**The Biology of Cancer – Week 3**

The Ten Cellular Hallmarks of Cancer

* The Human Cell and Hallmarks of Cancer (1-5)

Eukaryotic Cell – smallest functional unit of life that replicates independently

This replication is called mitosis.

Cells make up the body’s tissues

Organs of the body are comprised of tissues

Innerphase, Mitotic Phase,

Cell cycle check points, they are located in the Gap Phases (The G Phases)

Normal human cells have a finite ability to undergo mitosis due to the end replication problem. This is largely due in part to ends of the chromosomes (telomeres) shortening after each mitotic division. G0 = Cellular senescence.

Once normal human cells reach the Hayflick’s limit, cells can go into cellular senescence (F0 phase of cell cycle).

Cancer cells are greatly able to exceed Hayflick’s limit and continue to undergo mitosis.

They do this using enzyme called telomerase, which elongates telomeres. This extends the chromosomal ends, repeatedly, via enzyme activity.

Telomerase is a reverse transcriptase enzyme. Adds short bases to the end in the 3’ direction.

#1) Replicative Immortality

#2) Genome Instability

Gene is a unit of inheritance that consists of two alleles.   
Normal eukaryotic cells have 23 pairs of chromosomes per cell, in the nucleus.

During normal cycle division (S phase), a DNA mutation will arrest the cycle and repair the mutation before resuming cycle. This is regulated by genes known as tumor suppressor genes.

Cancer cells can have an abnormal amount of chromosomes per cell and can bear mutations in their DNA with the ability to still undergo mitosis.

Genes commonly mutated or lossed are tumor suppressor genes. (TSGs).

Genes that are over-expressed are known as oncogenes, which cause cells to proliferate uncontrollably.

Notable gene alterations observed in cancer are point mutations, the deletion of regions of chromosomes, loss of heterozygosity (LOH), and several others.

Karyotyping to observe genomic instability in Chronic Myelogenous Leukemia (CML)

#3) Evasion of Growth Suppressor Signals

Most cancer cells are able to circumvent normal growth suppression in the G1 checkpoint in order to continue proliferating.

A TSG called retinoblastoma (Rb) inhibits the normal cell’s passage through the restriction point in the G1 cell cycle phase.

Another TSG, p53, functions as a central regulator of cell death because it arrests the cell cycle upon detection of DNA damage.

#4) Resistance to Cell Death

Normal cells can undergo apoptosis (cell death) in response to abundant DNA damage and other cellular stressed.

In contrast, cancer cells are generally less sensitive to DNA damage, growth factor deprivation, treatments, and similar stressed, and so they tend to avoid apoptosis.

Bcl-2 : Anti-apoptotic – Highly Pro-survival Proteins.

Within normal cells, growth factor signaling is tightly controlled to allow for cellular and tissue homeostatis.

Cancer cells have the ability to proliferate due to the aforementioned hallmarks (1-4), as well as to over-active oncogenes such as RAS.

Cancer cells can also stimulate cells in the microenvironment to provide growth factors. One such is EGF. Epidermal Growth Factor. EGF can activate RAS.

#5) Sustained Proliferation

* The Human Cell and Hallmarks of Cancer (6-8)

#6) Altered Metabolism

Key cancer difference: altered metabolism. To sustain uncontrolled proliferation, the cells must adjust their energy production. Cancer cells do this by finding and using alternate sources for energy and alternate metabolic pathways.

Cancer cells are very different, can convert glucose to lactate irrespective of oxygen. They are able to divert metabolites for useful anabolic processes such as mitosis.

Aerobic Glycolysis - This metabolic change is known as the Warburg Effect. This allows us to use FDG to visualize tumors using Positron Emission Topography.

#7) Avoiding Immune Detection

Immune system of collections of organs and biological processes to protect us from infection by viruses and bacteria, pathogens, and other foreign cell types, including tumor cells.

Cancer cells can protect themselves by inhibiting T cells that would normally attack these cancer cells.   
Increased Programmed Death 1 Ligand (PD L1) on Cancer Cells Allows Immune System Evasion. PDL1 is used to decrease autoimmunity, highjacked by the tumor cells.

#8) Tumor-Promoting Inflammation.

Tumor microenvironment (surrounding environment of tumor) is often infiltrated by cells from the immune system cells that enable tumors to mimic inflammatory conditions seen in normal tissues.

Immune cells provide the tumor cells with essential factors that allow them to survive, move, proliferate, and under epithelial-to-mesenchymal transition (EMT) and invade.

Immune cells secrete cytokines, proteases, and chemokines.

Cancer cells also secrete chemokines, which increase cellular motility, survival, and angiogenesis.

* Cellular Hallmarks of Cancer 9 & 10: Preparing the Cancer to Move and Metastasize

-Preparing the cell to move and metastasize.

#9) Induction of Angiogenesis – Formation of new blood vessels to support tumor growth.

All tumor cells require a blood supply to grow to a significant size.

Pro-angiogenic factors such as vascular endothelial growth factor (VEGF) become activated in tumor cells and signal endothelial cell proliferation and growth of blood vessels.

Immune infiltrating cells can also induce this.

Tumor cells can grow more quickly than normal cells and outgrow their source of nutrients-blood.

They make new blood vessels to provide necessary nutrients and oxygen.

These new vessels provide a way for tumor cells to get into the bloodstream.

#10) Activation of Metastasis

Cell-cell and cell-extracellular matrix interactions are altered.

Changes in or loss of structural proteins (integrins, adhesions)

Loss of genes known as metastasis suppressor genes (KAI1/CD82, NDRG1)

Recruitment of immune cells

EMT (epithelial to mesenchymal transition)

Epithelial cells: cuboidal, stationary, strong interactions with ECM and other cells.

Mesenchymal cells: stretched shape, mobile, weak/no interactions with ECM or other cells.

Extracellular matrix (ECM): molecules secreted by cells that provide structure and biochemical support to surrounding cells.

Invasive cancer has grown new blood vessels, lost cell to cell contact, cell to cell adhesion, and can move from original space to distant organ spaces.

The Process of Metastasis

-1 INVASION - Tumor cells are able to break through the ECM during invasion and are able to migrate outwardly, away from their natural location. Invasion allows cancer cells to move toward blood vessels. These cells are more aggressive, more motile. Invasion, pushing the severity of the cancer to a higher level.

-2 INTRAVASATION – Cancer cells enter the bloodstream. Actively: by pushing their way through endothelial cells. Passively: tumor cells are shed from a tumor and enter presumably leaky blood vessels.

-3 Survival during systemic circulation – Cell must traverse venous system, lungs, and arterial system.

Tumor cells that are circulating in the bloodstream are called circulating tumor cells (CTCs).

During this transit, these cells must avoid various sources of cellular death.

-4 EXTRAVASATION. Cells begin growing in the secondary site into metastatic tumors.

These cells may not begin to divide immediately when they get to their destination. The may go dormant and grow into a tumor later.