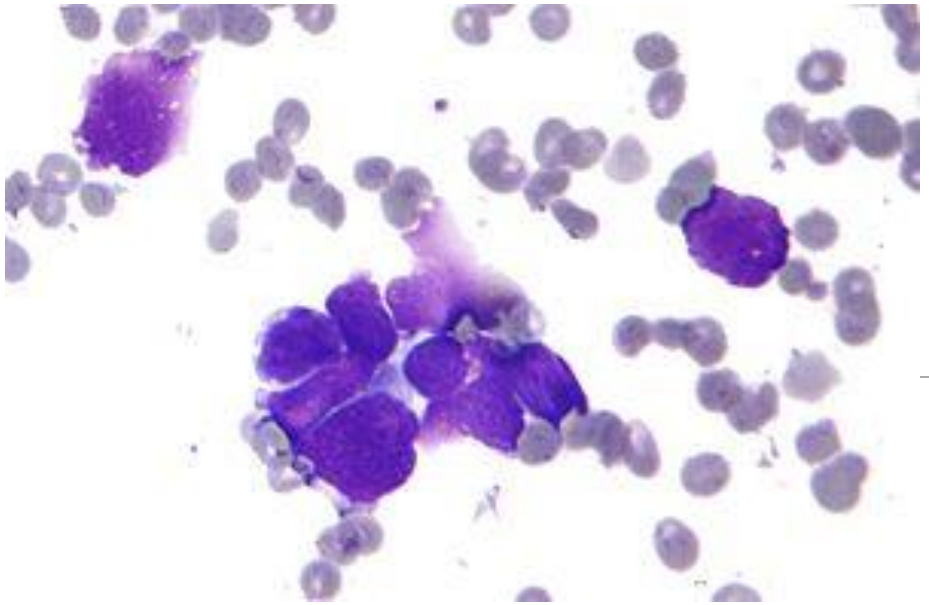
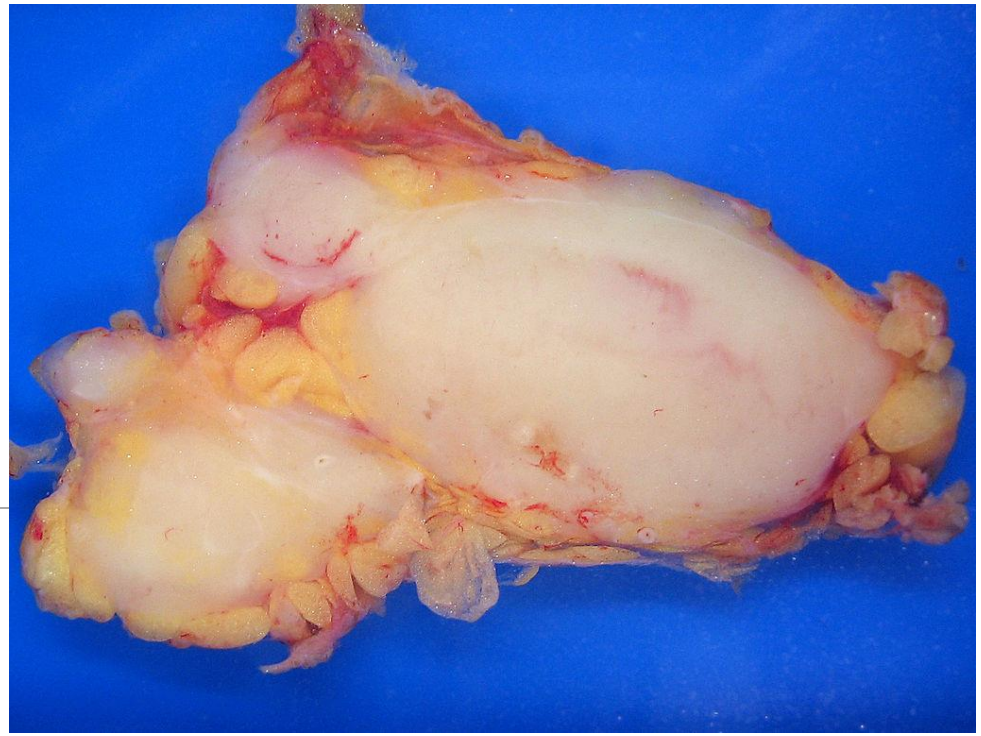
Biological Background of Cancer

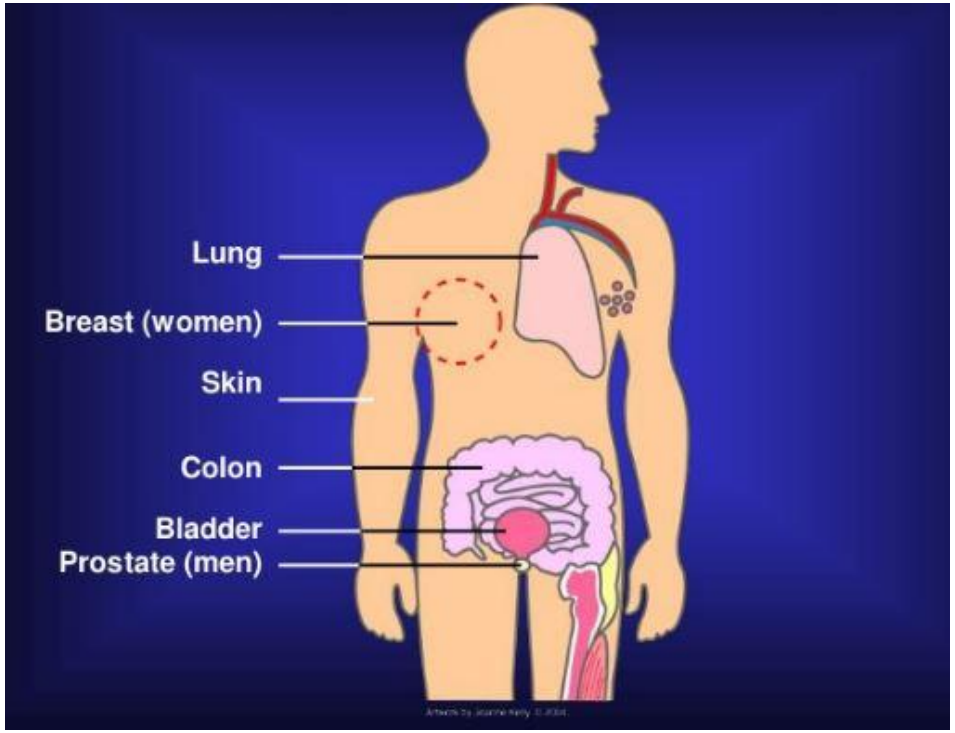


January 19, 2017



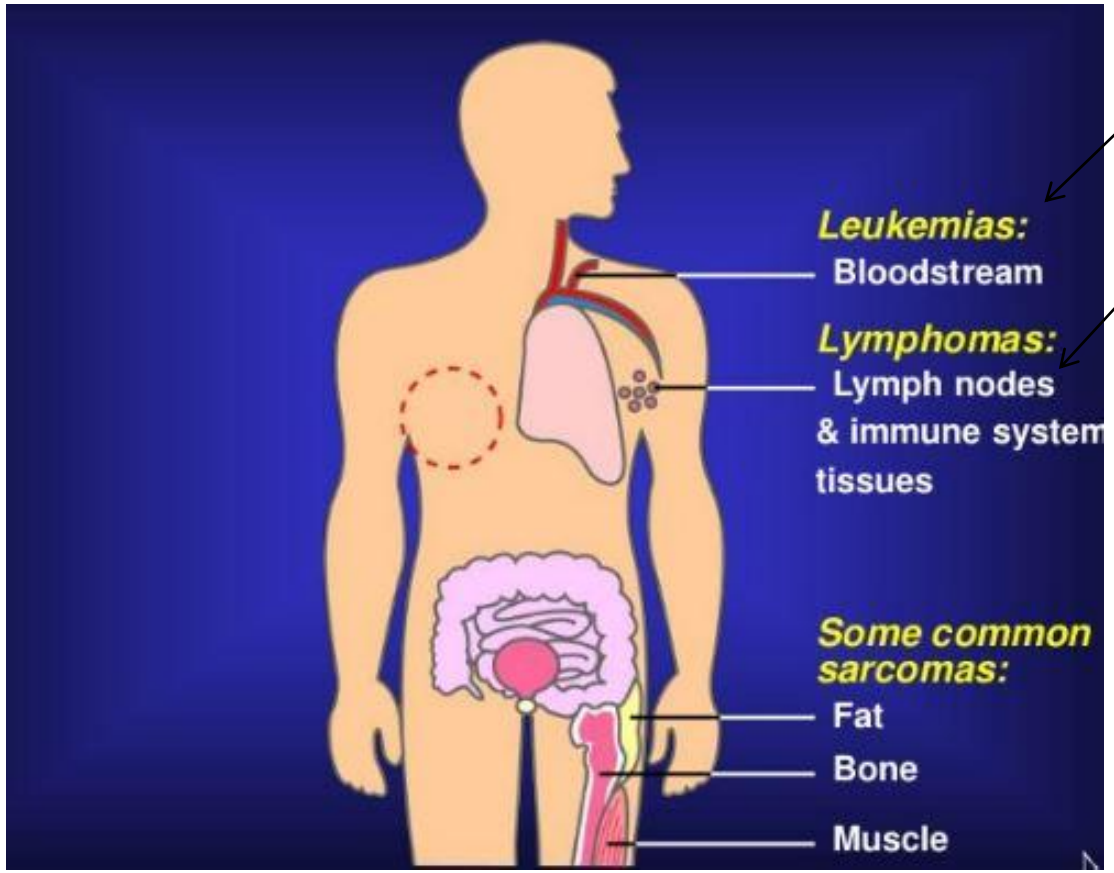
Cancer Basics

- As mentioned, cancer is a collection of diseases characterized by unchecked growth toward limitless expansion



- **Carcinomas** – cancer in tissue of skin or lining of internal organs (most common type)

Other Types of Cancers

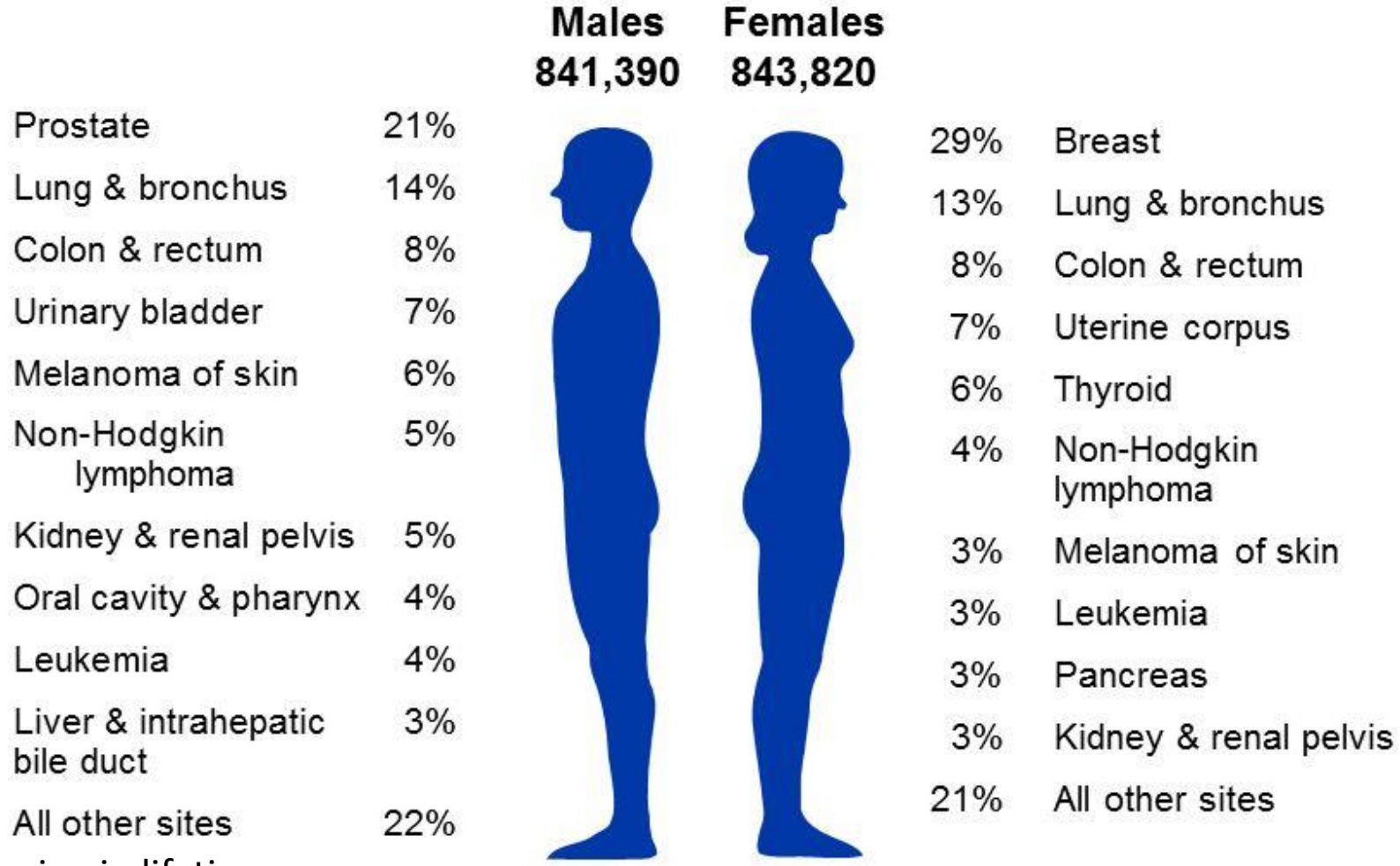


Bone marrow

Immune cells produced here
(e.g. B, T cells)

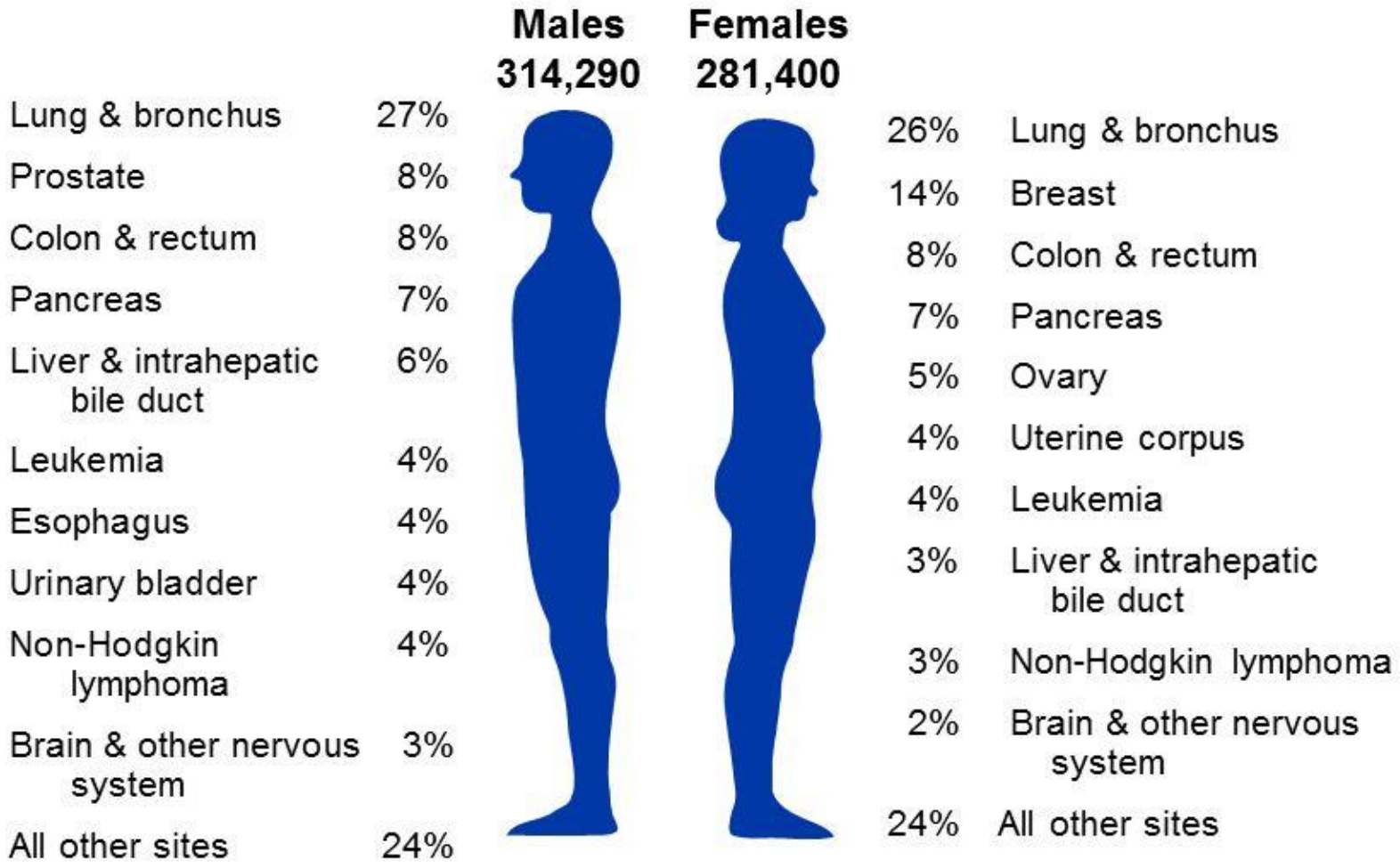
- **Sarcomas** – Non-epithelial cancer (cells of mesenchymal origin)
  - Very rare in humans

Estimated New Cancer Cases in 2016 (US)

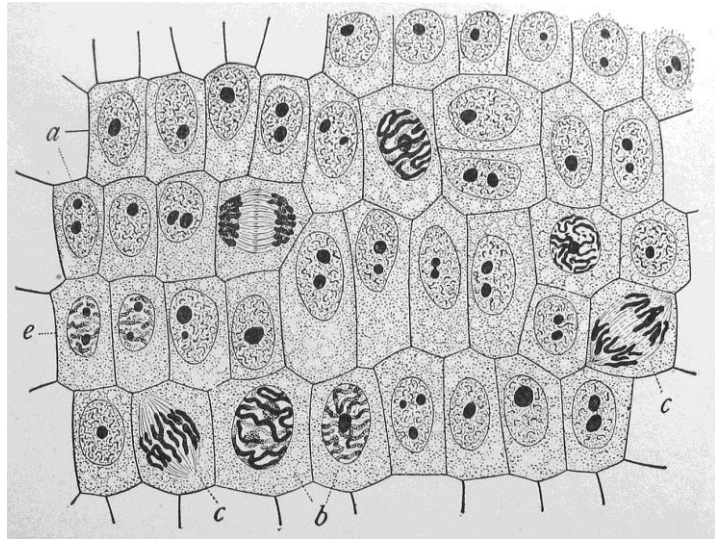


- Probability of developing in lifetime:
  - Men: 42%
  - Women: 38%

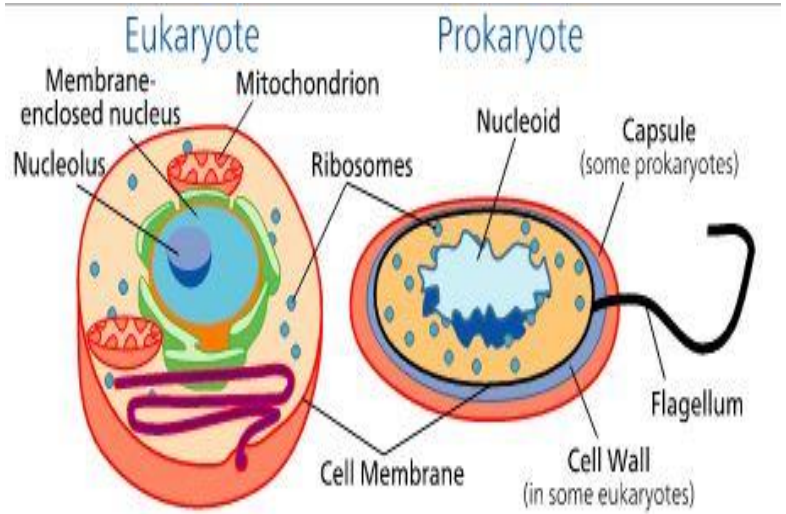
Estimated Cancer Deaths in 2016 (US)



Cell Basics



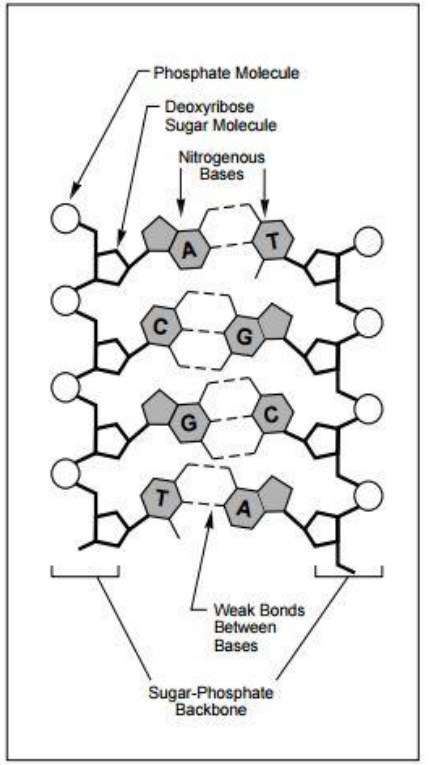
- Basic structural and functional unit of all known living organisms
  - Replicate independently
  - “Building blocks of life”
- Unicellular vs. multicellular
  - Humans – 10^{12} cells (10 trillion)
- Biomolecules (proteins and nucleic acids) contained inside a cell membrane
- Prokaryotes vs. Eukaryotes
  - Prokaryotes – bacteria, **no nucleus**, single chromosome, binary fission, 1-5 µm
  - Eukaryotes – animals and plants, **nucleus**, multiple chromosomes, mitosis or meiosis, 10-100 µm



Primer on Genetics (Eukaryotes)

- In Eukaryotic cells, genetic material is stored in the **cell nucleus**
  - Prokaryotes – DNA processing take place in the cytoplasm itself
- Nucleus contains **genes** – basic functional unit of heredity
  - Segment of DNA used to synthesize a protein (or RNA molecule)
  - Humans – DNA organized into tightly packed structures called chromosomes (1.8 m in length)
  - 46 chromosomes in humans – 22 pairs of autosomes and a pair of sex chromosomes (XX – female, XY – male)
  - One member of each pair comes from mother (egg) and father (sperm)

Fig. 2. DNA Structure. *The four nitrogenous bases of DNA are arranged along the sugar-phosphate backbone in a particular order (the DNA sequence), encoding all genetic instructions for an organism. Adenine (A) pairs with thymine (T), while cytosine (C) pairs with guanine (G). The two DNA strands are held together by weak bonds between the bases. A gene is a segment of a DNA molecule (ranging from fewer than 1 thousand bases to several million), located in a particular position on a specific chromosome, whose base sequence contains the information necessary for protein synthesis.*



Chromosomes and karyotype

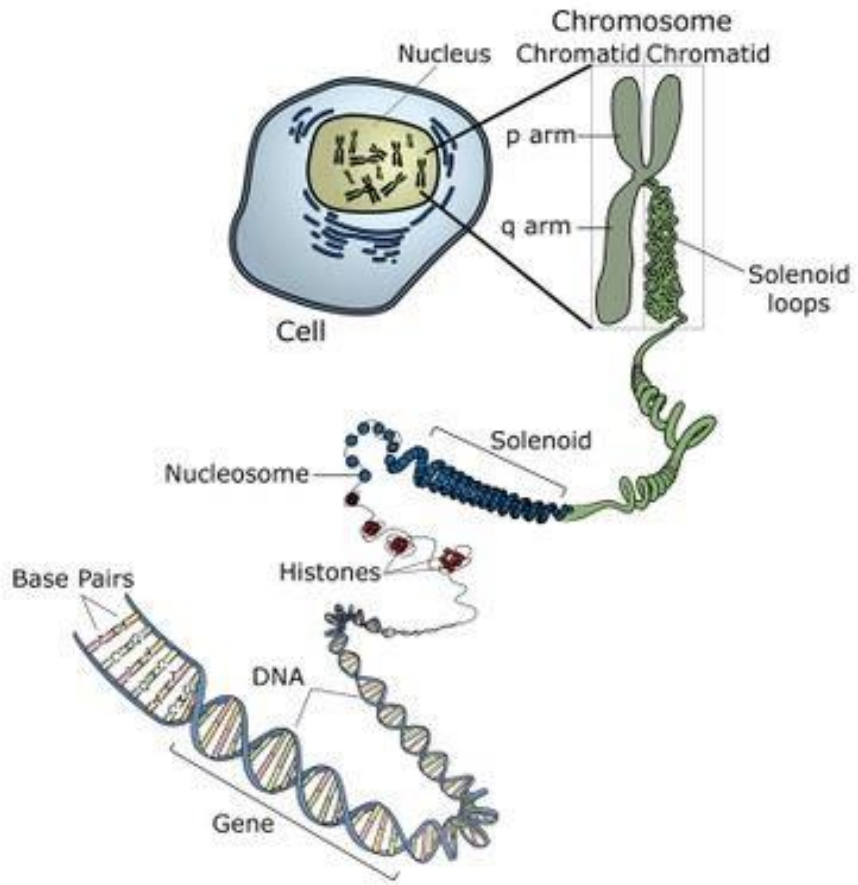
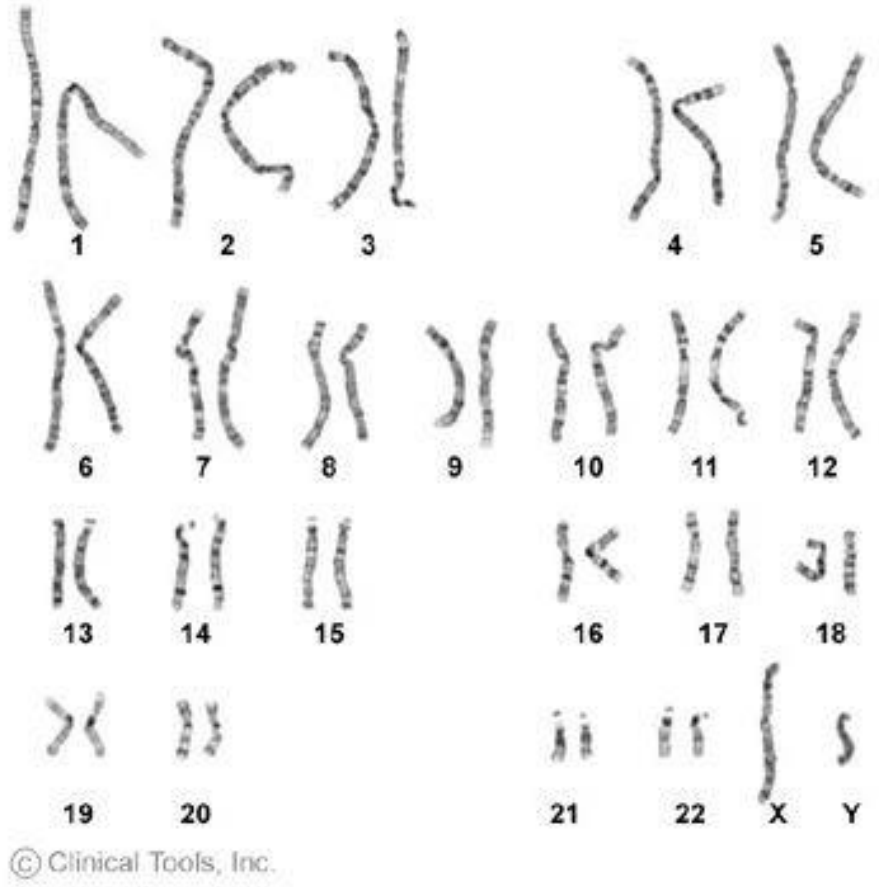
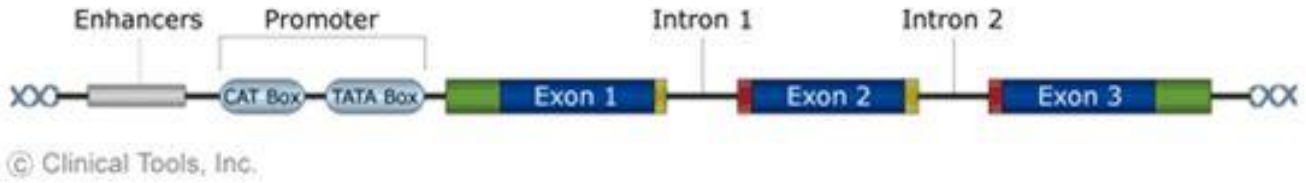


Image adapted from: National Human Genome Research Institute.



Karyotype of a human male

Genes and Proteins



The structural components of a gene

- Genes – specific sequence of nucleotide bases, whose sequence carry the information required for constructing **proteins**
  - Proteins – provide structural components of cells and tissues, as well as enzymes
    - Large, complex molecules made up of amino acids
    - Synthesize over 100,00 different kinds
  - Humans – over 100,000 genes and 3 billion base pairs in 23 chromosomes
- In a gene, codons direct for a specific sequence of amino acids to produce proteins

Transcription and Translation

- Process by which genes, **when expressed**, are used in the synthesis of a functional gene product (usually proteins)
- “Central Dogma of Molecular Biology”

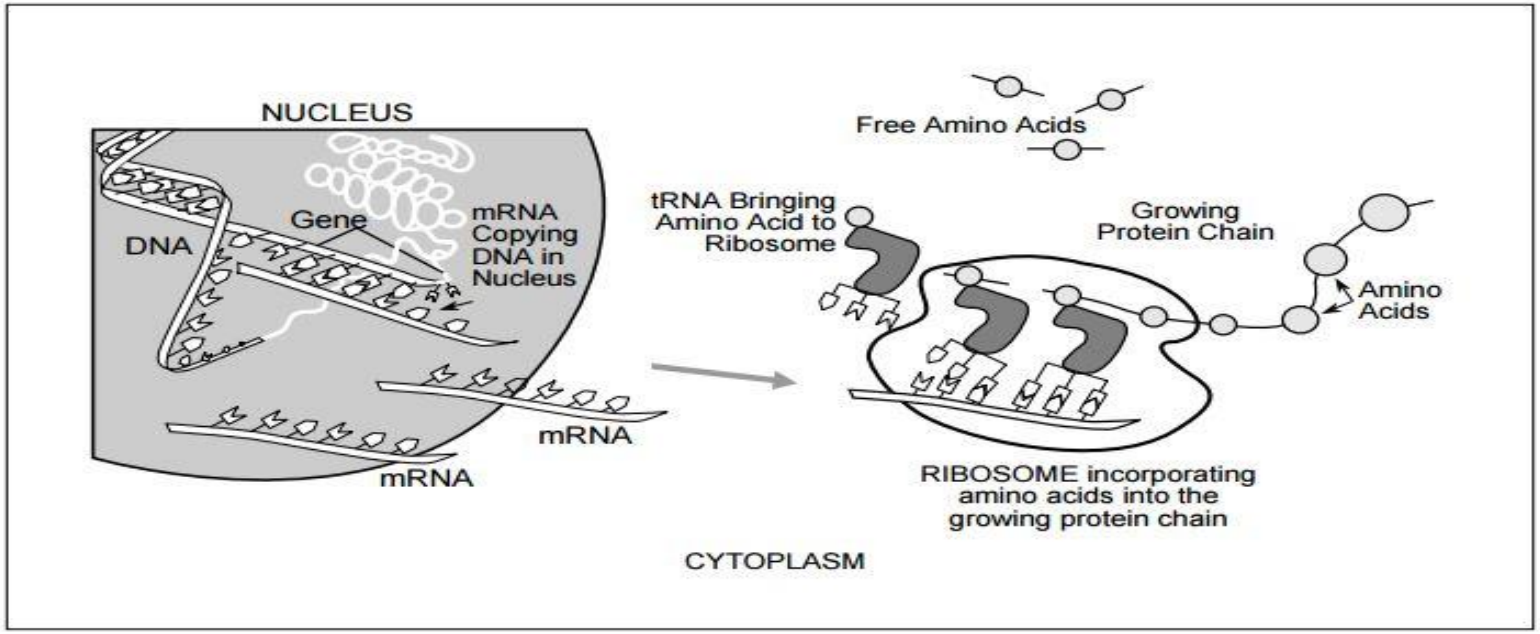
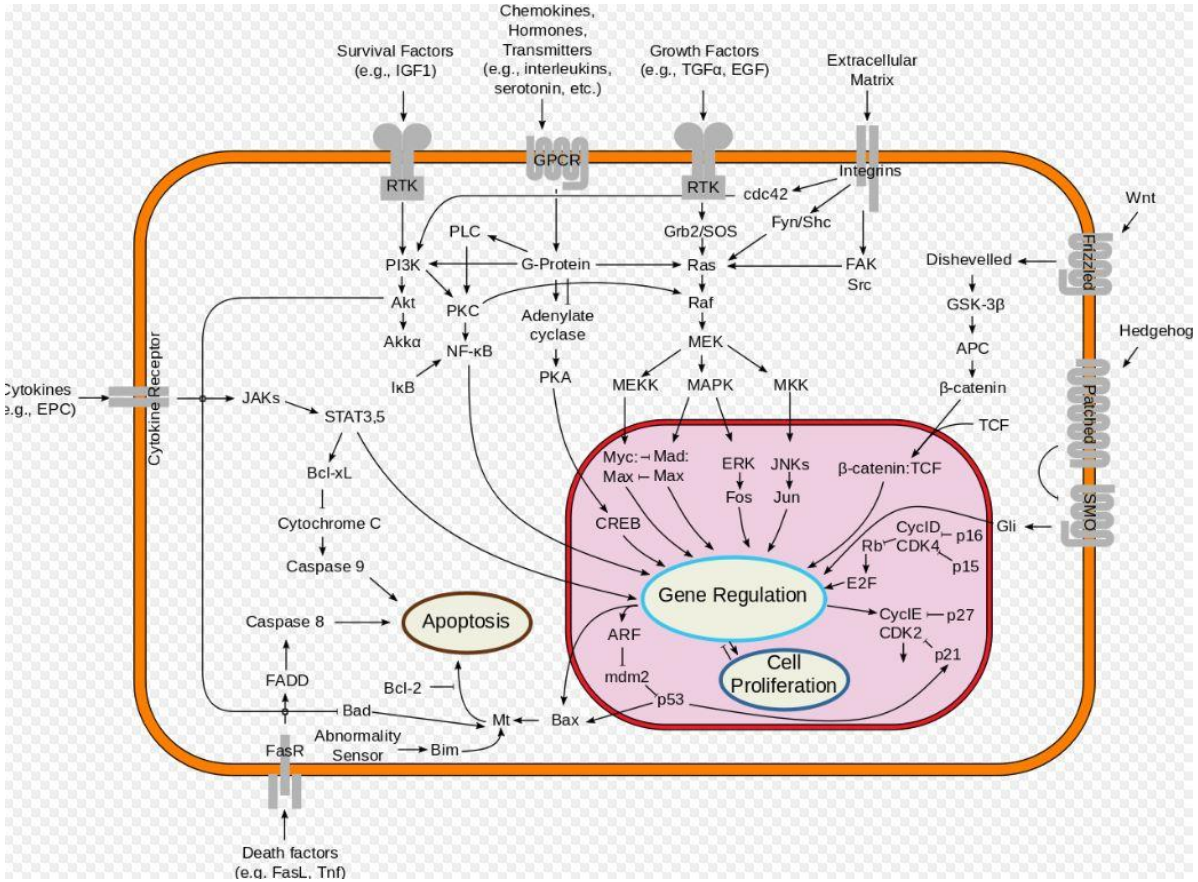
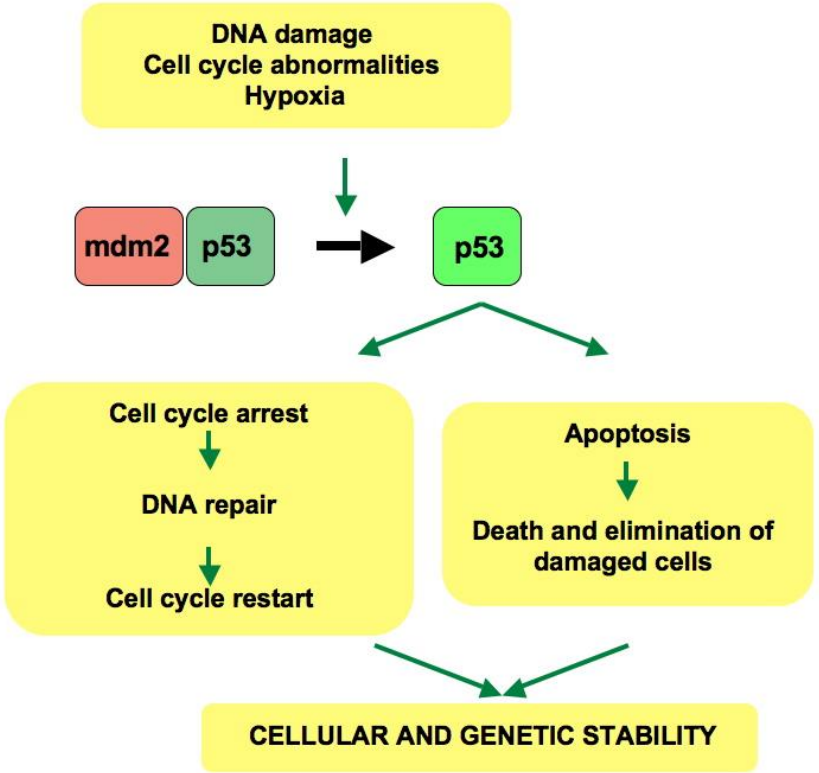


Fig. 5. Gene Expression. *When genes are expressed, the genetic information (base sequence) on DNA is first transcribed (copied) to a molecule of messenger RNA in a process similar to DNA replication. The mRNA molecules then leave the cell nucleus and enter the cytoplasm, where triplets of bases (codons) forming the genetic code specify the particular amino acids that make up an individual protein. This process, called translation, is accomplished by ribosomes (cellular components composed of proteins and another class of RNA) that read the genetic code from the mRNA, and transfer RNAs (tRNAs) that transport amino acids to the ribosomes for attachment to the growing protein. (Source: see Fig. 4.)*

Proteins and Function

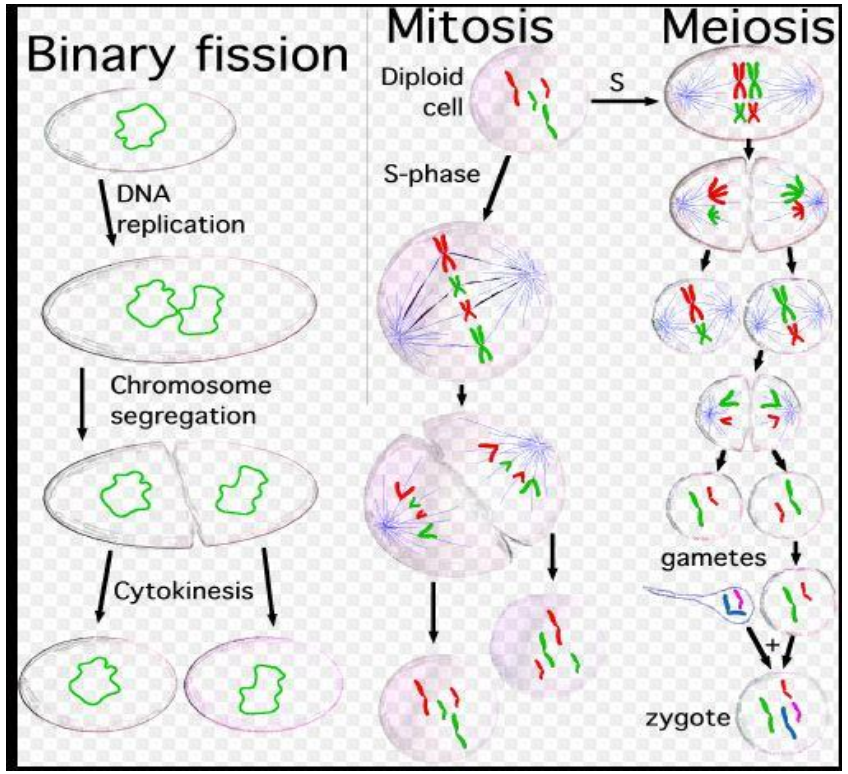
- Genes make proteins (and RNA), which **control the cell**
  - Decide type of cell, what it does, when it will divide, when it will die, etc.





Cell Division

- Cell division – process by which parent cell divides into two or more daughter cells
  - Mitosis or meiosis

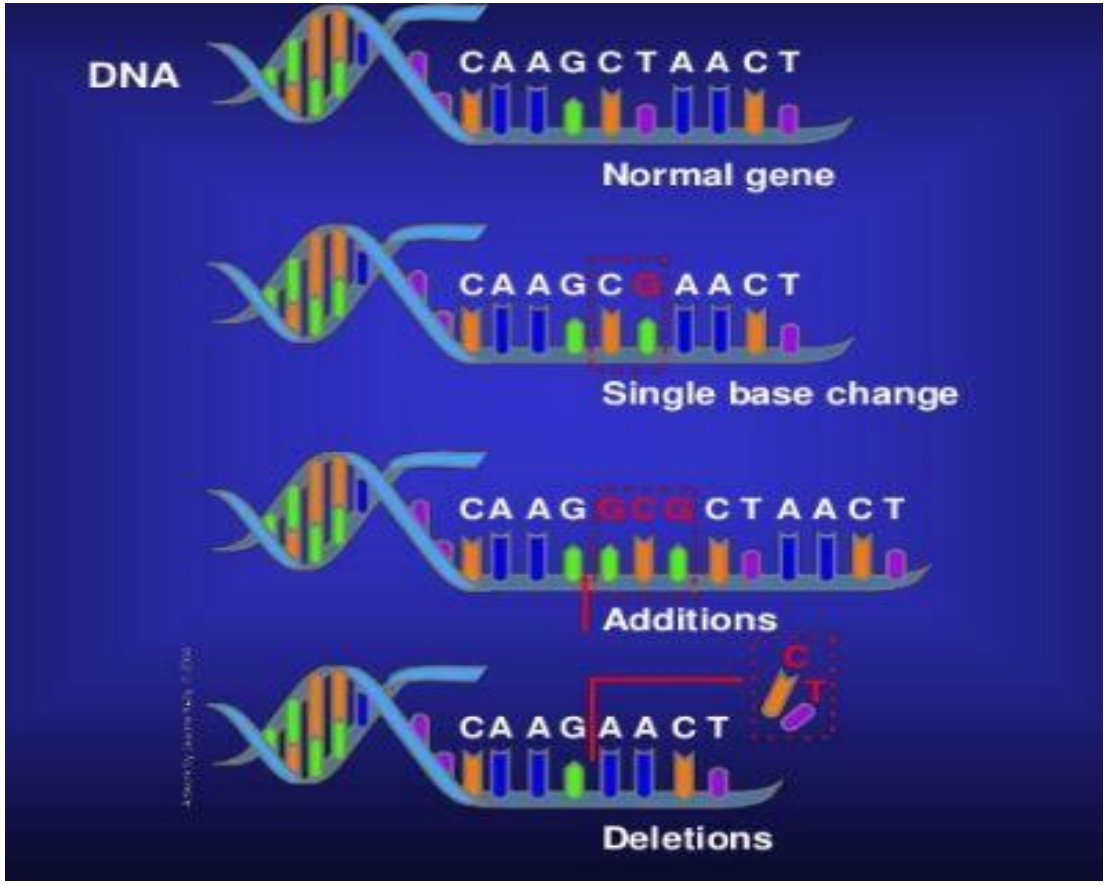


- Continual construction and repair in organisms
  - 10^{16} in a human lifetime

Mutations

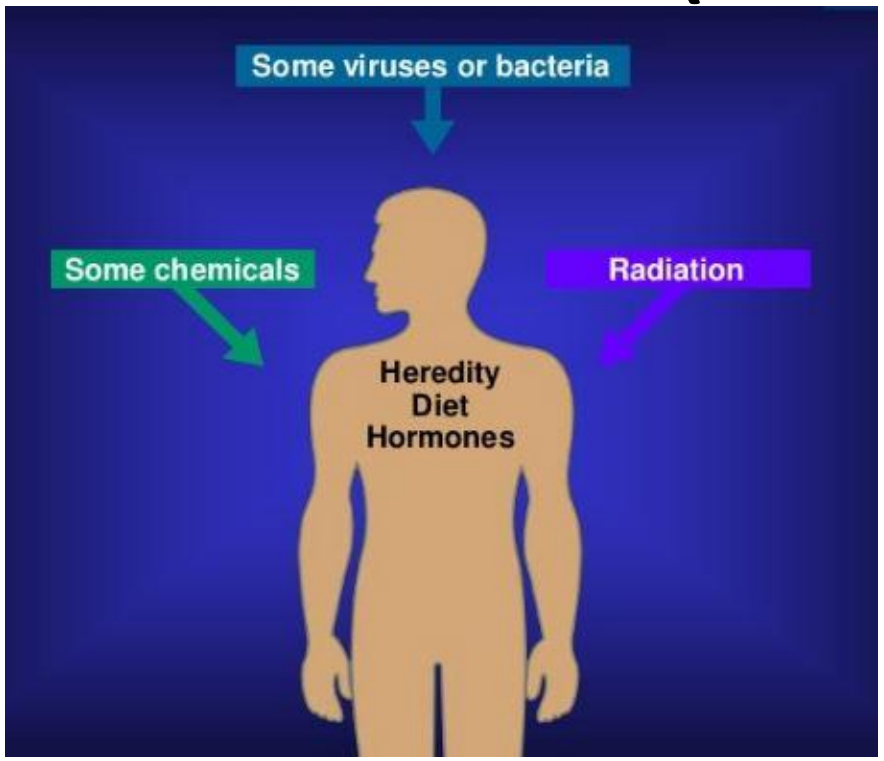
adenine [A]
thymine [T]
cytosine [C]
guanine [G]

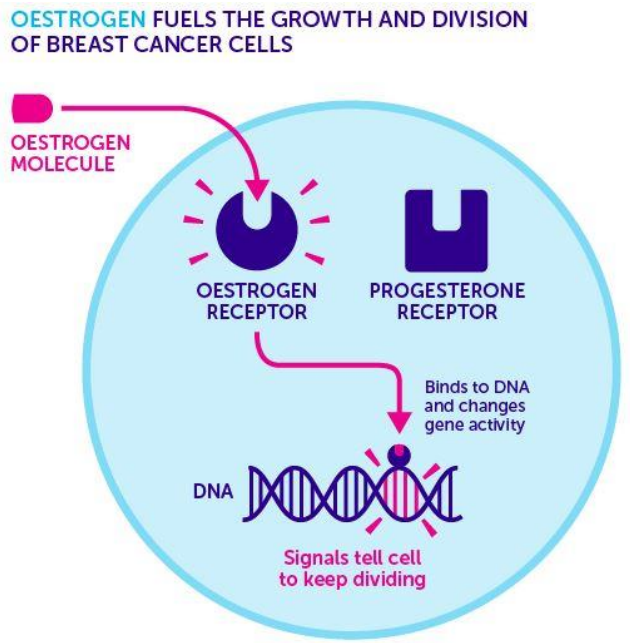
- **Mutation** – change in a cell's gene that occurs during cell division
  - Typos in the base sequence
  - Gene has been damaged
    - Or duplicated (gene amplification)
  - Affects **protein production**
    - Too much (divide too often)
    - Not enough (tell cell to stop)
    - Change function (abnormal proteins)
- Enough mutations occur, and cancer forms
  - 6 or so mutations



(https://youtu.be/m5_yo6uEeEc)

Causes of Mutations (Carcinogens)





- Chemicals – tobacco smoke , asbestos, lead, benzene, aflatoxins, alcohol
- Viruses – Hepatitus B, HPV
- Hormones – estrogen, for example (drives cell proliferation, breast and ovarian cancer)

Classification of Genes causing Cancer

- Uncontrolled growth as the result of alterations (mutations) in genetic material
  - Break out of regulatory networks which ensure cooperation (**multi-stage carcinogenesis)**
  - Higher **fitness** and selected via Darwinian evolution (**clonal expansion**)

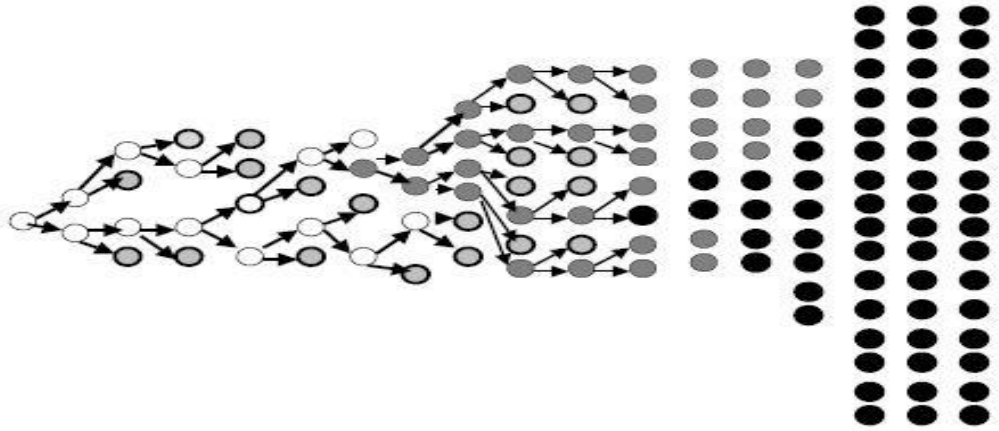


Fig. 2.7 Diagram explaining the concept of somatic evolution and cancer progression. Cancer originates with the generation of a mutant cell. This cell divides and the population grows. This is called clonal expansion. Further mutations can subsequently arise which have a higher fitness. They grow and expand further. Consecutive mutations and rounds of clonal expansion allow the cancer to grow to ever increasing sizes.

- Categories of cancer causing genes:
  - **Oncogenes** (gain of function)
  - **Tumor suppressor genes** (loss of function)
  - **Repair genes**

Oncogenes

- Healthy cells – promote regulated proliferation of cells in the presence of appropriate growth signals
- Mutations – induce cells to divide continuously, **independent of presence or absence of growth signals**

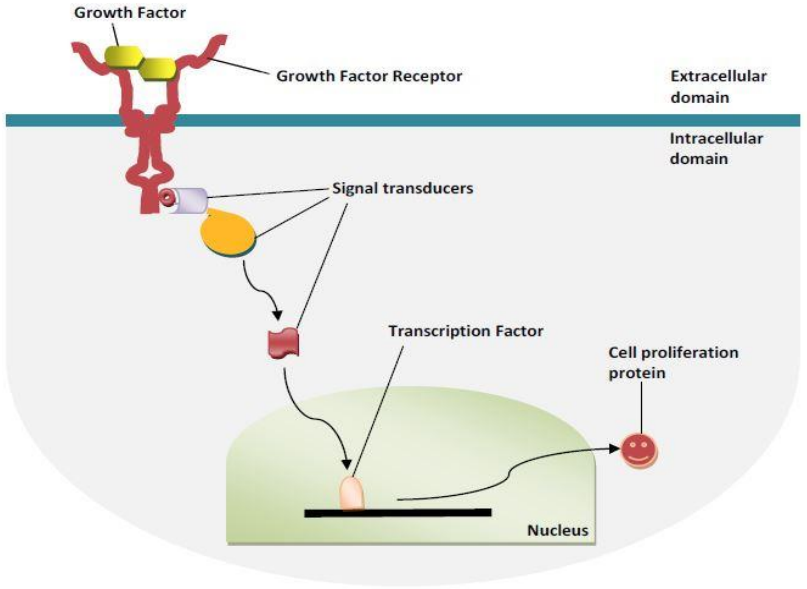


Fig 3.1: Components of a typical growth factor signaling cascade. Growth factors can be hormones or cell-bound signals that stimulate cell proliferation. Receptors are membrane bound proteins that accept signals. Signal transducers are molecules (proteins and others) that transmit the signal from the receptor to other intracellular molecules involved in cell proliferation. Transcription Factor are proteins that bind to DNA and allow expression of proteins involved in cell proliferation.

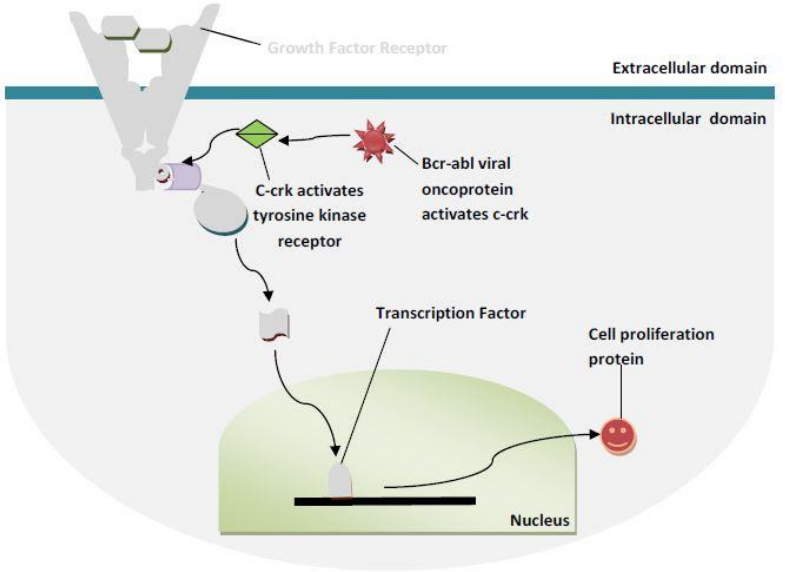
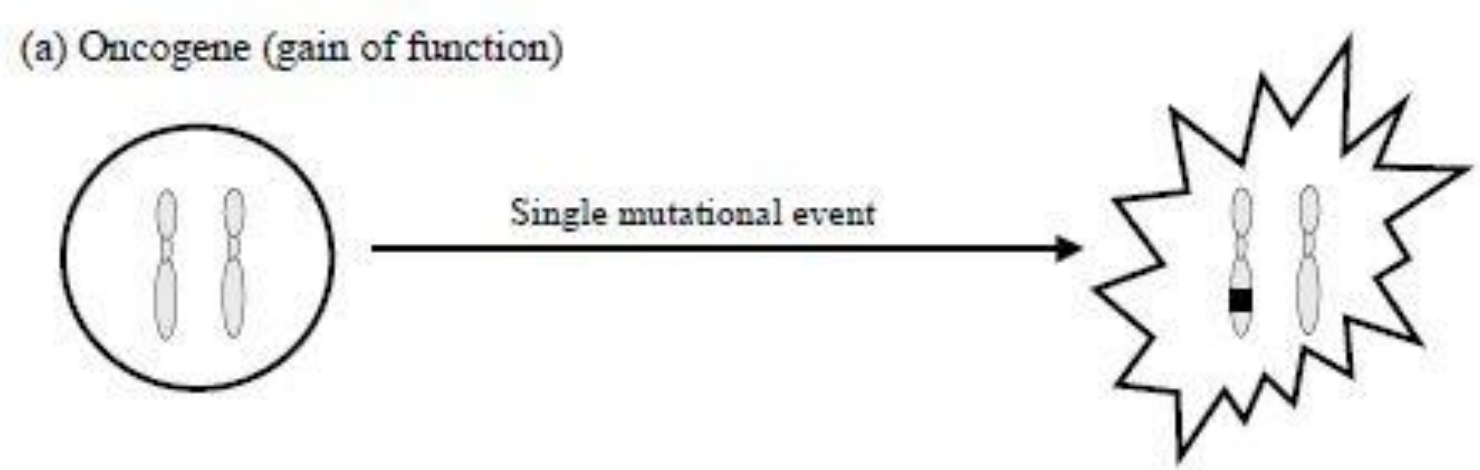


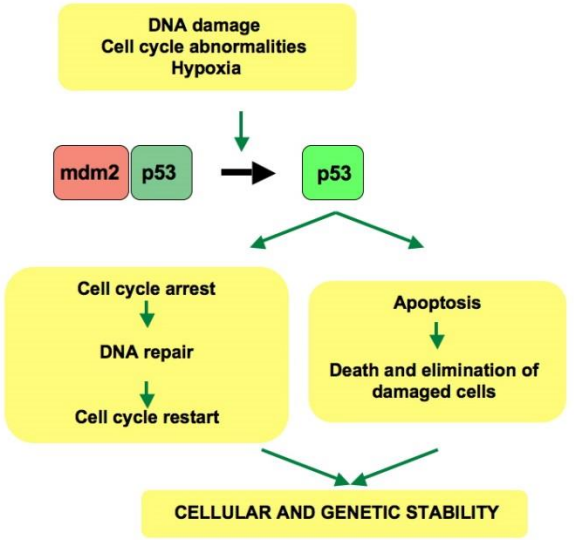
Fig 3.4: Activation of tyrosine kinase receptors by c-crk.

Oncogenes continued

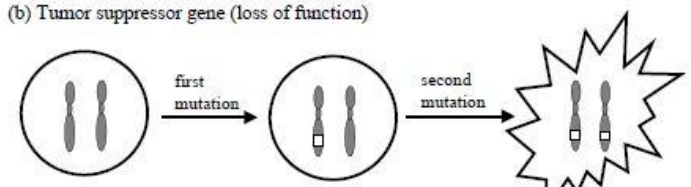
- Examples – Ras (25% of all cancers) and BCL-2
- Remember, each cell has **2** copies of every gene (one from mother, one from father on each chromosome, except for sex chromosome)
  - Thus, only needs **1** mutation to obtain activation (**gain of function)** and thus gain new behavior



Tumor Suppressor Genes

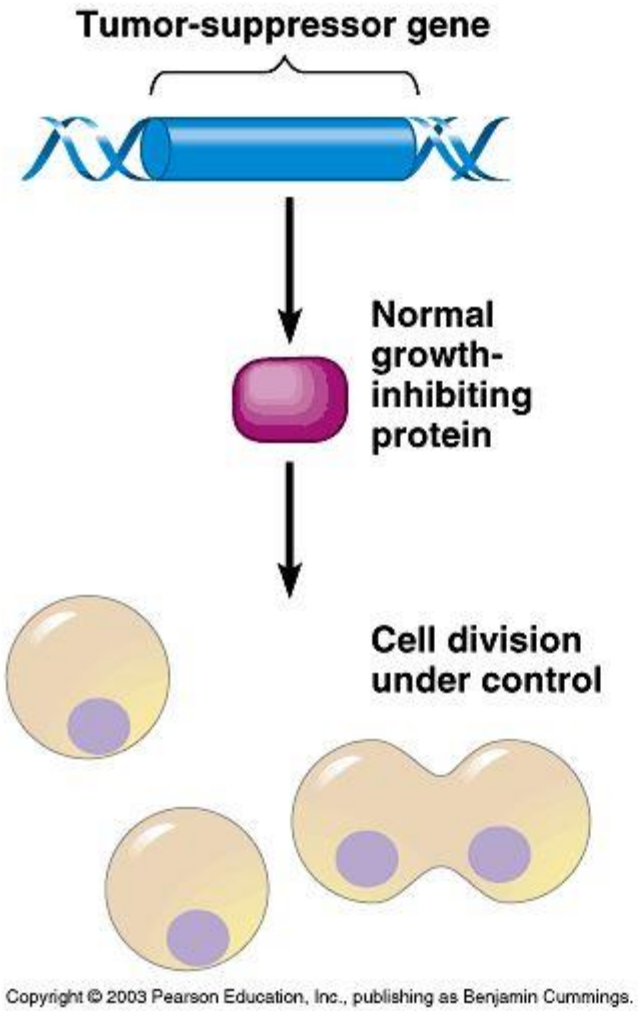


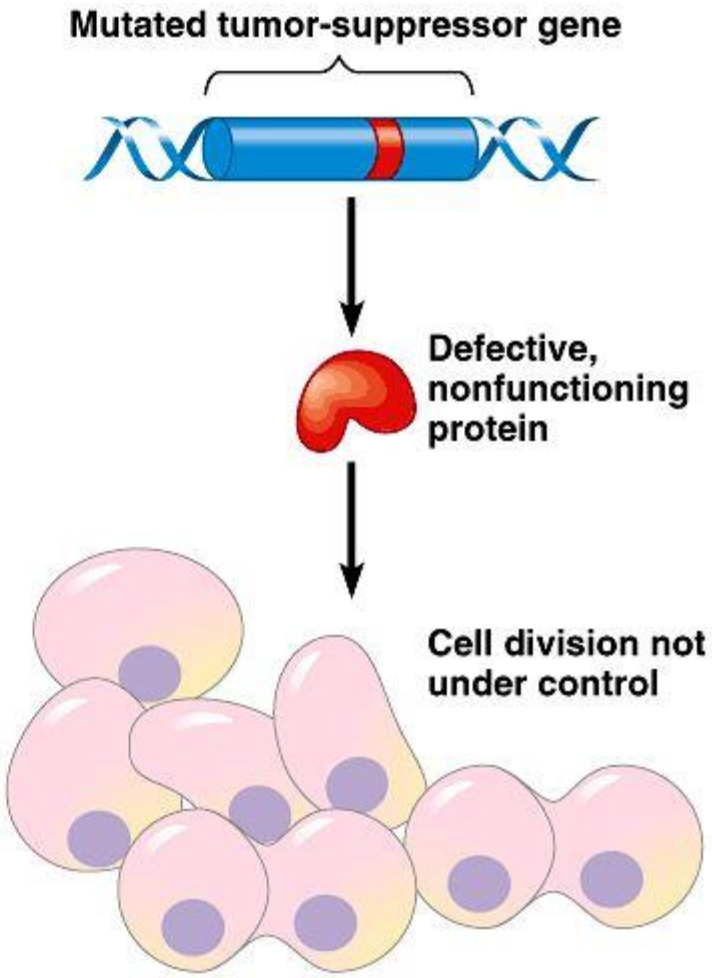
- Protect cells by stopping growth in normal cells
- Many reasons why may want growth to stop:
  - Cell becomes damaged or mutated
  - Cell death required for normal tissue homeostasis
- Cell can either halt progress in cell-cycle (**cell-cycle arrest**, **senescence**), or go through programmed cell death (**apoptosis**)
- Inactivation or loss: growth is not prevented, hence promotes development of cancer (**loss of function**)
  - Note: harder to detect (difficult to see what's NOT there)
- Require "two-hits" – two mutational events to inactivate both genetic copies
  - Fundamental in initiation (theorized to come first)



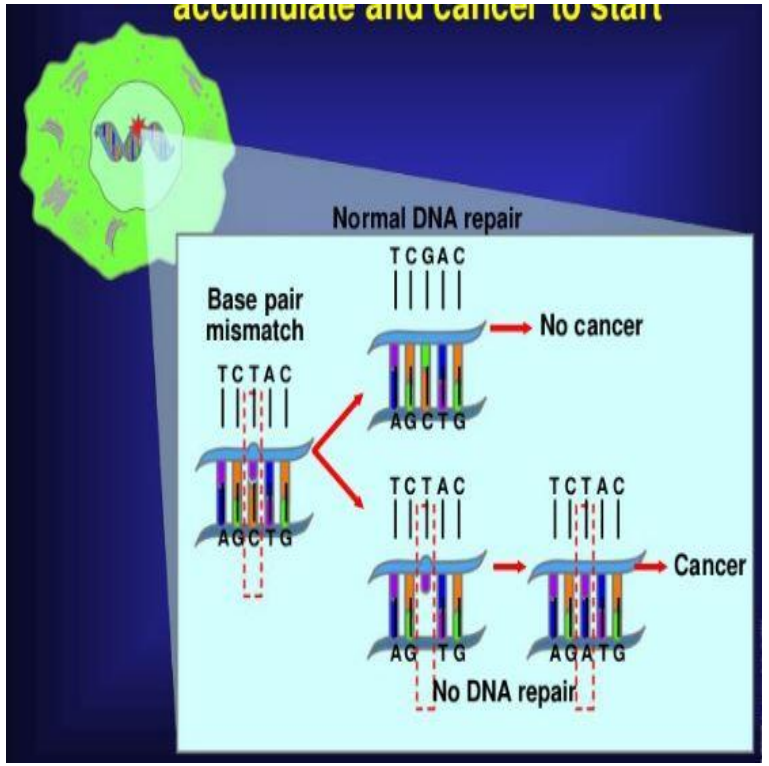
- Examples: Rb (retinoblastoma protein pRb), APC, p53 (inactivated in 50% of human cancers)

Tumor Suppressor Genes contiuned





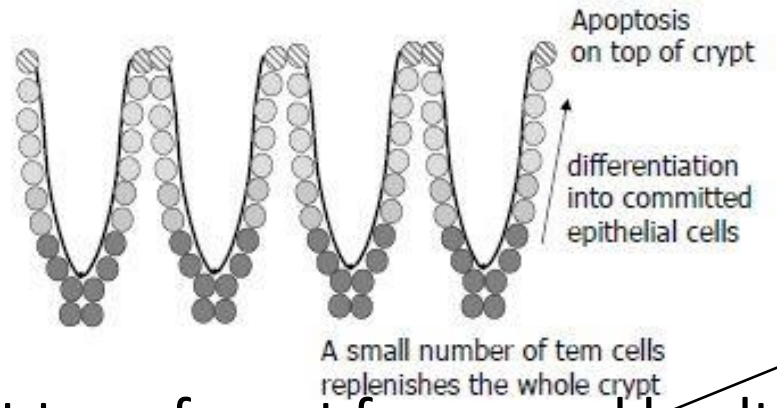
Repair Genes



- Maintain integrity of the genome, by fixing DNA damage
- When normally function, do one of two things:
  - Remove DNA damage (make sure cell is healthy), or
  - Mark for cell death (apoptosis)
- **If damaged**: obtain mutations in oncogenes and/or tumor suppressor genes at a faster rate (**genetic instability**)
  - Cells acquire “mutator phenotype” which promotes the process of **carcinogenesis** (development of cancer)
- Usually require two mutations (hits), but may be compromised with only one

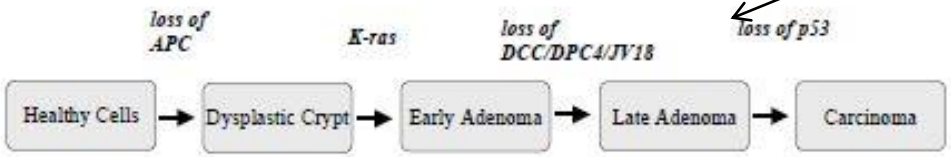
Colon Cancer (Mutations and Carcinogenesis)

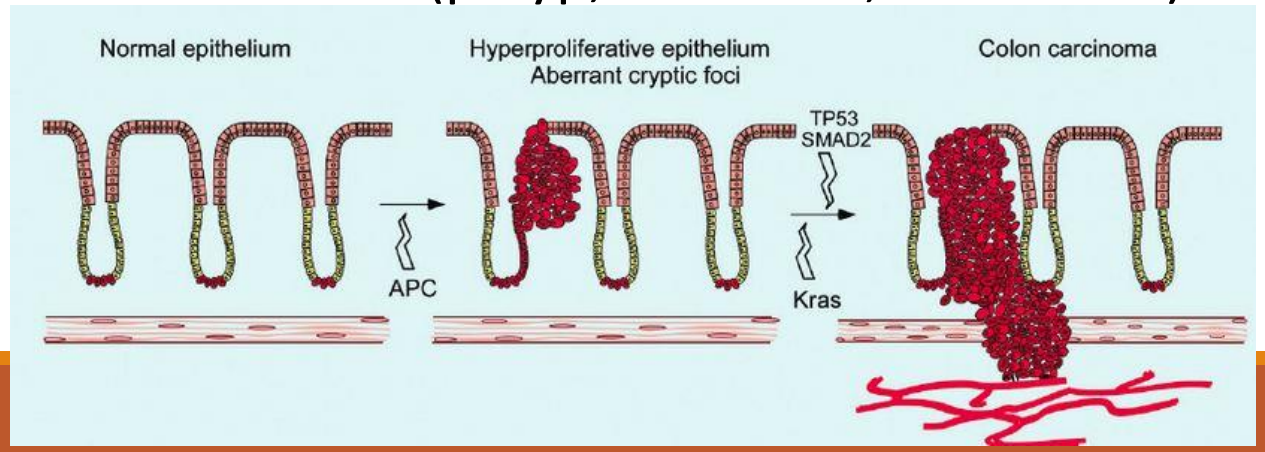
- Example of how multiple mutations (oncogenes and tumor suppressor) lead to the formation of cancer
- Colon: consists of **crypts** in epithelium



Note: a caricature (order is not precise)

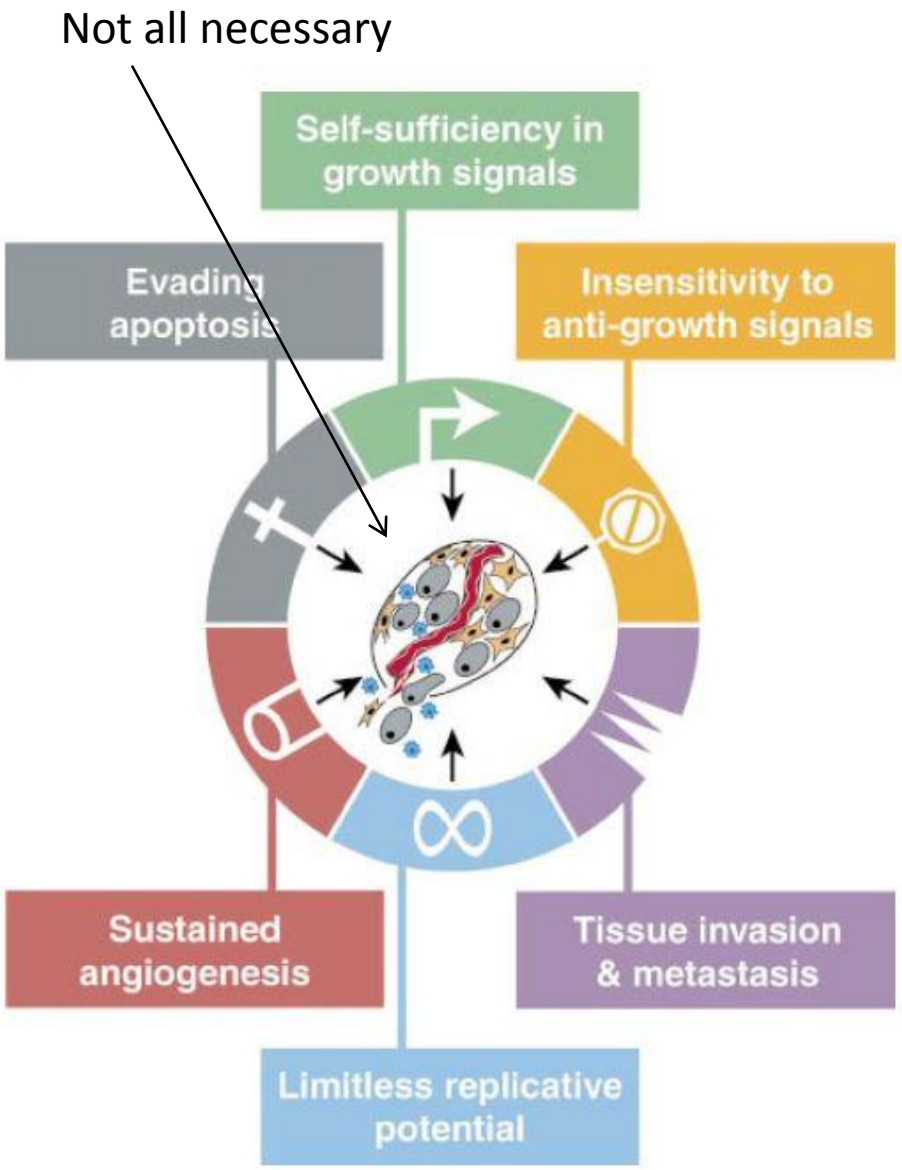
- Cell death must occur at top of crypt for normal health
  - Successive mutations lead to varying levels of disease (polyp, adenoma, carcinoma)





Hallmarks of Cancer

- Cancer cells have defects in regulatory “circuits” that govern normal cell proliferation and homeostasis (come from genetic mutations and epigenetics (later))
- Huge number of genetic variations and cell types (and subtypes) mean that the complexity is enormous
  - More than **100** cancer types
  - Hence why a single cure seems unlikely
- However, complexity can be reduced to a small number of **traits** (“hallmarks”) that govern transformation of normal cells to cancer
  - **Phenotype** arising from **genotype** (redundancies in genotype)



Self-Sufficiency of Growth Signals

- Activation of **oncogenes** – autonomy of growth signals (normal cells all need external signals to divide)
  - Produce growth factors themselves (**autocrine signaling**, e.g. PDGF and TGFα in glioblastomas and carcinomas)
  - Alter cell surface receptors (overexpress, structural alteration, type of receptor)
  - Alter downstream pathways (activation of Ras without normal upstream regulators, such as bound ligand in receptors)

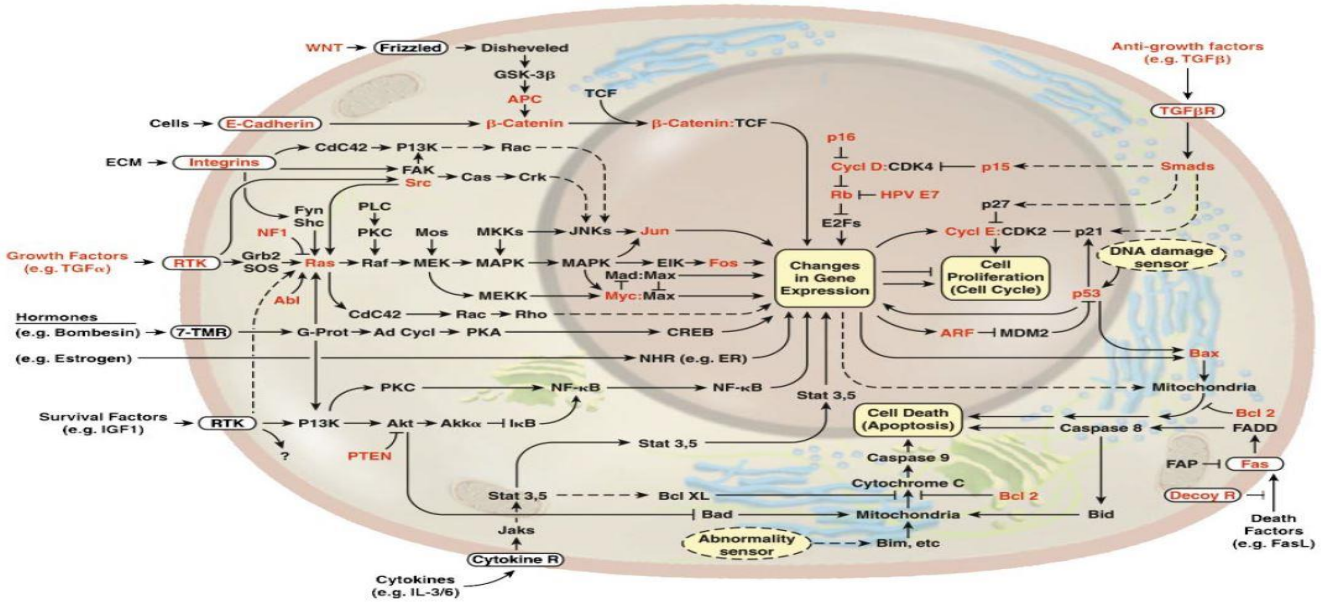
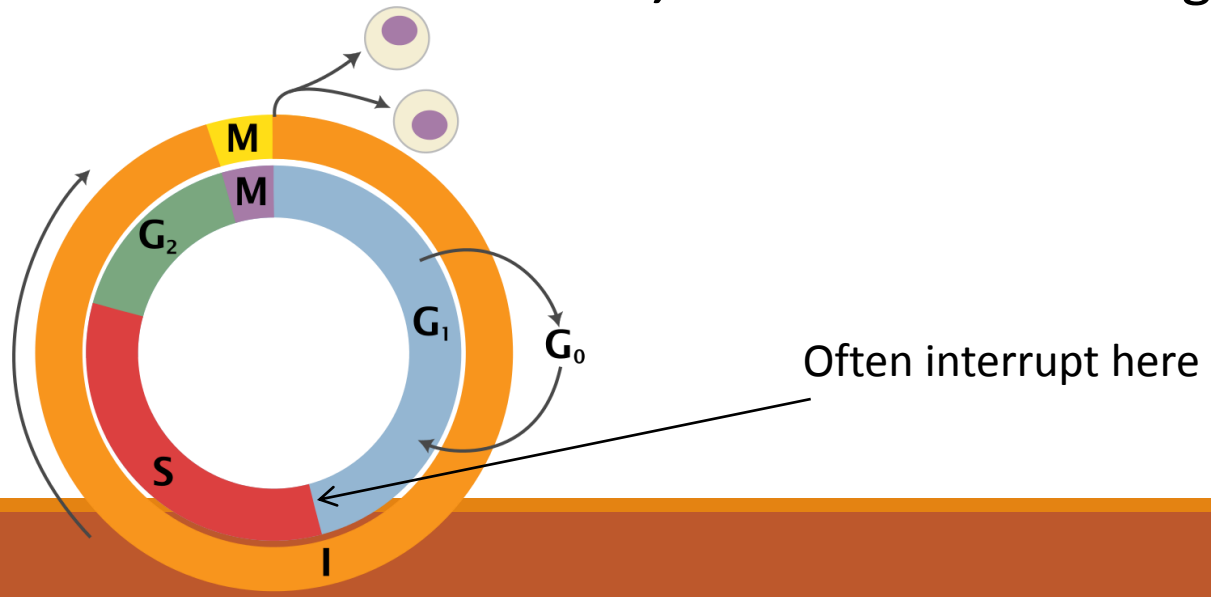


Figure 2. The Emergent Integrated Circuit of the Cell

Progress in dissecting signaling pathways has begun to lay out a circuitry that will likely mimic electronic integrated circuits in complexity and finesse, where transistors are replaced by proteins (e.g., kinases and phosphatases) and the electrons by phosphates and lipids, among others. In addition to the prototypical growth signaling circuit centered around Ras and coupled to a spectrum of extracellular cues, other component circuits transmit antigrowth and differentiation signals or mediate commands to live or die by apoptosis. As for the genetic reprogramming of this integrated circuit in cancer cells, some of the genes known to be functionally altered are highlighted in red.

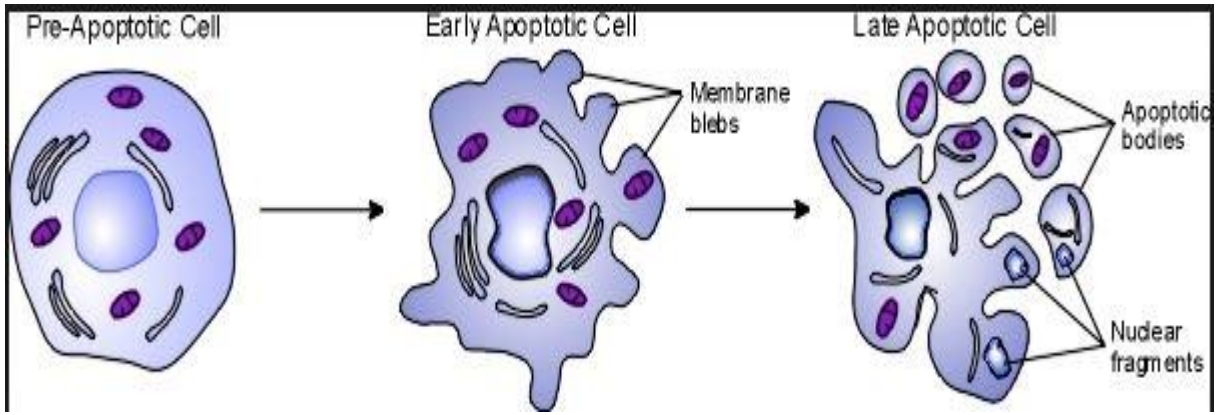
Insensitivity to Anti-Growth Signals

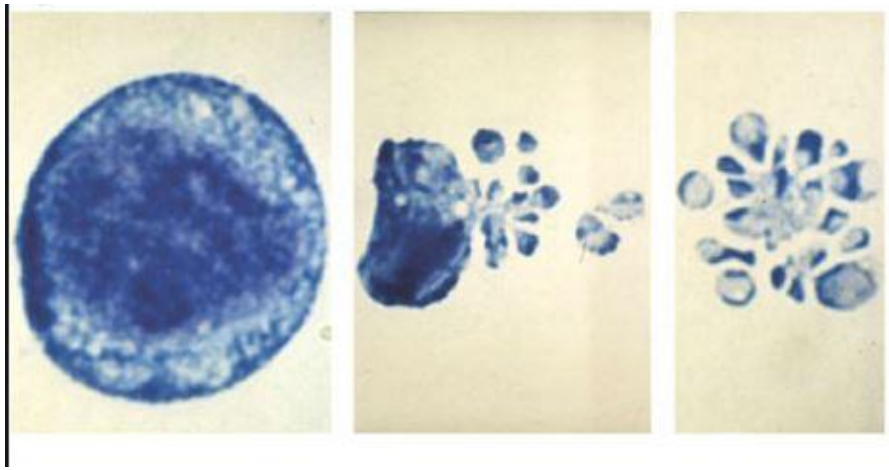
- Cancer cells are generally resistant to growth-preventing signals from their neighbors
  - Mutations in **tumor suppressor genes**
- Often based on internal clock (**cell-cycle**)
  - Genes take information from cell and its environment and determine if it should divide (**mitosis**)
  - Cancer – proteins from these genes are altered so as not to function, so that a cell will divide regardless of signal (pRb, p53)
- Normal cells – stop dividing due to **contact inhibition,** which cancer cells ignore



Evading Cell Death

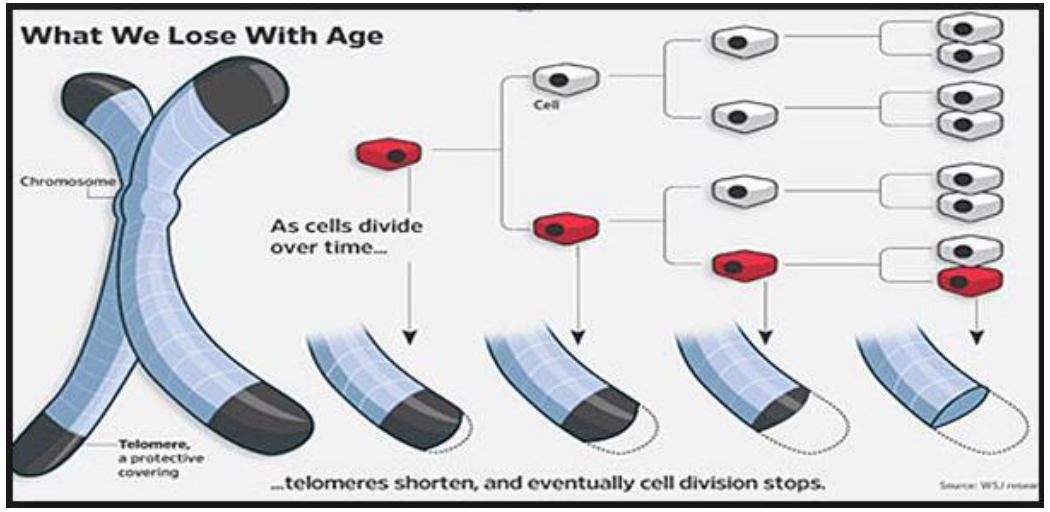
- Similar to the previous, cancer cells obtain the ability to evade programmed cell death (**apoptosis**)
  - Again related to **tumor suppressor genes**
- Even though cell is grossly abnormal (DNA damage, hypoxic, viral infection, etc.)
  - Note: if exhibiting, DNA damage therapies may be ineffective





Limitless Replicative Potential

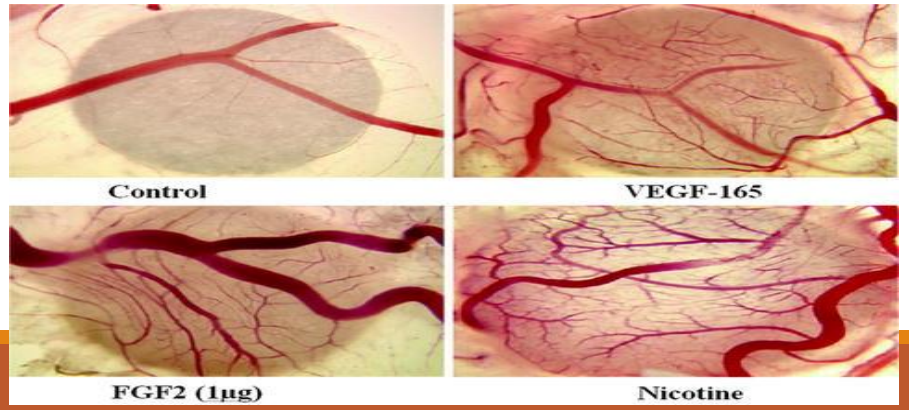
- Healthy cells have a limit on the number of cell divisions that can occur before **senescence** or cell death (**crisis**)
  - Hayflick limit: 60-70 doublings in a lifetime
- Why?
  - **Telomeres** (DNA at end of the chromosomes) shorten during every cell division
  - Eventually, becomes too short to divide (activates senescence)



- Cancer cells upregulate **telomerase** (enzyme that maintains telomeres)

Developing Blood Vessels

- Cells need oxygen and other nutrients to survive and grow
  - Most lie within 100 µm of a capillary
- Typically, capillaries don't grow
  - Certain exceptions: wound healing, menstruation
- However, tumors can obtain mutations to prompt **angiogenesis** – process by which new blood vessels are formed
  - Key transition from in situ tumor into large malignant growth capable of spreading
  - No bigger than pea beforehand



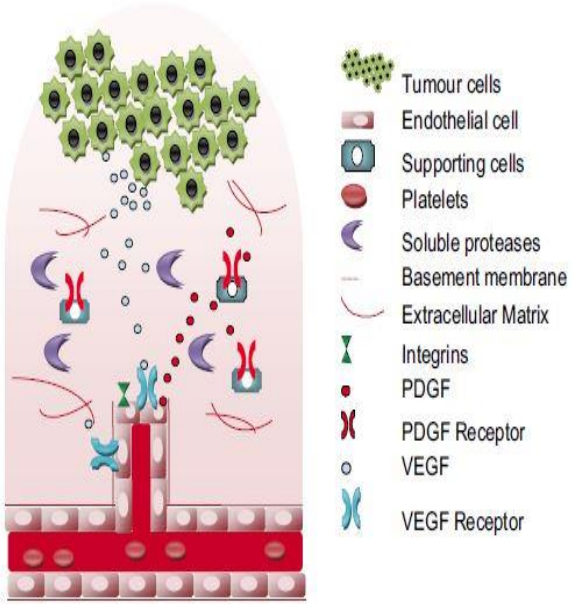


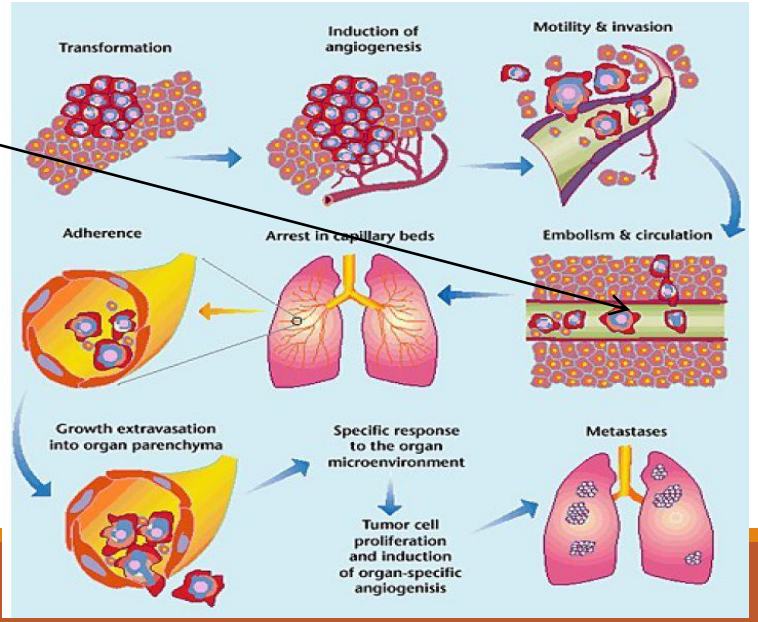
Fig 6.1. Angiogenesis in tumour growth. Tumour cells release pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), which diffuse into nearby tissues and bind to receptors on the endothelial cells of pre-existing blood vessels, leading to their activation. Such interactions leads to the secretion and activation of various soluble proteases (such as matrix metalloproteinases MMPs), which degrade the basement membrane and the extracellular matrix. Degradation allows activated endothelial cells to divide and migrate towards the tumour. Integrin molecules help to pull the sprouting new blood vessel forward. The endothelial cells deposit a new basement membrane and secrete growth factors, such as platelet-derived growth factor (PDGF), which attract supporting cells to stabilize the new vessel.

- Very complicated (linked with suppressor p53 via thrombospondin-1)
- Attractive treatment target (anti-angiogenic)

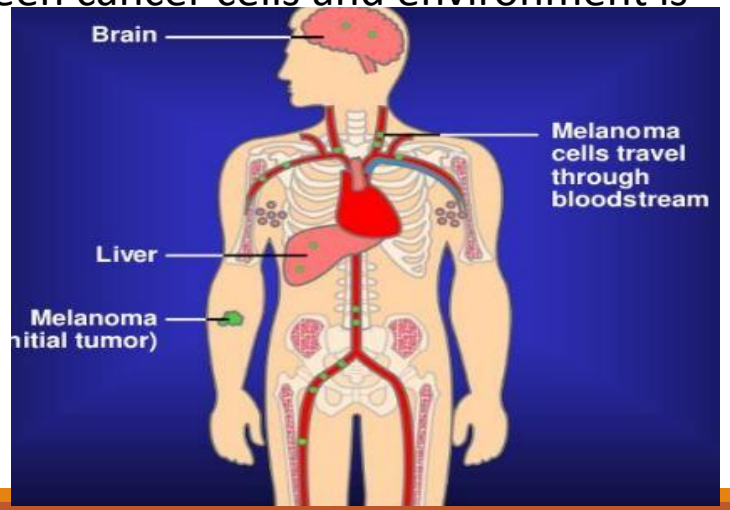
Tissue Invasion and Metastasis

- Cancer cells can break away from their site or organ or origin to invade surrounding tissue and spread **(metastasize**) to colonize body parts
  - Secondary tumors – **metastases** (responsible for almost 90% of cancer-related deaths)
- Survive and grow in new environments where there are no restrictions on space or nutrients
- Use newly developed blood vessels (angiogenesis) to travel (and survive, which is harsh) blood supply (or lymph), escape circulatory system, and invade (i.e. divide in) foreign tissue (also hard, since environment may be very different than evolved in)
  - Most likely lodge in (from microthrombi) lungs, brain, liver (most highly vascularized)

Most die



Interaction between cancer cells and environment is very important



Other Traits of Cancer

- New traits that are (more recently) coming to light

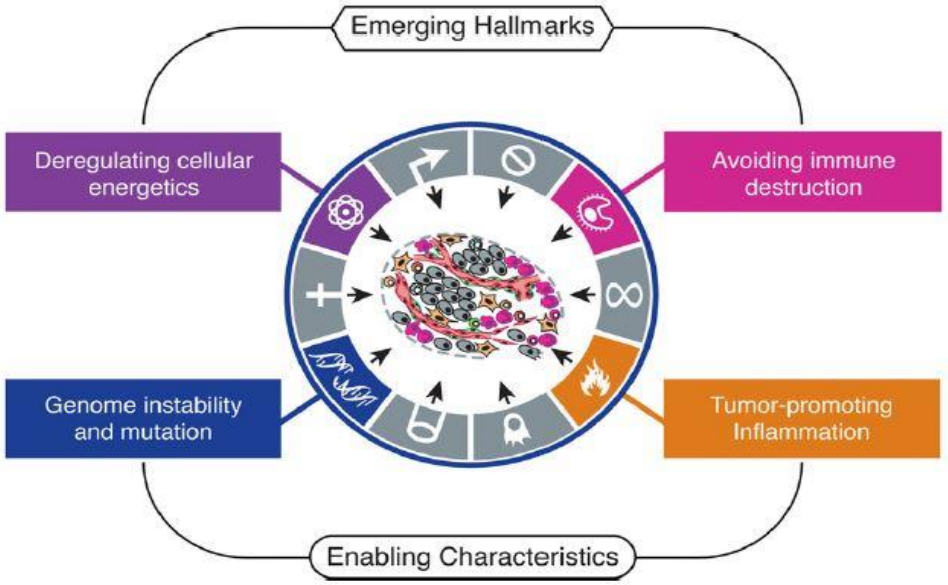


Figure 3. Emerging Hallmarks and Enabling Characteristics
An increasing body of research suggests that two additional hallmarks of cancer are involved in the pathogenesis of some and perhaps all cancers. One involves the capability to modify, or reprogram, cellular metabolism in order to most effectively support neoplastic proliferation. The second allows cancer cells to evade immunological destruction, in particular by T and B lymphocytes, macrophages, and natural killer cells. Because neither capability is yet generalized and fully validated, they are labeled as emerging hallmarks. Additionally, two consequential characteristics of neoplasia facilitate acquisition of both core and emerging hallmarks. Genomic instability and thus mutability endow cancer cells with genetic alterations that drive tumor progression. Inflammation by innate immune cells designed to fight infections and heal wounds can instead result in their inadvertent support of multiple hallmark capabilities, thereby manifesting the now widely appreciated tumor-promoting consequences of inflammatory responses.

- **Genomic instability** – increased rates at which cells acquire genetic abnormalities
  - Intuitive (but not necessary), since a number of mutations are required
  - Epigenetic (DNA methylation, histone modification) mechanisms as well
- **Deregulated metabolism** – energy production primarily via glycolysis
- **Inflammation and tumor progression** - tumour microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process