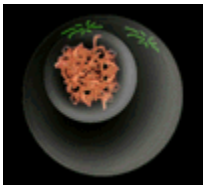
Once a daughter cell exits mitosis, it has the choice of starting in the cell cycle all over again by entering G1 or it can enter a resting state called G0. Once the cell enters G1, there is a rise in a protein called Cyclins, in this case, Cyclin D. Also in the cells are cyclin-dependent kinases (CDKS). These are enzymes that exist in the cell at a constant level, but are inactive until they complexed with cyclins. This is why they are called cyclin-dependent kinases. They are dependent upon cyclins for their activity. Once Cdk4 or Cdk6 are active by binding to cyclin D, they are able to phosphorylate (add phosphate groups) to a protein called Rb. When Rb is hypophosphorylated (under-phosphorylated), it is complexed with a protein called E2F. E2F is a transcription factor, meaning it helps transcribe genes (make RNA from DNA). When Rb is bound to E2F, E2F is unable to perform its function, which is to help transcribe genes that are necessary for the cells to transition into S phase. When the Cdks hyper-phosphorylate Rb (over-phosphorylated) Rb is no longer able to bind E2F, and the free E2F can transcribe genes that are necessary for the G1 to S phase transition. One of the genes that E2F helps transcribe is cyclin E and cyclin A. CyclinE/A, complexed with Cdk2 drives the cell into the S phase of the cell cycle.

Cyclin A/Cdk2 enter the nucleus and prepares the cell to duplicate its DNA into two copies. As DNA replication continues, cyclin E is destroyed and the level of mitotic cyclins and cdks being to rise. Once in G2, the cell continues to grow in size and prepare for mitosis. Mitotic cyclins (cyclin B and cyclin A) complexed with cdk1 initiates the cells to: 1. assemble the mitotic spindle; 2. breakdown the nuclear envelope and 3. condense the chromosomes.

Mitosis:

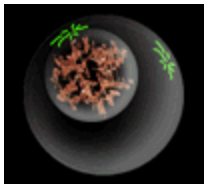
Mitosis is nuclear division plus cytokinesis, and produces two identical daughter cells during prophase, prometaphase, metaphase, anaphase, and t elophase. Interphase is often included in discussions of mitosis, but interphase is technically not part of mitosis, but rather encompasses stages G1, S, and G2 of the cell cycle.

Interphase: (remember interphase includes G1, S, and G2M phases)



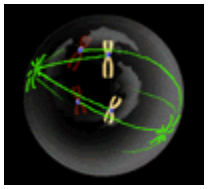
The cell is engaged in metabolic activity and performing its prepare for mitosis (the next four phases that lead up to and include nuclear division). Chromosomes are not clearly discerned in the nucleus, although a dark spot called the nucleolus may be visible. The cell may contain a pair of centrioles (or microtubule organizing centers in plants) both of which are organizational sites for microtubules.

Prophase



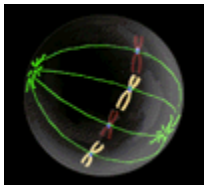
Chromatin in the nucleus begins to condense and becomes visible in the light microscope as chromosomes. The nucleolus disappears. Centrioles begin moving to opposite ends of the cell and fibers extend from the centromeres. Some fibers cross the cell to form the mitotic spindle.

Prometaphase



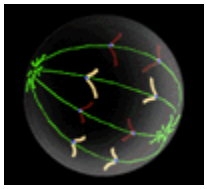
The nuclear membrane dissolves, marking the beginning of prometaphase. Proteins attach to the centromeres creating the kinetochores. Microtubules attach at the kinetochores and the chromosomes begin moving.

Metaphase



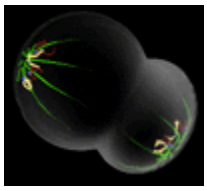
Spindle fibers align the chromosomes along the middle of the cell nucleus. This line is referred to as the metaphase plate. This organization helps to ensure that in the next phase, when the chromosomes are separated, each new nucleus will receive one copy of each chromosome.

Anaphase



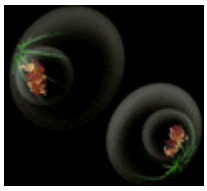
The paired chromosomes separate at the kinetochores and move to opposite sides of the cell. Motion results from a combination of kinetochore movement along the spindle microtubules and through the physical interaction of polar microtubules.

Telophase



Chromatids arrive at opposite poles of cell, and new membranes form around the daughter nuclei. The chromosomes disperse and are no longer visible under the light microscope. The spindle fibers disperse, and cytokinesis or the partitioning of the cell may also begin during this stage.

Cytokinesis



In animal cells, cytokinesis results when a fiber ring composed of a protein called actin around the center of the cell contracts pinching the cell into two daughter cells, each with one nucleus.

Mitosis pictures and information from:
http://www.biology.arizona.edu/cell_bio/tutorials/cell_cycle/cells3.html
Go to this website for an animation of mitosis.

CHECKPOINTS AND RESTRICTION POINTS

A checkpoint in the cell cycle is a critical control point where signals will tell the cell to go ahead and progress forwards or stop because there is a mistake of some kind. There are three checkpoints, one in G1, G2 and M phase. One cell produces two and your entire genome is duplicated and separated during this event. Therefore it is very important that everything gets checked properly at different points in the cell cycle to make sure no mistakes are made. If mistakes are made, and not caught, they will get inherited into every daughter cell thereafter.

Cell cycle progression is monitored by surveillance mechanisms, or cell cycle checkpoints, that ensure initiation of a later event is coupled to the completion of an early cell cycle event. For example, a cell will not enter mitosis until it completes DNA replication. Thus, checkpoint mechanisms ensure the integrity of the genome and the fidelity of chromosome separation through ordered execution of cell cycle events. Inactivation of cell cycle checkpoints is a major cause of genomic instability and cancer in cells.

Restriction point: The restriction point is found at the end of G1. The cells must is checked for two things: 1) cell size- the cell must be big enough to start synthesis of DNA and 2) no damage in the genetic material; if DNA is damaged, the cell will not progress to S phase. In cancer cells, this restriction point is often abnormal, allowing damaged DNA to be replicated and passed to daughter cells. This is how mutations get from one cell to the next. If it is a mutation in a gene that normally controls growth, then the cell will not have normal regulation of growth.

Cell Cycle Checkpoints

Two major checkpoints function in mitosis, one at entry into mitosis (G2/M checkpoint) and the other at the metaphase to anaphase transition (metaphase checkpoint).

The G2/M checkpoint functions as cells enter mitosis. It monitors microtubule-dependent events, such as separation of duplicated centrosomes at G2, and delays the G2/M transition in the presence of microtubule

poisoners. Thus, this checkpoint determines the timing of mitotic entry and ensures a productive mitosis.

The metaphase checkpoint monitors the attachment of the mitotic spindle to kinetochores and the tension generated by mitotic spindle attachment. In the presence of a single unattached kinetochore, the metaphase checkpoint halts the separation of sister chromatids and thereby provides additional time for spindle attachment. Thus, the metaphase checkpoint ensures a high fidelity of chromosome separation and prevents aneuploidy during mitosis.

Resting State: G0

Many times a cell will leave the cell cycle, temporarily or permanently. It exits the cell cycle at G1 and enters a stage called G0. Cells in G0 are called "quiescent" cells. Cells that are quiescent are still alive and producing secreted molecules and attacking pathogens in the immune system, they are just not dividing into daughter cells.
Cells in G0 may never reenter the cell cycle and will eventually die, or they can reenter the cell cycle depending on if the cell receives the signal to enter G1 (the signal is usually growth factors)

Lesson 2 Activity: The Cell Cycle and Cancer

Activity 1: Making a cell cycle

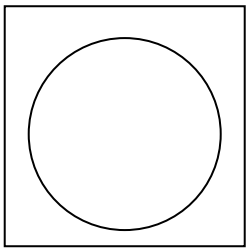
The student will need:

Cardboard or Posterboard
Brass Fasteners (shown below)

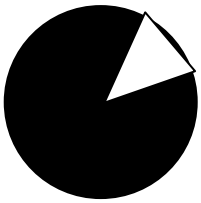
Scissors
Markers (all different colors)

The objective of this activity have students make their own cell cycle model. Two pieces of board will be fasten together by punching a hole in the center of each and placing a brass fastener through them.

The board on top will have a portion of it cut out in pie form.



Bottom



Top

The bottom board will be cut into a square and a circle should be drawn in the center. The student can then divide the circle up as he/she sees fit into sections, G1, S, G2, and M for each phase of the cell cycle. The student can divide it up using a marker. Within each section, the student should describe the events that take place, in the right order, clearly marking restriction points, checkpoints and various requirements for a cell to continue on to the next phase. These should all be in one color. In a different color, have the student identify which parts of the cell cycle can be prone to abnormal regulation during the onset of cancer. All of this information should be in the circle of the bottom piece. After they have completed this, they can attach the top piece on to the bottom board with the brass fastener and they have their very own cell cycle. As the top piece

spins around, it will reveal various parts of the cell cycle and the cell progresses.

If the students have space, encourage them to draw pictures, pathways, etc. Drawings of synthesis of DNA in S phase can be done, or what the DNA looks like in prophase, anaphase, metaphase and telophase of mitosis. These are just a few of examples of how they can be creative with the project and make it their own.

Lesson 2 Activity: The Cell Cycle and Cancer continued

Activity 2: News Report on the Cell Cycle or Tour of the Cell Cycle

The objective of this activity is to allow the students to have fun pretending, either that cancer is a convict that is breaching all phases of the cell cycle in a breaking news report, or that they are giving a tour of the cell cycle.

Allow the students to decide whether they would like to give a news report, or pretend they are giving a VIP tour of the cell cycle.

NEWS REPORT:

1. Divide the classroom into the different phases of the cell cycle, G1, S, G2, M by making signs, or putting masking tape on the floor, protruding outward from the center of the room, to make "pies".

2. Split students up into their groups from Lesson I Activity.

3. Give the students some class time and time at home to come up with creative ideas for this product.

4. The students should come up with clever ways of making a news report on the cell cycle and how it goes awry in cancer.

5. One student each could be a news reporter in each phase of the cell cycle and perhaps two as the reporters in the studio. Each student would give a report of what is going on at their location (or phase).

6. For example, the student in G1, would act as a field reporter and describe what G1 is normally like, and how cancer might have breached the restriction point and has fled to the S phase of the cell cycle. Each reporter will take turns describing what is going on.

The students can choose how to do the news report as long as their presentation includes what goes on in the cell cycle and what goes wrong in cancer.

CELL CYCLE TOUR:

"Welcome, to the fabulous new Cell Cycle Museum. I will be _____, your tour guide. Feel free at any time to interrupt me and ask me questions at any time."

1. Have the students come up with a way to pretend that they are giving a tour through the cell cycle as they walk through the classroom and the other students watch.

2. The students can pretend all of them are different tour guides of each phase of the cell cycle, or one student can be the main tour guide the entire time. The student can use their imagination and pretend they are cyclins/Cdks or other molecular players in the cell cycle. It is up to them, as long as they come up with displaying how cells cycle and how cancer cells are abnormally cycling.

Lesson 2 Problem Set: "Cell Cycle and Cancer"

Multiiple Choice:

1. In which stage of the cell cycle is each chromosome composed of two chromatids in preparation for mitosis?

A. G1
B. S
C. G2
D. M

2. CDKs increase their enzymatic activity by complexing with:

A. Rb
B. Cyclins
C. E2F transcription factors
D. All of the above

3. Vinblastine is a drug used to treat cancer, since it is known to stop the cell cycle. The drug interferes with the assembly of microtubules, and therefore its effectiveness must be related to:

A. disruption of mitotic spindle formation
B. inhibition of regulatory protein phosphorylation.
C. suppression of cyclin production.
D. inhibition of DNA synthesis.

Short Answer:

1. Describe what a checkpoint is and why it is important in preventing cancer cells from arising.

2. What is G0?

3. Describe the function of a kinase. What specific kinases regulate the cell cycle?

4. What are histones? How do they appear under an electron microscope?

5. What is the difference between chromosomes and chromatids?

6. If a researcher treated a cancer cell that prevented it from synthesizing DNA. What stage of the cell cycle would the cell be trapped in? Explain.

True/False: Determine whether the following statements are true or false. If you choose false, please explain why part or all of the statement is incorrect.

1. The stage in which cells are preparing for DNA replication is in S phase.

2. The first stage in which chromosomes become visible in mitosis is called anaphase.

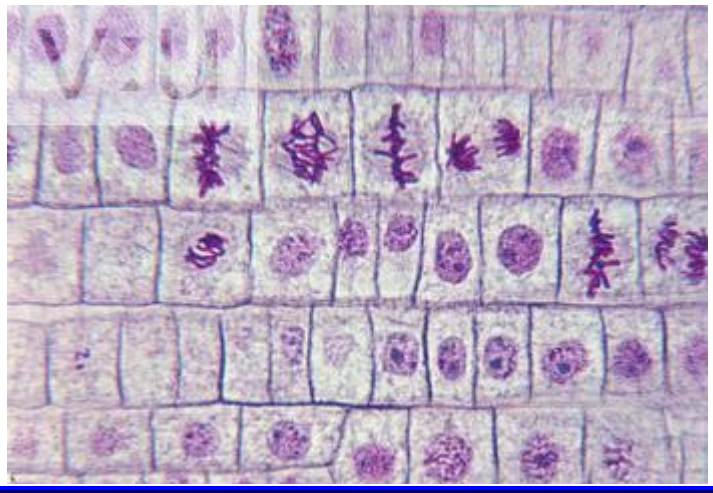
3. Cancer cells are different from normal cells, in that, they have escaped cell cycle control.

4. Cells in G0 will eventually die.

5. Interphase is a phase in mitosis:

Below are pictures taken of cells from an onion root tip. Please identify one cell that is in:

A: Prophase
B: Metaphase
C: Anaphase
D: Telophase



Lesson II Problem Set: "Cell Cycle and Cancer"

Teacher's Answers

Multiiple Choice:

1. In which stage of the cell cycle is each chromosome composed of two chromatids in preparation for mitosis?

A. G1
B. S
C. G2
D. M

A: G2; S phase resulted in the duplication of each chromatid. Since there is only one centromere on the sister chromatids, we still call them one chromosome. When completed, the cells are in G2 and preparing for M.

2. CDKs increase their enzymatic activity by complexing with:

A. Rb
B. Cyclins
C. E2F transcription factors
D. All of the above

A: Cyclins. CDKs or cyclin-dependent kinases do just that—they depend on cyclins for enzymatic activity. Once they are complexed with cyclins, and therefore active, they can phosphorylate their targets.

3. Vinblastine is a drug used to treat cancer, since it is known to stop the cell cycle. The drug interferes with the assembly of microtubules, and therefore its effectiveness must be related to:

A. disruption of mitotic spindle formation
B. inhibition of regulatory protein phosphorylation.
C. suppression of cyclin production.
D. inhibition of DNA synthesis.

A: A. Vinblastine disrupts the mitotic spindle formation by interfering with microtubule assembly.

Short Answer:

1. Describe what a checkpoint is and why it is important in preventing cancer cells from arising.

A: Checkpoints are surveillance mechanisms within the cell, throughout the cell cycle. At the checkpoints, the cell checks for various requirements necessary for progression through the cell cycle, and if the cell does not meet the requirements, it does not proceed to the next phase. If checkpoints become defective, a cell will proceed through the cell cycle without control and possibly with errors. If those errors are within the DNA causing mutations, those mutations will be allowed to be passed on to the next generation of cells.

2. What is G0?

A: G0 is a resting state for cells. Cells that exit mitosis can either continue to G1 to divide again, or they can exit the cell cycle temporarily or permanently in G0. G0 cells are still alive, but not dividing.

3. Describe the function of a kinase. What specific kinases regulate the cell cycle?

A: Kinases add phosphate to molecules, and the modification can serve as a "switch" to turn events in the cell on or off. Cdk or cyclin dependent kinases regulate the cell cycle.

4. What are histones? How do they appear under an electron microscope?

A: The histones form structural complexes with DNA. In the electron microscope, these can take the appearance of beads on a string.

5. What is the difference between chromosomes and chromatids?

A: Chromatids are each of a pair of identical DNA molecules after DNA replication, joined at the centromere. Chromosomes are molecules of DNA complexed with specific proteins responsible in eukaryotes for storage and transmission of genetic information.

6. If a researcher treated a cancer cell that prevented it from synthesizing DNA. What stage of the cell cycle would the cell be trapped in? Explain.

A: G1; During G1, the cells prepare for replication of DNA. During S phase, the cells will proceed by actually replicating the DNA. If the replication of DNA is prevented, the cells would be stuck in G1.

True/False:

1. The stage in which cells are preparing for DNA replication is in S phase.

A: False; In S phase, DNA is being replicated. In G1 is when the cells are preparing for replication.

2. The first stage in which chromosomes become visible in mitosis is called anaphase.

A: False; Chromosomes are condensed and visible during prophase in mitosis.

3. Cancer cells are different from normal cells, in that, they have escaped cell cycle control.

A: True

4. Cells in G0 will eventually die.

A: False: Cells in G0 may stay there and eventually die, or they can reenter the cell cycle.

5. Interphase is a phase in mitosis:

A: False: Interphase encompases G1, S, and G2 phases of the cell cycle. Mitosis includes prophase, anaphase, metaphase, and telophase.