102e Cancer Cell Biology

Jeffrey W. Clark, Dan L. Longo

Cancers are characterized by unregulated cell division, avoidance of cell death, tissue invasion, and the ability to metastasize. A neoplasm is *benign* when it grows in an unregulated fashion without tissue invasion. The presence of unregulated growth and tissue invasion is characteristic of *malignant* neoplasms. Cancers are named based on their origin: those derived from epithelial tissue are called *carcinomas*, those derived from mesenchymal tissues are *sarcomas*, and those derived from hematopoietic tissue are *leukemias*, *lymphomas*, and *plasma cell dyscrasias* (including *multiple myeloma*).

Cancers nearly always arise as a consequence of genetic alterations, the vast majority of which begin in a single cell and therefore are monoclonal in origin. However, because a wide variety of genetic and epigenetic changes can occur in different cells within malignant tumors over time, most cancers are characterized by marked heterogeneity in the populations of cells. This heterogeneity significantly complicates the treatment of most cancers because it is likely that there are subsets of cells that will be resistant to therapy and will therefore survive and proliferate even if the majority of cells are killed.

A few cancers appear to, at least initially, be primarily driven by an alteration in a dominant gene that produces uncontrolled cell proliferation. Examples include chronic myeloid leukemia (*abl*), about half of melanomas (*braf*), Burkitt's lymphoma (c-*myc*), and subsets of lung adenocarcinomas (*egfr, alk, ros1*, and *ret*). The genes that can promote cell growth when altered are often called *oncogenes*. They were first identified as critical elements of viruses that cause animal tumors; it was subsequently found that the viral genes had normal counterparts with important functions in the cell and had been captured and mutated by viruses as they passed from host to host.

However, the vast majority of human cancers are characterized by a multiple-step process involving many genetic abnormalities, each of which contributes to the loss of control of cell proliferation and differentiation and the acquisition of capabilities, such as tissue invasion, the ability to metastasize, and angiogenesis. These properties are not found in the normal adult cell from which the tumor is derived. Indeed, normal cells have a large number of safeguards against uncontrolled proliferation and invasion. Many cancers go through recognizable steps of progressively more abnormal phenotypes: hyperplasia, to adenoma, to dysplasia, to carcinoma in situ, to invasive cancer with the ability to metastasize (Table 102e-1). For most cancers, these changes occur over a prolonged period of time, usually many years.

In most organs, only primitive undifferentiated cells are capable of proliferating and the cells lose the capacity to proliferate as they differentiate and acquire functional capability. The expansion of the primitive cells is linked to some functional need in the host through receptors that receive signals from the local environment or through hormonal and other influences delivered by the vascular supply. In the absence of such signals, the cells are at rest. The signals that keep the primitive cells at rest remain incompletely understood. These signals must be environmental, based on the observations that a regenerating liver stops growing when it has replaced the portion that has been surgically removed after partial hepatectomy and regenerating bone marrow stops growing when the peripheral blood counts return to normal. Cancer cells clearly have lost responsiveness to such controls and do not recognize when they have overgrown the niche normally occupied by the organ from which they are derived. A better understanding of the mechanisms of growth regulation is evolving.

TABLE 102e-1 PHENOTYPIC CHARACTERISTICS OF MALIGNANT CELLS

Deregulated cell proliferation: Loss of function of negative growth regulators (tumor-suppressor genes, i.e., *Rb*, *p53*), and increased action of positive growth regulators (oncogenes, i.e., *Ras, Myc*). Leads to aberrant cell cycle control and includes loss of normal checkpoint responses.
Failure to differentiate: Arrest at a stage before terminal differentiation. May retain stem cell properties. (Frequently observed in leukemias due to transcriptional repression of developmental programs by the gene products of chromosomal translocations.)
Loss of normal apoptosis pathways: Inactivation of p53, increases in Bcl-2 family members. This defect enhances the survival of cells with oncogenic mutations and genetic instability and allows clonal expansion and diversification within the tumor without activation of physiologic cell death pathways.
Genetic instability: Defects in DNA repair pathways leading to either single-nucleotide or oligonucleotide mutations (as in microsatellite instability, MIN) or more commonly chromosomal instability (CIN) leading to aneuploidy. Caused by loss of function of *p53, BRCA1/2*, mismatch repair genes, DNA repair enzymes, and the spindle checkpoint. Leads to accumulation of a variety of mutations in different cells within the tumor and heterogeneity.
Loss of replicative senescence: Normal cells stop dividing in vitro after 25–50 population doublings. Arrest is mediated by the Rb, $p16^{INK4a}$, and p53 pathways. Further replication leads to telomere loss, with crisis. Surviving cells often harbor gross chromosomal abnormalities. Relevance to human in vivo cancer remains uncertain. Many human cancers express telomerase.
Nonresponsiveness to external growth-inhibiting signals: Cancer cells have lost responsiveness to signals normally present to stop proliferating when they have overgrown the niche normally occupied by the organ from which they are derived. We know very little about this mechanism of growth regulation.
Increased angiogenesis: Due to increased gene expression of proangiogenic factors (VEGF, FGF, IL-8) by tumor or stromal cells, or loss of negative regulators (endostatin, tumstatin, thrombospondin).
Invasion: Loss of cell-cell contacts (gap junctions, cadherins) and increased production of matrix metalloproteinases (MMPs). Often takes the form of epithelial-to-mesenchymal transition (EMT), with anchored epithelial cells becoming more like motile fibroblasts.
Metastasis: Spread of tumor cells to lymph nodes or distant tissue sites. Limited by the ability of tumor cells to survive in a foreign environment.
Evasion of the immune system: Downregulation of MHC class I and II molecules; induction of T cell tolerance; inhibition of normal dendritic cell and/or T cell function; antigenic loss variants and clonal heterogeneity; increase in regulatory T cells.
Shift in cell metabolism: Energy generation shifts to aerobic glycolysis.

Abbreviations: FGF, fibroblast growth factor; IL, interleukin; MHC, major histocompatibility complex; VEGF, vascular endothelial growth factor.

CELL CYCLE CHECKPOINTS

Normal cells have a number of control mechanisms that are targeted by specific genetic alterations in cancer. Critical proteins in these control processes that are frequently mutated or otherwise inactivated in cancers are called tumor-suppressor genes. Examples include p53 and Rb (discussed below). The progression of a cell through the cell division cycle is regulated at a number of checkpoints by a wide array of genes. In the first phase, G_1, preparations are made to replicate the genetic material. The cell stops before entering the DNA synthesis phase, or S phase, to take inventory. Are we ready to replicate our DNA? Is the DNA repair machinery in place to fix any mutations that are detected? Are the DNA replicating enzymes available? Is there an adequate supply of nucleotides? Is there sufficient energy? The main brake on the process is the retinoblastoma protein, Rb. When the cell determines that it is prepared to move ahead, sequential activation of cyclin-dependent kinases (CDKs) results in the inactivation of the brake, Rb, by phosphorylation. Phosphorylated Rb releases the S phase–regulating transcription factor, E2F/DP1, and genes required for S phase progression are expressed. If the cell determines that it is unready to move ahead with DNA replication, a number of inhibitors are capable of blocking the action of the CDKs, including $p21^{Cip2/Waf1}$, $p16^{Ink4a}$, and $p27^{Kip1}$. *Nearly every cancer has one or more genetic lesions in the G_1 checkpoint that permits progression to S phase.*

At the end of S phase, when the cell has exactly duplicated its DNA content, a second inventory is taken at the S checkpoint. Have all of the chromosomes been fully duplicated? Were any segments of DNA copied more than once? Do we have the right number of chromosomes and the right amount of DNA? If so, the cell proceeds to G_2, in which the cell prepares for division by synthesizing mitotic spindle and other proteins needed to produce two daughter cells. When DNA damage is