BIOLOGY OF CANCER

Cancer is disease characterized by uncontrolled cell growth. Although there are many different types of cancer, and the causes vary widely, most cancers are a result of a cell accumulating mutations that ultimately cause a loss of control over the cell cycle.

Characteristics of Cancer Cells

Although the effects of cancer are often noticed at the tissue, organ, or organismal level, cancer is ultimately a cellular disease. Despite the large number of different cancer types, cancer cells share general traits that distinguish them from normal cells.

1) Lack of Differentiation

- **Differentiation** is the process of cellular development by which a cell acquires a specific structure and function.
- Red blood cells are examples of differentiated cells in the circulatory system.
- In comparison, cancer cells are nonspecialized and do not contribute to the functioning of a body part.
- A cancer cell does not look like a differentiated epithelial, muscle, nervous, or connective tissue cell. Instead, it looks distinctly abnormal.

2) Abnormal Nuclei

- The nuclei of cancer cells are enlarged and may contain an abnormal number of chromosomes.
- In addition to nuclear abnormalities, cancer cells often have chromosomal mutations. Some portions of the chromosomes may be duplicated, and/or some may be deleted.
- In addition, gene amplification (extra copies of specific genes) is seen much more frequently than in normal cells.
- Ordinarily, cells with damaged DNA undergo **apoptosis**. Cancer cells fail to undergo apoptosis, even though they are abnormal cells.

- Tissues that divide frequently, such as those that line the respiratory and digestive tracts, are more likely to become cancerous. Cell division gives them the opportunity to undergo genetic mutations, each one making the cell more abnormal and giving it the ability to produce more of its own type.

3) Unlimited Replication Potential

- Ordinarily cells divide about **60 to 70 times** and then just stop dividing and eventually undergo apoptosis.
- Cancer cells are immortal and keep on dividing for an unlimited number of times.
- Recall that human chromosomes end with special repetitive DNA sequences called **telomeres.** Specific proteins bind to telomeres in both normal and cancerous cells.
- These telomere proteins protect the ends of chromosomes from DNA repair enzymes. Though the enzymes effectively repair DNA in the center of the chromosome, they always tend to bind together the naked ends of chromosomes.
- In a normal cell, the telomeres get shorter after each cell cycle and protective telomere proteins gradually decrease. In turn, repair enzymes eventually cause the chromosomes' ends to bind together, causing the cell to undergo apoptosis.
- **Telomerase** is an enzyme that can rebuild telomere sequences and, in that way, prevent a cell from ever losing its potential to divide.
- The gene that codes for telomerase is constantly turned on in cancer cells, and telomeres are continuously rebuilt. The telomeres remain at a constant length, and the cell can keep dividing over and over.

4) Tumours Formation

- Normal cells anchor themselves to a substratum and/or adhere to their neighbours.
- They exhibit ***contact inhibition***, meaning that when they come in contact with a neighbour, they stop dividing.

- Cancer cells have lost all restraint. They pile on top of one another and grow in multiple layers, forming a **tumour.** As cancer develops, the most aggressive cell becomes the dominant cell of the tumour.

5) Disregard of Growth Factors

- **Growth factors** are chemical signals between cells that tell them whether or not they should be dividing.
- These chemical signals are of two types: **stimulatory growth factors** and **inhibitory growth factors**.
- Cancer cells keep on dividing even when stimulatory growth factors are absent, and they do not respond to inhibitory growth factors.

6) Cancer Cells Gradually Become Abnormal

- **Carcinogenesis** is a multistage process that result in the development of cancer and can be divided into three phases:
  - ***Initiation:*** A single cell undergoes a mutation that causes it to begin to divide repeatedly.
  - ***Promotion:*** A tumor develops, and the tumor cells continue to divide. As they divide, they undergo mutations.
  - ***Progression:*** One cell undergoes a mutation that gives it a selective advantage over the other cells. This process is repeated several times; eventually there is a cell that has the ability to invade surrounding tissues.

7) Angiogenesis and Metastasis

- To grow larger than about a billion cells (about the size of a pea), a tumor must have a well-developed capillary network to bring it nutrients and oxygen.
- **Angiogenesis** is the formation of new blood vessels.
- Due to mutations, cancer cells tend to be motile. They have a disorganized internal cytoskeleton and lack intact actin filament bundles.

- To metastasize, cancer cells must make their way across the basement membrane and invade a blood vessel or lymphatic vessel.
- Invasive cancer cells are abnormally shaped and don't look at all like normal cells nearby.
- Cancer cells produce **proteinase** enzymes that degrade the basement membrane and allow them to invade underlying tissues.
- Malignancy occurs when cancer cells are found in nearby lymph nodes.
- When these cells begin new tumors far from the primary tumor, **metastasis** has occurred.
- Not many (maybe 1 in 10,000) cancer cells achieve this ability, but those that successfully metastasize to various parts of the body lower the prognosis (the predicted outcome of the disease) for recovery.

Correlation between Gene Mutation & Cancer Development

- Recall that the cell cycle consists of interphase, followed by mitosis. **Checkpoints** in the cell cycle monitor the condition of the cell and regulate its ability to divide. Normally, a protein called **cyclin** directs the movement of a cell through the cell cycle.
- At each checkpoint specific factors, such as DNA damage, are assessed by checkpoint proteins. However, mutations in these checkpoint proteins cause the cell to lose control of the cell cycle, resulting in cancer.
- The two classes of checkpoint proteins are as follows:
  1) **Proto-oncogenes** code for proteins that promote the cell cycle and prevent apoptosis.
  2) **Tumor suppressor genes** code for proteins that inhibit the cell cycle and promote apoptosis.

Mutation of Proto-Oncogenes

- When proto-oncogenes mutate, they become cancer-causing genes called **oncogenes.** These mutations can be called “gain-of function,” or dominant, mutations. Even though we possess two copies of each proto-oncogene, only one must be mutated to lose control of the cell cycle.
- Some proto-oncogenes code for a growth factor or for a receptor protein that receives a growth factor. When these proto-oncogenes become oncogenes, receptor proteins are easy to activate and may even be stimulated by a growth factor produced by the receiving cell.
- Several proto-oncogenes code for **Ras** proteins that promote mitosis by activating cyclin. *Ras* oncogenes are typically found in many types of cancers.
- *Cyclin D* is a proto-oncogene that codes for **cyclin** directly. When this gene becomes an oncogene, cyclin is readily available all the time.

Mutation of Tumor Suppressor Genes

- When tumor suppressor genes mutate, their products no longer inhibit the cell cycle or promote apoptosis. Therefore, these mutations can be called “loss-of-function,” or recessive, mutations.
- Unlike proto-oncogenes, both copies of the tumor suppressor gene in the cell must be mutated to lose cell cycle control.
- Mutation of the tumor suppressor gene *Bax* is a good example. Its product, the protein Bax, promotes apoptosis. When *Bax* mutates, Bax protein is not present and apoptosis is less likely to occur.
- Another tumor suppressor protein, p53, activates DNA repair enzymes. At the same time, p53 turns on genes that stop the cell cycle from proceeding. If repair is impossible, the p53 protein promotes apoptosis. Apoptosis is an important way for carcinogenesis to be prevented. Many tumors are lacking in p53 activity.
- The *BRCA1* gene codes for another DNA repair enzyme, one that is responsible for fixing breaks in the DNA molecule. In fact, it works very closely with the p53 protein. *BRCA1* mutations prevent the body from recognizing DNA damage, allowing the cells to progress through the cell cycle unchecked. *BRCA1* mutations are associated with a number of cancers, including breast cancer.