**Molecular Basis of Cancer**

* *Nonlethal genetic damage lies at the heart of carcinogenesis*. Such genetic damage (or mutation) may be acquired by the action of environmental agents, such as chemicals, radiation, or viruses, or it may be inherited in the germ line.
* *A tumor is formed by the clonal expansion of a single precursor cell that has incurred genetic damage (i.e., tumors are monoclonal)*.
* *Four classes of normal regulatory genes—the growth-promoting proto-oncogenes, the growth-inhibiting tumor suppressor genes, genes that regulate programmed cell death (apoptosis), and genes involved in DNA repair—are the principal targets of genetic damage*.
* *Carcinogenesis is a multistep process at both the phenotypic and the genetic levels, resulting from the accumulation of multiple mutations*. malignant neoplasms have several phenotypic attributes, such as excessive growth, local invasiveness, and the ability to form distant metastases. Furthermore, it is well established that over a period of time many tumors become more aggressive and acquire greater malignant potential. This phenomenon is referred to as tumor progression and is not simply a function of an increase in tumor size.

ESSENTIAL ALTERATIONS FOR MALIGNANT TRANSFORMATION

It is beneficial to consider cancer-related genes in the context of *seven fundamental changes in cell physiology that together determine malignant phenotype*:

* *Self-sufficiency in growth signals*: Tumors have the capacity to proliferate without external stimuli, usually as a consequence of oncogene activation.
* *Insensitivity to growth-inhibitory signals*: Tumors may not respond to molecules that are inhibitory to the proliferation of normal cells such as transforming growth factor β (TGF-β) and direct inhibitors of cyclin-dependent kinases (CDKIs).
* *Evasion of apoptosis*: Tumors may be resistant to programmed cell death, as a consequence of inactivation of *p53* or activation of anti-apoptotic genes.
* *Limitless replicative potential*: Tumor cells have unrestricted proliferative capacity.
* *Sustained angiogenesis*: Tumor cells, like normal cells, are not able to grow without formation of a vascular supply to bring nutrients and oxygen and remove waste products. Hence, tumors must induce angiogenesis.
* *Ability to invade and metastasize*: Tumor metastases are the cause of the vast majority of cancer deaths and depend on processes that are intrinsic to the cell or are initiated by signals from the tissue environment.
* *Defects in DNA repair*: Tumors may fail to repair DNA damage caused by carcinogens or incurred during unregulated cellular proliferation, leading to genomic instability and mutations in proto-oncogenes and tumor suppressor genes.

SELF-SUFFICIENCY IN GROWTH SIGNALS: ONCOGENES

Genes that promote autonomous cell growth in cancer cells are called *oncogenes*, and their unmutated cellular counterparts are called *proto-oncogenes*. **Oncogenes** are created by mutations in proto-oncogenes and are characterized by the ability to promote cell growth in the absence of normal growth-promoting signals. Their products, called *oncoproteins*, resemble the normal products of proto-oncogenes except that oncoproteins are often devoid of important internal regulatory elements, and their production in the transformed cells does not depend on growth factors or other external signals. In this way cell growth becomes autonomous, freed from checkpoints and dependence upon external signals.

* **Growth Factors**.

Normal cells require stimulation by growth factors to undergo proliferation. Most soluble growth factors are made by one cell type and act on a neighboring cell to stimulate proliferation (paracrine action). Many cancer cells, however, acquire the ability to synthesize the same growth factors to which they are responsive, generating an autocrine loop. For example, many glioblastomas secrete platelet-derived growth factor (PDGF) and express the PDGF receptor.

* **Growth Factor Receptors**

Several oncogenes that encode growth factor receptors have been found. To understand how mutations affect the function of these receptors**,** one important class of growth factor receptors are transmembrane proteins with an external ligand-binding domain and a cytoplasmic tyrosine kinase domain, In the normal forms of these receptors, the kinase is *transiently* activated by binding of the specific growth factors, followed rapidly by receptor dimerization and tyrosine phosphorylation of several substrates that are a part of the signaling cascade. *The oncogenic versions of these receptors are associated with constitutive dimerization and activation without binding to the growth factor*. Hence, the mutant receptors deliver continuous mitogenic signals to the cell, even in the absence of growth factor in the environment. **Signal-Transducing Proteins**

Several examples of oncoproteins that mimic the function of normal cytoplasmic signal-transducing proteins have been found. Most such proteins are strategically located on the inner leaflet of the plasma membrane, where they receive signals from outside the cell (e.g., by activation of growth factor receptors) and transmit them to the cell's nucleus. *The most well-studied example of a signal-transducing oncoprotein is the RAS family.*

* **Transcription Factors**

Just as all roads lead to Rome, all signal transduction pathways converge to the nucleus, where a large bank of responder genes that orchestrate the cell's orderly advance through the mitotic cycle are activated.

Growth autonomy may thus occur as a consequence of mutations affecting genes that regulate transcription. A host of oncoproteins, including products of the *MYC*, *MYB*, *JUN*, *FOS*, and *REL* oncogenes, are transcription factors that regulate the expression of growth-promoting genes, such as cyclins.

**INSENSITIVITY TO GROWTH INHIBITION AND ESCAPE FROM SENESCENCE: TUMOR SUPPRESSOR GENES**

Failure of growth inhibition is one of the fundamental alterations in the process of carcinogenesis. Whereas oncogenes drive the proliferation of cells, the products of *tumor suppressor genes apply brakes to cell proliferation***.**

It has become apparent that the tumor suppressor proteins form a network of checkpoints that prevent uncontrolled growth. Many tumor suppressors, such as RB and p53, are part of a regulatory network that recognizes genotoxic stress from any source, and responds by shutting down proliferation.

p53: Guardian of the Genome.

The *p53* gene is located on chromosome 17p13.1, and it is the most common target for genetic alteration in human tumors. *Little over 50% of human tumors contain mutations in this gene*.

*p53 links cell damage with DNA repair, cell cycle arrest, and apoptosis. In response to DNA damage, p53 is phosphorylated by genes that sense the damage and are involved in DNA repair. p53 assists in DNA repair by causing G*1 *arrest and inducing DNA-repair genes. A cell with damaged DNA that cannot be repaired is directed by p53 to undergo apoptosis*. *In view of these activities, p53 has been rightfully called a “guardian of the genome.” With loss of function of p53, DNA damage goes unrepaired, mutations accumulate in dividing cells, and the cell marches along a one-way street leading to malignant transformation*.

**EVASION OF APOPTOSIS**

Accumulation of neoplastic cells may result not only from activation of growth-promoting oncogenes or inactivation of growth-suppressing tumor suppressor genes, but also from mutations in the genes that regulate apoptosis**.** A variety of signals, ranging from DNA damage to loss of adhesion to the basement membrane can trigger apoptosis. A large family of genes that regulate apoptosis has been identified. *Best established is the role of BCL2 in protecting tumor cells from apoptosis*. approximately 85% of B-cell lymphomas of the follicular typeshow effect in this gene.

**ANGIOGENESIS**

Even with all the genetic abnormalities discussed above, solid tumors cannot enlarge beyond 1 to 2 mm in diameter unless they are vascularized. Like normal tissues, tumors require delivery of oxygen and nutrients and removal of waste products; presumably the 1- to 2-mm zone represents the maximal distance across which oxygen, nutrients, and waste can diffuse from blood vessels. Cancer cells can stimulate **neo-angiogenesis**, during which new vessels sprout from previously existing capillaries, or, in some cases, **vasculogenesis**, in which endothelial cells are recruited from the bone marrow**.** Tumor vasculature is abnormal, however. The vessels are leaky and dilated, and have a haphazard pattern of connection. **Neovascularization has a dual effect on tumor growth:** perfusion supplies needed nutrients and oxygen, and newly formed endothelial cells stimulate the growth of adjacent tumor cells by secreting growth factors. **Angiogenesis is required not only for continued tumor growth but also for access to the vasculature and hence for metastasis.** *Angiogenesis is thus a necessary biologic correlate of malignancy*.

**INVASION AND METASTASIS**

Invasion and metastasis are biologic hallmarks of malignant tumors. They are the major cause of cancer-related morbidity and mortality and hence are the subjects of intense scrutiny. the metastatic cascade will be divided into two phases: **(1) invasion of the extracellular matrix (ECM); (2) vascular dissemination, homing of tumor cells, and colonization.**

tissues are organized into compartments separated from each other by two types of ECM: basement membrane and interstitial connective tissue. A carcinoma must first breach the underlying basement membrane, then traverse the interstitial connective tissue, and ultimately gain access to the circulation by penetrating the vascular basement membrane. This process is repeated in reverse when tumor cell emboli extravasate at a distant site. Invasion of the ECM initiates the metastatic cascade and *is an active process that can be resolved into several steps***.**

* **Changes (“loosening up”) of tumor cell-cell interactions,** *Dissociation of cells from one another* is often the result of alterations in intercellular adhesion molecules. Normal cells are neatly glued to each other and their surroundings by a variety of adhesion molecules.

Presumably, this down-regulation reduces the ability of cells to adhere to each other and facilitates their detachment from the primary tumor and their advance into the surrounding tissues.

* **Degradation of ECM,** Tumor cells may either secrete proteolytic enzymes themselves or induce stromal cells (e.g., fibroblasts and inflammatory cells) to elaborate proteases.
* **Attachment to novel ECM components.** Normal epithelial cells have receptors, such as integrins, these receptors help to maintain the cells in a resting, differentiated state. Loss of adhesion in normal cells leads to induction of apoptosis, while, not surprisingly, tumor cells are resistant to this form of cell death. Additionally, the matrix itself is modified in ways that promote invasion and metastasis.
* **Migration of tumor cells.** propelling tumor cells through the degraded basement membranes and zones of matrix proteolysis. Migration is a complex, multistep process . Cells must attach to the matrix at the leading edge, detach from the matrix at the trailing edge, and contract the actin cytoskeleton to ratchet forward.