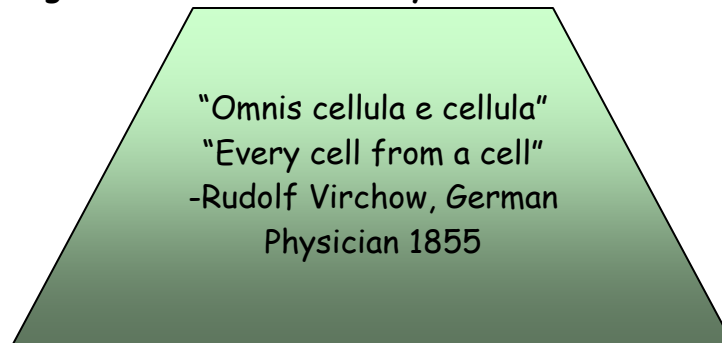


## Lesson 2 Reading Material: "The Cell Cycle and Cancer"



### **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**

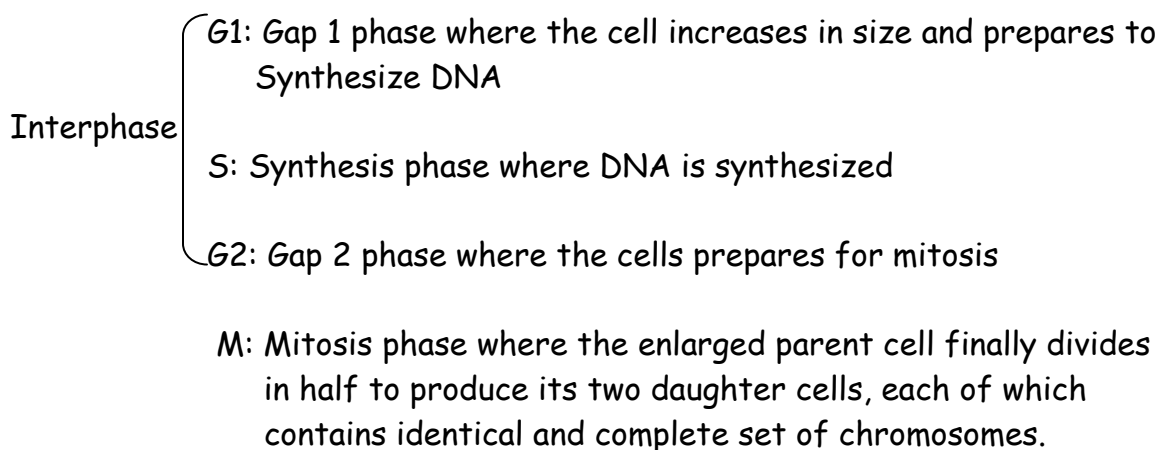
DNA, your genetic material, codes for proteins that carry out a lot of functions in your cell. DNA has many nitrogenous bases linked in certain sequences, or genes, that code for specific proteins. Genes are units that specify and organism's inherited traits. How much DNA is in one human cell? Each human 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.

The cell cycle is divided into four different phases:



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.

### **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  $G_1$  or it can enter a resting state called  $G_0$ . Once the cell enters  $G_1$ , 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 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 Cdk2 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 cdk2 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
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.

## 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 be 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 G<sub>2</sub>, and delays the G<sub>2</sub>/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: G<sub>0</sub>**

Many times a cell will leave the cell cycle, temporarily or permanently. It exits the cell cycle at G<sub>1</sub> and enters a stage called G<sub>0</sub>. Cells in G<sub>0</sub> 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 G<sub>0</sub> 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 G<sub>1</sub> (the signal is usually growth factors)