1. Origin of Cancer
Cancers mostly originate in tissues and cell types that undergo continuous regeneration- e.g., skin, and epithelium, or that retain the potential to proliferate- e.g. hepatocytes, hematopoietic stem cells and progenitor cells. Terminally differentiated neurons and muscle cells are more prone to degenerative diseases than to neoplastic transformation.

Cancer stem cells, also known as cancer initiating cells, are a subpopulation of cancer cells that have the potential to regenerate malignant cancers with higher efficiency than other cells from the same cancer sample. Cancer stem cells may arise from the normal tissue stem cells or from progenies of the tissue stem cells that still possess the potential to proliferate. Currently, there are two schools of thoughts on cancer stem cells: the deterministic view proposes the cancer stem cell fate is a fixed property and this property is lost in the progenies of the cancer stem cell; the plasticity view proposes the cancer stem cell fate is a property that is not fixed, it can be induced in any cancer cell. Both schools agree on one point, that is, cancers are not a homogenous ball of cells. Rather, cancers are abnormal tissues, consisting of malignant cells with varying degrees of tumorigenic potential.

2. Biological Framework Underlying Cancer Development
Cancer development is driven by genetic defects that are either inherited or acquired as a result of gene-environment interactions. The formation of malignant tumors (cancers) require a large number of defects that can be categorized into two groups: (a) cancer cell autonomous defects and (b) cancer tissue microenvironment defects.

(a) Cancer cell autonomous defects:
• Proliferation deregulated (note, cancer cells do not growth faster than normal cells, they just grow in an uncontrollable fashion).
• Differentiation compromised (note, the concept of cancer stem cells dictate that there is still some forms of differentiation within a malignant tumor, it also dictates that the cancer stem cells can self-renew, i.e., only some of their progenies will lose the stem cell fate, while others retain the stem cell proliferative potential).
• Senescence blocked.
• Apoptosis reduced.
• Mutation rate elevated (through defects in DNA repair mechanisms).

(b) Cancer tissue microenvironment defects:
• Angiogenesis (cancer cells are known to produce VEGF to stimulate the formation of new blood vessels that feed the growth of the malignant tissue).
• Tissue remodeling (cancer cells are known to attracts white blood cells- granulocytes and macrophages into the tumor tissues)
• Immune Evasion (cancer cells must develop ways to evade immune surveillance that kills transformed cells)
• Invasion/Metastasis (cancer cells are known to secret proteases to digest their ways around the local tissues and to enter the blood vessels and travel to distant sites. Cancers that originate in non-vital tissues such as the breasts only kill when they metastasize to colonize vital organs such as the brain).

3. Oncogenes
Oncogenes encode products (mostly proteins; recent studies suggest some non-coding RNAs, for example, microRNAs, may also have oncogenic function) that promote cancer development.

Oncogenes were discovered in viruses- DNA tumor virus or RNA tumor virus (mostly Retrovirus).

Studies of retroviral oncogenes that cause various types of cancers in vertebrate animals (chicken, rat, mouse, monkey) have led to the discovery of human oncogenes, which are altered versions of normal human genes (aka proto-oncogenes).

4. Genetic Accidents Convert Proto-Oncogenes into Oncogenes
(a) Mutations that alter protein function, e.g., RAS.
(b) Chromosomal translocation that create fusion proteins with oncogenic functions, e.g., BCR-ABL.
(c) Chromosomal translocation that juxtapose strong promoters next to a proto-oncogene to cause excessive production, e.g., Myc.
(d) Gene amplification to increase the copy number of a proto-oncogene and cause excessive production, e.g., Myc, ErbB2, MDM2.

5. Proto-Oncogenes Encode Proteins of Growth Factor-Activated RTK Signaling Pathways
(a) Sis encodes PDGF-B
(b) ErbB encodes EGFR
(c) Crk encodes an adaptor protein consisting of SH3-SH2 domains
(d) RAS encodes a small GTPase activated by RTK
(e) Raf encodes a serine/threonine kinase that phosphorylates and activates Mek kinase.
(f) Myc encodes a transcription factor, the expression of which is activated by multiple pathways downstream of RTK signaling.

6. Oncogene-Targeted Drugs Have Revolutionized Cancer Therapy
(a) Imatinib (aka Gleevec™) inhibits BCR-ABL tyrosine kinase.
(b) Herceptin is an antibody that binds ErbB2 receptor and induces its downregulation (through endocytosis and degradation in the lysosome).

7. Tumor Suppressors
Tumor suppressor genes are lost from cancer cells, either by mutations or by epigenetic silencing of gene expression. Tumor suppressor genes (TSGs) were discovered through studies of hereditary cancer syndromes.
The paradigm for TSG is the human retinoblastoma suppressor gene, Rb. Retinoblastoma is a childhood cancer that originates from the developing retinoblasts (precursor cells to the retinal neurons). Approximately 40% of the retinoblastoma patients have a family history of this cancer; these patients develop retinoblastoma as early as 2 months of age and invariably present with tumors in both eyes. The other 60% of retinoblastoma patients do not have a family history, the non-hereditary (or sporadic) cases are older and their tumors are limited to one eye. Retinoblastoma cells lack a functional Rb gene. The hereditary retinoblastoma patients carry a germline mutation in the Rb gene. Ninety per cent of these patients develop bilateral retinoblastomas as a result of the loss of the single copy of wild-type Rb. The non-hereditary retinoblastoma patients are born with two good copies of Rb. They develop retinoblastoma only when both copies of Rb are lost in a single retinoblast cell, the result of an unlucky series of spontaneous and random mutations occurring at the physiological rate. Sporadic retinoblastoma occurs at a population of 1 in 300,000 live births (not 30,000 stated in Alberts, 5th Ed.).

A large number of tumor suppressors have been discovered and cloned from patients of hereditary cancer syndromes. The retinoblastoma paradigm applies to virtually all of these cancer syndromes in that the patients inherit only one good copy of a TSG. Because it is easy to lose a single copy of a TSG through spontaneous, random mutation, these patients are predisposed to cancer, and their cancer cells invariably lose that single copy of TSG.

TSGs encode proteins of diverse functions. In addition to proteins that inhibit growth factor signaling and the cell cycle, many TSGs encode DNA repair proteins, demonstrating the importance of DNA repair in tumor suppression.

8. **Apoptosis (Programmed Cell Death) as a Failsafe Mechanism to Control Proliferation**

Excessive production of Myc simultaneously activates gene expression programs to stimulate cell division and to stimulate apoptosis. In order for Myc to induce cancer, its pro-apoptotic activity must be neutralized. Survival factors, such as insulin-like growth factor-1, IGF-1), stimulates the PIP3-Akt survival pathway. Without IGF-1, excessive production of Myc leads to cell death. With IGF-1, excessive production of Myc stimulates cell proliferation.

Similarly, E2F, a transcription factor that is activated by mitogenic factor and inhibited by RB, simultaneously activates DNA synthesis and apoptosis. In order for the loss of RB to induce cancer, the pro-apoptotic activity of E2F needs to be dealt with, and this is achieved through the mutation of p53, which mediates in part the pro-apoptotic activity of E2F.

Oncogenic RAS mutant protein alone does not transform normal human cells. Instead, oncogenic RAS activates p53 to induce cell cycle arrest. Oncogenic RAS readily transforms p53-deficient cells. Therefore, p53 is an important tumor
suppressor because it is activated by abnormal mitogenic signals to either induce apoptosis or growth arrest. Whether a cell will undergo apoptosis or cell cycle arrest in response to p53 is determined by the cell context, there is not a simple rule by which we can predict how a cell would respond to p53.

9. Exploiting TSG Loss in Cancer Therapy

With TSGs, the obvious thing to do is to restore their functions in cancer cells. The restoration of gene function through gene therapy is still an unrealized dream due to technical difficulties.

Turning the table around, scientists have tried to exploit the TSG loss to kill cancer cells. This strategy is particularly useful with cancer cells that have lost DNA repair proteins, e.g., BRCA1 or BRCA2. The conventional cancer therapeutic agents, such as chemotherapy and radiation therapy kill cancer cells by inducing DNA damage. Persistent DNA damage interferes with DNA replication and activates programmed cell death. DNA repair-deficient cancer cells are hypersensitive to agents that cause DNA damage. To selectively target repair-deficient cancer cells, we can inhibit a repair pathway that the cancer cells depend upon to repair their DNA. For example, in BRCA1 or BRCA2 deficient breast cancer cells, the homologous recombination repair pathway is defective and as a result these cancer cells are much more sensitive than normal cells to inhibitors of basic excision repair (BER).