CHAPTER

1 Biology of Cancer

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Introduction

Many in the lay public describe a diagnosis of "cancer" as if it is one disease. In reality, it encompasses more than 200 diseases that will occur at different ages with different rates of growth, differentiation, abilities to be detected, invasiveness, capacities to spread or metastasize, treatment responses, and prognoses. However, at the cellular and molecular levels, cancer is beginning to be viewed as a few diseases caused by genetic alterations and defective cell function that are actually very similar (Muñoz-Pinedo, El Mjiyad, & Ricci, 2012). These alterations can be associated with "nature," such as inherited cancer syndromes like hereditary breast and ovarian cancer syndrome or immune deficiencies. Or, the genetic alterations can be caused by "nurture," which includes obesity, poor diet, and social habits, such as smoking. A malignant growth is the result of changes in DNA, gene transcription, or translation. The resultant defective protein or proteins lead to transformation of normal cell components into uncontrolled proliferation, spread, or metastasis (Muñoz-Pinedo et al., 2012). This chapter focuses on a description of the malignant changes of a cell that will provide nurses new to oncology with a foundation for understanding the growth of cancer and its treatment, along with the basis to provide education to patients and their families.

Models of Cancer Development

Two models are commonly used to describe how a cancer develops. The first is the Stochastic Model, previously including Knudson's random "two hit" model. This model suggests that each cancer cell has the ability to multiply and form new tumors. The malignant cells have a selective advantage over their normal neighbors and begin to proliferate rapidly, accumulating genetic damage with each generation. As the damage collects, the most aggressive characteristics promote immortalized growth and the formation of a tumor (Beck & Blanpain, 2013; Hanahan & Weinberg, 2011).

The individual cancer stem cell is the focus of the second model. This model states that many different types of cancer cells exist in addition to endothelial, hematopoietic, stromal, and other types of cells to meet the functioning needs of the tumor, demonstrating heterogeneity. With proliferation, cell division occurs. All of these cells have the ability to multiply, but only one cell type—the cancer stem cell—has the ability to become a new tumor (Kreso & Dick, 2014). This is becoming the model most supported by cancer researchers. Once the new tumor is established, the heterogeneous cells begin to proliferate, allowing the tumor to enlarge, and the cancer stem cell moves into the resting phase (G_0) of the cell cycle. Cells in this phase are resistant to treatment and would remain as one surviving cancer cell while treatment destroys the other rapidly dividing non-

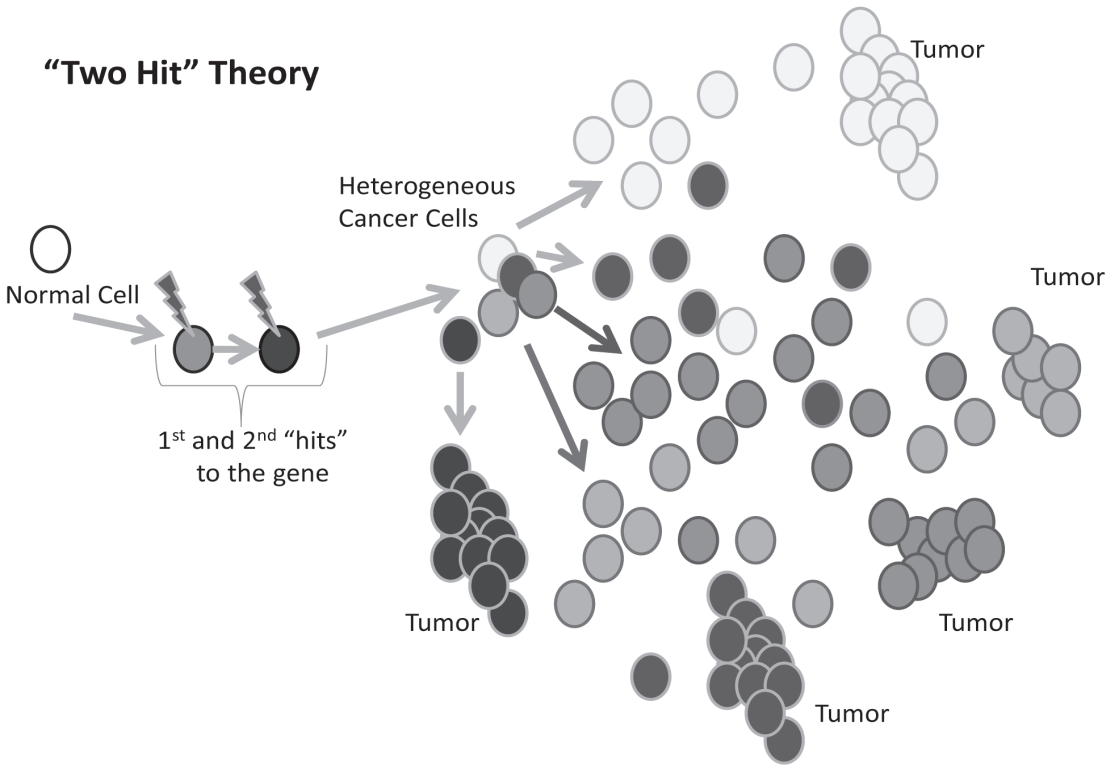
cancer stem cells (Junttila & de Sauvage, 2013). Thus, months or years later, the "resting" cancer stem cell could move into the active phases of the cell cycle, proliferate, and cause exacerbation of the once-dormant cancer believed to be destroyed during the original treatment (Kreso & Dick, 2014). See Figures 1-1 and 1-2 for comparison of these theories of tumor development.

An update of the cancer stem cell model is known as the Plasticity Model of Cancer Stem Cells. This newer model suggests that plasticity (the ability to change throughout the life of the cell) allows cancer stem cells to become heterogeneous with the ability to come out of remission, whereas noncancer stem cells have very low potential to become tumorigenic (Marjanovic, Weinberg, & Chaffer, 2013).

Structure and Function of DNA and Chromosomes

The human genome consists of 23 pairs of chromosomes. Each chromosome is a single double-helix DNA molecule with millions

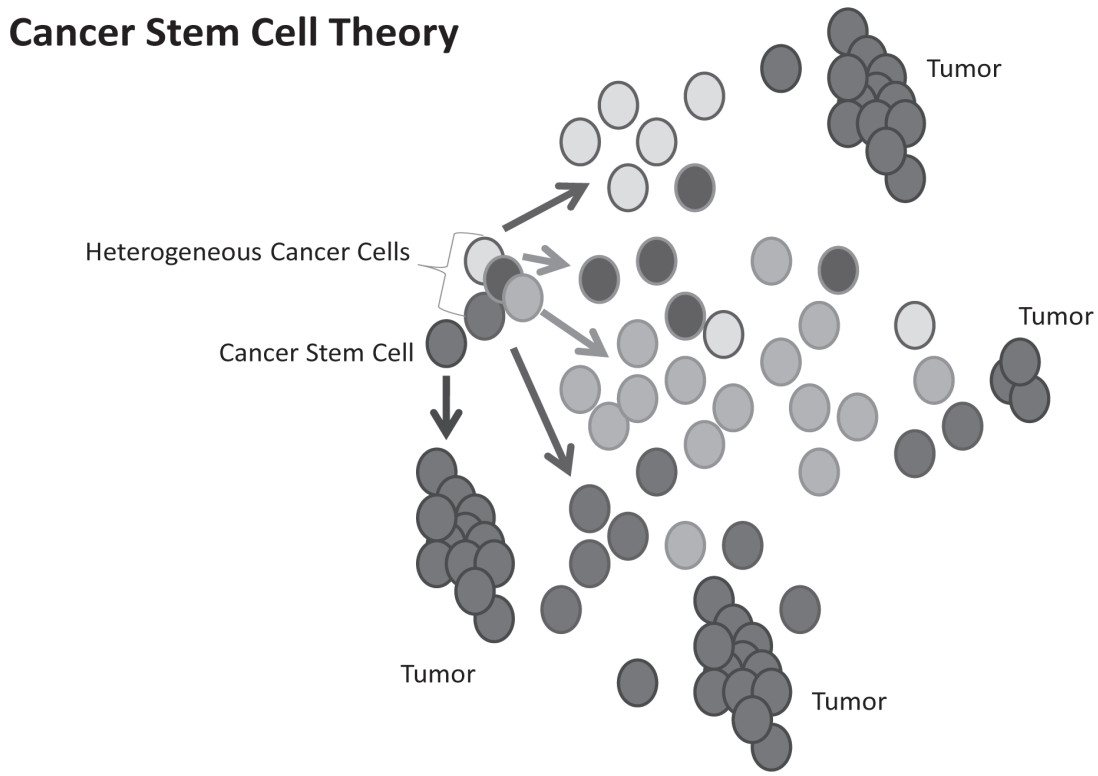
Figure 1-1. Knudson "Two Hit" Theory of Cancer Development



Theory: Two genes within a cell, one on each of a pair of chromosomes, each receive damage-causing hits prior to the development of cancer. The malignant cells are heterogeneous and all have the capability of developing a tumor.

Note. Based on information from Hanahan & Weinberg, 2011; Knudson, 1971; Reya et al., 2001; Wicha et al., 2006.

Figure 1-2. Cancer Stem Cell Theory of Cancer Development



Theory: Cancer stem cells are the only type of heterogeneous cancer cells to develop into tumors.

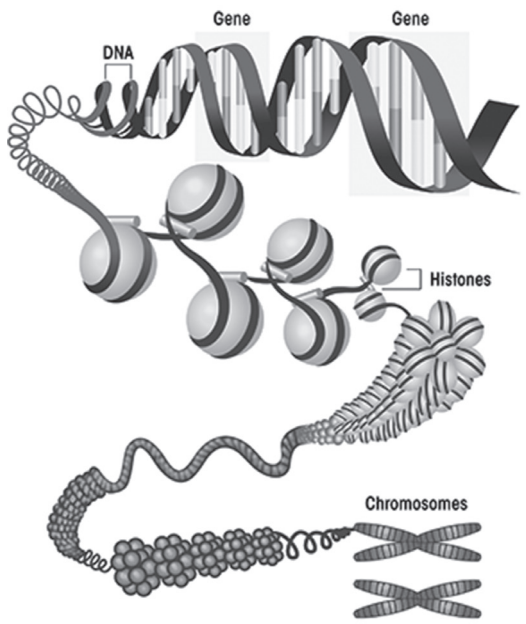
Note. Based on information from Reya et al., 2001; Wicha et al., 2006.

of base pairs connected in a long, unbroken string that intricately coils back on itself and is scattered with proteins, called *histones* (see Figure 1-3).

Similar to sewing bobbins, histones organize and control the long threads of DNA, wrapping them into a tight coil so that the DNA is able to fit inside the nucleus of a cell. The coiling is necessary because the strands of DNA in a person's body would stretch about five feet but would be only fifty-trillionths of an inch (2 nanometers [nm]) wide. For comparison, the "membrane" of a brightly colored soap bubble is between 100–400 nm wide (UCSB Science-Line, n.d.). This long but thin physical structure would be extremely fragile, hence the need for tight packaging to keep the DNA message intact. Once it is coiled around the histones, DNA continues twisting back upon itself (much like the continued twisting of a jump rope) until it is tightly wound, forming the chromatid seen in Figure 1-3. These chromatids enable the chromosomes to be visualized for karyotyping during the metaphase of cell division (Klug & Cummings, 2003).

Within the nucleus of each normal human cell, 23 pairs of chromosomes are present. These consist of 22 pairs of nonsex chromo-

Figure 1-3. DNA Packaging



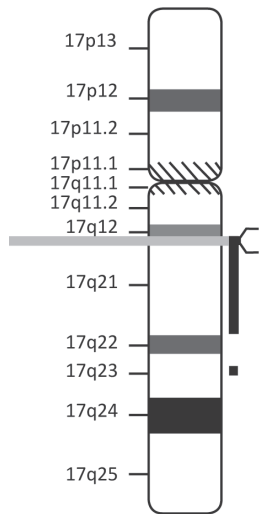
DNA is tightly wound around proteins called histones and packaged into cells' nuclei in the form of chromosomes. Genes are sections of DNA that, under the right circumstances, can be transcribed into proteins. Epigenetics determines which genes each cell transcribes at any given moment.

Note. From "Epigenetics—A New Frontier for Alcohol Research," by National Institute on Alcohol Abuse and Alcoholism, *Alcohol Alert, 86,* p. 2. Retrieved from http://pubs.niaaa.nih.gov/publications/aa86/aa86.htm.

somes (autosomes) and one pair of sex chromosomes (XX for female, XY for male). A person inherits one chromosome of the pair from the father and the other from the mother. A chromosome has a short arm (*p* for "petite") and a long arm (*q* because it follows *p* in the alphabet) with a unique banding pattern that identifies specific regions. These regions are numbered from the centromere to the end of each arm (Genetics Home Reference, 2016c). For example, the breast cancer gene (*BRCA1*) is found on chromosome 17, with a band position of q21 on the long arm (see Figure 1-4). If the position of a gene is uncertain, a range might be noted, such as 17q21–24 (Genetics Home Reference, 2016a). *BRCA2* is located on chromosome 13 at band position 13.2 on the long arm (q) as seen in Figure 1-5 (Genetics Home Reference, 2016b).

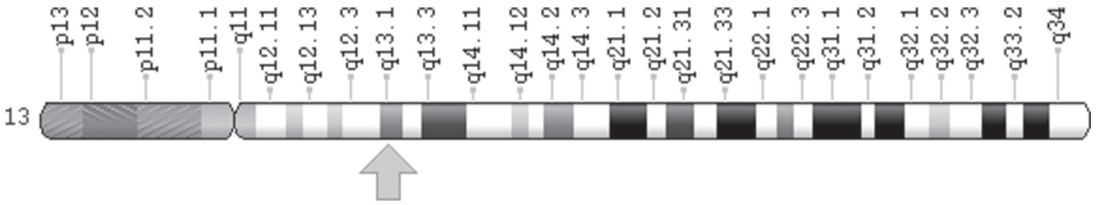
The central dogma of molecular biology states that DNA (adenine [A], cytosine [C], guanine [G], and thymine [T]) is transcribed to RNA (adenine [A], cytosine [C], guanine [G], and uracil [U] instead of thymine) and then translated into proteins (Klug & Cummings, 2003) (see Figure 1-6). For example, the DNA (ACTGTC) would be transcribed as RNA (ACUGUC) and then to messenger RNA (mRNA), where it is divided into codons (three nucleotides used to specify an amino acid) (UGA CAG) for translation from amino

Figure 1-4. *BRCA1* Gene Location



Note. From "Ideogram: Breast Cancer 1 (BRCA1)," by NCBI Map Viewer, n.d. Retrieved from http://www.ncbi.nlm.nih.gov/projects/mapview/maps.cgi?TAXID=9606&CHR=17&MAPS=genes-r%2Cpheno%2Cmorbid%2Cgenec&QUERY=BRCA1&BEG=17q21.1&END=17q21.1&thmb=on.

Figure 1-5. *BRCA2* Gene Location



Note. From "Ideogram: Breast Cancer 2 (BRCA2)," by NCBI Map Viewer, n.d. Retrieved from https://ghr.nlm.nih.gov/gene/BRCA2#location.

Figure 1-6. Modified Central Dogma of DNA Model

miRNA—microRNA; siRNA—small interfering RNA

Note. Based on information from Crick, 1970; Hayes et al., 2014.

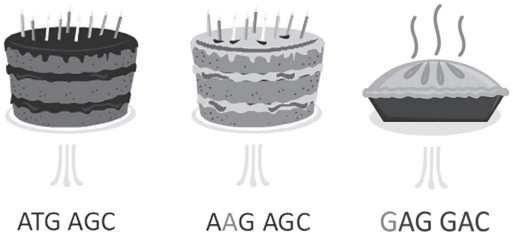
acid to protein. This is important to remember because any changes in the codon "spelling" (mRNA triplet) could change the protein outcome. Some amino acids have multiple codon spellings. One example is leucine, which has six spellings (Algorithmic Arts, n.d.). These would allow several mistakes without creating a problem protein. However, tryptophan has one spelling (Algorithmic Arts, n.d.). Any error in this codon spelling would cause the assembly of a dysfunctional or nonfunctional protein (Adams, 2014).

Changes in DNA nucleotides can be either a mutation or a polymorphism. The distinction depends on the frequency with which the change occurs in the general population: If it occurs in at least 1% of the population, it is called a *polymorphism.* If it occurs in less than 1%, it is labeled as a *mutation* (National Cancer Institute [NCI], n.d.).

To further explain, a normal length of DNA is similar to a recipe for the most common type of cake—for example, a chocolate cake. Although this is the most common, other types of cakes exist, including strawberry, white, spice, pineapple upside-down, and lemon. These would be polymorphisms. They are good-tasting cakes but are not the most common. Sometimes the recipe is misread, and the cake comes out of the oven as a pudding (see Figure 1-7). This is uncommon and not the desired outcome. This is a mutation (NCI, n.d.).

Several types of mutations exist. The most common type is the *point mutation*, in which only one nucleotide base is altered. A *nonsense mutation* occurs when there is a premature termination of the protein. This happens when the stop codon, which signals termination of the length of amino acids, has been "spelled" incorrectly and gives an early or late signal to

Figure 1-7. Polymorphisms Versus Mutations



The wild-type genotype is transcribed to a codon that correctly spells a protein (e.g., recipe for a chocolate cake). When there is a polymorphism in the codon spelling, it can still spell a correct amino acid (e.g., a cake, just a different flavor). When the amino acid spelling is rare and uncommon, it is a mutation and creates an undesirable outcome (e.g., cookie, pie, or another undesired result).

end the compilation of amino acids into a protein (NCI, n.d.).

Mutations that occur within any of the cells of the body are labeled as *somatic*. They accumulate over a lifetime and are believed to cause sporadic cancers, which typically occur after an individual has reached 50 years of age. Mutations that are present in the ova or sperm are labeled as *germ line* and are associated with inherited cancers, which typically occur in people younger than 50 years old (see Table 1-1). The results of this genomic instability affect all future generations, depending on the pattern of inheritance (NCI, n.d.).

Most patterns of inheritance follow the dominant or recessive model developed by Gregor Mendel (Klug & Cummings, 2003). Each individual normally has two sets of chromosomes. On each chromosome is a gene, or allele, for a particular characteristic. Although an allele may have a collection of many different traits (such as blue, green, hazel, or brown eyes), each chromosome can exhibit only one of these. So, one chromosome may have the blue-eyes allele, and the second chromosome could have the brown-eyes allele. All of the other eye colors are still allelic options but are not displayed by this set of chromosomes. Each allele is either a dominant type or a recessive type; for example, the brown-eyes allele is dominant over the recessive blue-eyes allele. If the dominant allele is inactivated or lost, then the recessive allele will become active (Klug & Cummings, 2003).

Sometimes an individual will have the dominant allele without it being expressed. This is known as *incomplete penetrance*. The gene is there, but the phenotype (the observable physical trait) is not expressed. An example that illustrates this is a house in a fog; the house is there but is not visible because of the denseness of the low-lying cloud cover. Age, modifier genes, carcinogens, repair enzymes, and hormonal or reproductive factors affect penetrance (Klug & Cummings, 2003).

New descriptions of mutations associated with cancer include "drivers" and "passengers." Driver mutations (such as *TP53*) are commonly

Table 1-1. Somatic Versus Germ-Line Mutations

Somatic Cell	Germ-Line Cell (Egg or Sperm)
No known DNA damage is present at conception.	DNA in egg or sperm already has mutation at conception.
DNA damage may occur in one cell (not an egg or sperm) and accumulate over an extended period of time, after conception.	As cells duplicate, DNA damage is incorporated into every body cell and tissue type of the offspring.
DNA damage is replicated in cell lineage and a tumor develops in one organ or tissue type.	Potential for malignancy exists in multiple tissue types over time.
It is not inheritable.	It is passed to future generations.

Note. Based on information from National Cancer Institute, 2015.

associated with the development of cancer (oncogenesis) and are known to offer clonal advantage in the microenvironment of the evolving cancer cell. Within the same tumor, passenger mutations are found but do not offer growth advantage and at this point have no known contribution to the development of the cancer type. They seem to be "along for the ride" (Merid, Goranskaya, & Alexeyenko, 2014; Stratton, Campbell, & Futreal, 2009). Different cancers may have a varying mixture of driver and passenger mutations but still appear with similar phenotypes. The drivers in this group of mutated gene sets are the ones targeted for treatment either individually or in a staggered approach (Lee et al., 2012; Merid et al., 2014; Stratton et al., 2009).

In healthy cells, driver and passenger mutations can be restored to predamage level by normal DNA repair mechanisms, which are obviously important for cancer-free survival. These systems include (a) the nucleotide excision repair groups with mutations associated with xeroderma pigmentosum, (b) mismatch repair genes accompanying inherited colorectal cancer predisposition, (c) DNA crosslink repair genes (Fanconi anemia), and (d) the well-known DNA repair genes exemplified by the breast cancer genes (*BRCA1* and *BRCA2*). Approximately 130 genes are linked to DNA repair (Goldstein & Kastan, 2015).

Much of the scientific evidence about the development of cancer and its progression suggests that genomic instability is a precursor to changes associated with transformation of a cell into malignancy. Of question in this hypothesis is how the instability circumvents the careful security provided within the cell to monitor and guarantee genomic stability and purity for continued survival of the human cell. These protective teams include DNA monitoring and repair enzymes. Checkpoint gatekeepers function at significant points in the active phases of the cell cycle prior to DNA synthesis (S phase) and mitosis (M phase) to guarantee the accuracy of the genome and cell cycle processes. If an error is present, the P53 or retinoblastoma protein (pRB) tumor suppressor proteins cause cell cycle arrest for repair or apoptosis (programmed cell death) if too much damage has occurred (Feitelson et al., 2015; Hanahan & Weinberg, 2011).

Much research has confirmed that most human cancers have loss of function in the P53 tumor suppressor pathway. Other genes involved in targeting and repairing DNA damage also have been found to have loss of function in multiple cancers (American Cancer Society, 2014; Jeggo, Pearl, & Carr, 2016). Acquiring genomic damage permits evolving populations of precancerous cells to gain functional capabilities associated with malignant transformation. These include (a) self-sufficiency in growth signals, (b) insensitivity to antigrowth signals, (c) evasion of apoptosis, (d) sustained angiogenesis, (e) tissue invasion and metastasis, and (f) limitless replicative potential (Hanahan & Weinberg, 2011).

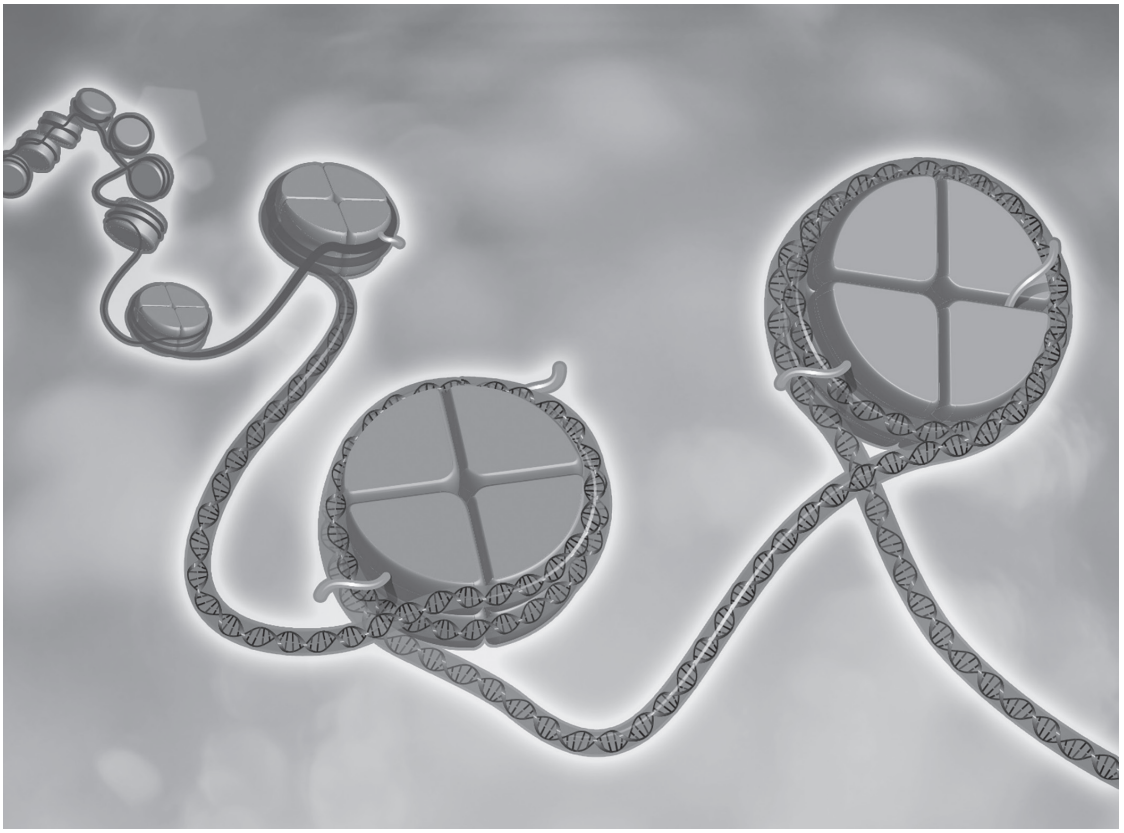
Epigenetics

Changes that occur to DNA activity beyond the actual sequence of the base pairs are termed *epigenetics* (Hanahan & Weinberg, 2011). These changes occur "above and over" the DNA so there is no effect to the basic sequence and the genotype is not changed, although the phenotypic outcome may be altered. These phenotypic changes occur through loosening or alteration of the tightly wound chromatin by binding of different chemicals in such a way that can determine when and where genes might be expressed, or turned on (Dawson & Kouzarides, 2012).

Chromatin consists of proteins and DNA as part of the chromosomes (Tonna, El-Osta, Cooper, & Tikellis, 2010). The major proteins of chromatin are histones, which are responsible for compacting the primary DNA by twisting it tightly like a jump rope while wrapping it tightly (like thread on a spool) so it fits within

the nucleus of the cell. These continuous strands of DNA and histones appear like "beads on a string" (euchromatin) (see Figure 1-3). Multiple histones wrapped tightly together (heterochromatin) prevent transcription and contain inactive genes (Dawson & Kouzarides, 2012; Tonna et al., 2010). The nucleosome is composed of eight separate histone molecules with two loops of DNA wrapped around each group of eight histones (Dawson & Kouzarides, 2012). Figure 1-8 shows some epigenetic modifications of DNA and histones by chemical tags. The changes associated with epigenetics are caused when both the DNA and the histone proteins become modified with addition or removal of chemical groups (tags). Methyl groups can be added to DNA at the cytosine and guanine nucleotides (CpG islands) and cause silencing or stopping of transcription. Acetyl groups loosen the interactions between histones and DNA, allowing easier access to the DNA for transcription (Ho, Turcan, & Chan,

Figure 1-8. Epigenetics



DNA and histones are covered with chemical tags. A variety of tags affect how histones interact with DNA. Some will open a gap between for transcription and others will close a gap to prevent transcription.

Note. Image by Darryl Leja, National Human Genome Research Institute. Retrieved from https://www.genome.gov/dmd/img.cfm?node=Photos/Graphics/Illustrations&id=97352.

2013). Because histones are proteins, they can be modified after translation by attachment of acetyl, phosphate, or ubiquitin groups (Rodríguez-Paredes & Esteller, 2011). The genome tightly wraps genes to make them unreadable, and, when relaxed, the active genes are easily accessible.

Recently, collections of enzymes were identified to have functions as readers, writers, and erasers in the epigenome. Epigenetic "readers" are types of enzymes that look for specific marks on post-translational histones or DNA where they can be modified with chemical groups. Tightly packed histones do not allow changes, so DNA translation is prevented. "Writers" promote attachment of the chemical groups, like acetyl groups, to cause loose packing of the histones for DNA expression (writing) with active protein growth. These chemical groups cause changes that alter the shape of the chromatin in specific places on the genome, making some areas more available to gene expression. "Erasers" are collections of enzymes that remove (erase) histone modifiers (Dawson, Kouzarides, & Huntly, 2012; Gillette & Hill, 2015).

Self-Sufficiency in Growth Signals

Growth Factors

Cell behavior is controlled by circulating proteins known as growth factors (ligands) that have the ability to act as chemical signals. They direct cell growth, differentiation, and survival in addition to determining tissue architecture and morphology. Growth factors must interact with their particular receptor to accomplish signaling (Kolch, Halasz, Granovskaya, & Kholodenko, 2015; Reimand, Wagih, & Bader, 2013).

Growth factors associated with the development of cancer include epidermal growth factor, transforming growth factor, and colony-stimulating factor. Other growth factors exist that are overproduced and are associated with different types of cancer. For example, platelet-derived growth factor is associated with sarcomas and glioblastomas (Kolch et al., 2015).

Growth Factor Receptors

As the first component in signaling pathways, growth factors bind to receptors to initiate signal transduction across the cell membrane. Once a growth factor is bound to a receptor, a signal activates other markers in the cytoplasm, causing transmission of a message to the cell nucleus. The message causes a change in the expression of certain genes that help to usher the cell through its growth cycle (Kolch et al., 2015; Reimand et al., 2013). Overproduction of some growth factors causes altered cellular communication and is associated with cancers. One of these, vascular endothelial growth factor (VEGF), has an important role in tumor neoangiogenesis—that is, the new growth of vessels on a tumor.

Tumor cells induce hypoxia. This lack of oxygen leads to transcription of the VEGF-α protein by binding to its designated cell surface receptors. The binding trips a signal indicating the need for increased blood vessel permeability, resulting in angiogenesis with even more proliferation of cells (Goel & Mercurio, 2013). VEGF is overexpressed in metastases of breast and colorectal cancers.

Tyrosine Kinase Activity

Many cancer-related growth factor receptors are stationed on the surface of the cell. Once they are bound by a ligand that causes activation, proliferative signals are sent into the cytoplasm. Most growth factor receptors possess tyrosine kinase (TK) activity, which leads to reactions that stimulate mitotic cell division, thereby allowing rapid growth of the malignant cell (Kolch et al., 2015; Reimand et al., 2013).

Examples of growth factor receptors that are cancer-causing (oncogenic) when over-

expressed are epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and transforming growth factor-beta (TGF-β). A variety of cancers express EGFR, including non-small cell lung cancer and breast, ovarian, and colorectal cancers. Approximately 80%–100% of head and neck cancers overexpress EGFR, which also is associated with lower survival. Increased HER2 expression corresponds with more aggressive cancers, including ovarian and breast cancers. When EGFR and TGF-β are both expressed, it is a prognostic marker for tumor relapse and decreased survival (Kolch et al., 2015; Reimand et al., 2013).

Nonreceptor Tyrosine Kinases

Some oncogenes do not require a receptor to initiate TK activity at the cell membrane. One example is the *SRC* gene family. The protein from this gene initiates TK activity at the C-terminus of the DNA where biosynthesis is supposed to end. Because no endpoint exists, the protein function persists, allowing continued signaling to the cell nucleus and persistent cell growth. Such *SRC*-initiated activity is increased in colon cancer and other malignancies such as neuroblastoma, small cell lung cancer, breast adenocarcinomas, and rhabdomyosarcoma (GeneCards, n.d.-b; Wiener & Gallick, 2012).

Intercellular Signaling Enzymes

Oncoproteins with certain enzyme activity are important for sending signals within cells and are called *intracellular signaling enzymes*. A common example is the enzymatic protein produced by the *RAF1* gene (GeneCards, n.d.-a). In the cytoplasm, TK activates the *RAF1* enzyme. Once activated, the enzyme acts as a mediator between the *RAS* (associated with the *RAS* oncogene) receptor on the cell membrane and the processes occurring in the cell nucleus by activating a series of other kinases, including mitogen-activated protein (referred to as MAP) kinases. These kinases are critical for regulating the onset of cell division, apoptosis, differentiation, and migration (GeneCards, n.d.-a; Kolch et al., 2015; Reimand et al., 2013).

Membrane-Associated G Proteins

The guanine nucleotide-binding proteins (G proteins) are products of a family of genes, the *RAS* proto-oncogenes, which normally act as "on-off switches" for cell-surface growth factor receptors. Instead of being transmitted inside the cell membrane, they transform adjacent G protein subunits below the membrane surface, which then begin the signaling cascade inside the cell (O'Hayre et al., 2013; Stephen, Esposito, Bagni, & McCormick, 2014).

When the *RAS* gene mutates into the "on" position, it becomes a cancer-causing gene (oncogene), and the changes interrupt a cascade of normally occurring signals that take place in the cell cytoplasm. Normal *RAS* genes wait for prompting to send stimulatory signals from growth factor receptors to other proteins. Mutant *RAS* genes activate signaling pathways even when unprompted. Mutant *RAS* is found in virtually all types of human cancer and occurs in approximately two-thirds of all malignant tumors (Stephen et al., 2014). G proteins act at the cell membrane to cause malignant transformation (O'Hayre et al., 2013; Stephen et al., 2014).

Transcription Factors

Proteins that bind to DNA and cause changes in gene expression are called *transcription factors*. These proteins have structures that can recognize specific DNA sequences (genes) involved in growth and survival. Mutation of the transcription factors that bind to genes involved in cell growth and survival allows for the malignant transformation found in many tumors. Examples of cancers caused by this mechanism include Ewing sarcoma, clear cell

sarcoma, alveolar rhabdomyosarcoma, and many kinds of leukemia. Many of the transcription factor–induced cancers are characterized by translocation of chromosomes (Byrne et al., 2014). One of the tumor suppressor genes, *TP53*, also acts as a transcription factor. In this role, *TP53* "senses" DNA damage and halts cell division by controlling the expression of other genes that directly regulate the cell cycle (Feitelson et al., 2015).

Tumor Suppressor Genes

Tumor suppressor genes (also called antioncogenes) normally suppress or negatively regulate cell proliferation by encoding proteins that block the action of growth-promoting proteins. Using the example of a car, with cell growth caused by the accelerator, the tumor suppressor genes are the brakes, which can prevent cellular proliferation or suppress malignant transformation. At the cellular level, mutations in the cell cause tumor suppressor genes to lose function of both alleles. In other words, the loss of function or mutation of both copies of the gene is required for uncontrolled cell growth, leading to tumorigenesis (National Center for Biotechnology Information [NCBI], n.d.).

Loss of Heterozygosity

Homozygosity refers to the similarity between alleles. If there is an inherited mutation of a tumor suppressor gene, it is termed *heterozygous* because the alleles are different. Because a normal allele is present, the function of the gene and its protein product is maintained. Once the remaining allele is mutated, the gene and its product will lose normal functioning. The heterozygosity has been further altered and is now labeled as *loss of heterozygosity* (LOH). Cells can experience LOH with the loss of an entire chromosome, translocation of a piece of the chromosome, reduplication of a piece of chromosome that already has an abnormal gene, or the development of a point mutation in the second functioning allele. LOH is associated with cancer susceptibility genes, such as oncogenes and tumor suppressor genes (e.g., *TP53*). Basic research is identifying an increasing number of tumor suppressor genes that, when mutated, are closely associated with the development and progression of human cancers (American Cancer Society, 2014; Burrell, McGranahan, Bartek, & Swanton, 2013; NCI, n.d.; NCBI, n.d.).

The tumor suppressor gene *TP53* (located on 17p13) commonly has deletions and mutations associated with a wide variety of cancers, including lung, breast, esophageal, liver, bladder, and ovarian carcinomas; brain tumors; sarcomas; 1ymphomas; and leukemias. It is believed to contribute to half of all sporadic human cancers, making *TP53* the most common genetic target for mutations leading to cancers (NCBI, n.d.). When *TP53* is inherited in the germ line as a mutation, it is transmitted in an autosomal dominant fashion, a hallmark of Li-Fraumeni syndrome. This is a rare disorder causing multiple types of cancers, including soft tissue sarcomas, osteosarcomas, breast cancers, and different types of leukemias (Genetics Home Reference, 2016d; NCBI, n.d.).

Specific Functions of Tumor Suppressor Genes

Tumor suppressor gene products have specific functions in the cell nucleus and cytoplasm. If deregulation of the cell cycle occurs, which results in excess cell proliferation, the normal *TP53* gene can halt cell division and induce apoptosis (NCBI, n.d.) (see also Apoptosis later in this chapter).

Tumor suppressor genes also can encode for proteins in the cytoplasm. The *NF1* (neurofibromatosis) gene encodes a protein similar to the proteins that modulate the *RAS* oncogene function (Genetics Home Reference, 2016e). Loss of *NF1* may keep *RAS* activated and prolong the signal for cell proliferation (Yap et al., 2014). Loss of other tumor suppressor genes, such as *NF2* and *APC* (adenomatous polyposis

coli), may cause cellular disorganization that leads to abnormal cell proliferation.

Insensitivity to Antigrowth Signals

In a normal cell, antigrowth signals move the cell out of the cell cycle growth phases into the resting from proliferation, or G_0, phase. The TGF-β, referred to as both *tumor* or *transforming growth factor*, pathway is the best example of a signaling mechanism that causes inhibition of cell growth and proliferation. This occurs in two ways in the normal pathway. First, TGF-β prevents inactivation of pRB, a tumor suppressor protein, and synthesis of the proteins from the tumor suppressor genes *p15*$^{INK4\alpha}$ and *p21*. Second, if cyclins are blocked, then cells are not able to move into and through the cell cycle. If the p15 protein is not synthesized, cyclins are not blocked, thereby allowing cells to continuously move into the active cell cycle with growth and proliferation. Finally, pRB tumor suppressor function is lost. Any of these interfering mechanisms, alone or in combination, allow continued cell growth and proliferation (Feitelson et al., 2015; Genetics Home Reference, 2016f).

Much like lights on a Christmas tree, when the circuit works well, all of the lights will come on and blink or not blink based on their function. In a cell, the signal is turned on at the gene/protein level, and as long as the pathway is active, all of the cell functions correctly. If an interruption occurs because of a genetic mutation or protein dysfunction, the pathway is interrupted and the "light" is not turned on, causing poor function or a nonfunctional pathway. As an option, another pathway could be available but lead to a different, potentially cancer-causing outcome. Examples are nonproliferation of cells versus continued proliferation of cells, or apoptosis versus no cell death, both leading to cancer.

If the Hedgehog, Notch, or Wnt pathways overexpress the wild-type (normal) signaling molecules or have activated mutations, malignant conversion of adult stem cells to cancer stem cells occurs (Takebe et al., 2015). Mutation of *BRCA1* can prevent DNA repair. If *PTEN* is mutated or deleted, it can result in increased expression of genes that promote continued movement through the cell cycle (Laukkanen & Castellone, 2016). New therapies are targeting some of these and other signaling pathways, potentially initiating programmed cell death (see also Chapter 10).

Evasion of Programmed Cell Death

Three types of "programmed" cell death are controlled by internal cell mechanisms: autophagy, apoptosis, and necrosis.

Autophagy

During stress, autophagy degrades parts of the cell (e.g., proteins, endoplasmic reticulum) that are dysfunctional or damaged (Glick, Barth, & Macleod, 2010). This begins with the formation of an autophagosome that surrounds the macromolecules and organelles destined for recycling (Liu, Lin, Yu, Liu, & Bao, 2011). Different from apoptosis and programmed necrosis, autophagy regulates starvation, cell differentiation, and cell survival in addition to other physiologic processes in the cell (Ouyang et al., 2012) (see Figures 1-9 through 1-11).

Apoptosis

When DNA damage is not repairable, apoptosis is the major type of cell death to occur. With this process, cell death is a controlled, deliberate, and distinct series of biochemical and cellular changes that allow an organism to remove old, dead, or unwanted cells. No inflammation occurs, and some of the cellular materials are ingested by neighboring cells and reused. Apop-

tosis is a normal process that occurs in the presence of severe or irreparable damage to the DNA to prevent duplication of inaccurate messages. This process comprises cell shrinkage, nuclear condensation and fragmentation, and blebbing of the cell membrane with loss of adhesion to neighboring cells plus cleavage of the chromosomal DNA into fragments (Ouyang et al., 2012). When a death signal occurs, the proteins of the *BCL2* family of genes (such as Bax, Bak, Bad, Bid, Bik, Bim, and Hrk) are modified, activated, and translocated to the mitochondria, where apoptosis is initiated by the release of these proapoptotic molecules (see Figure 1-10). Increased expression of *BCL2* is associated with resistance to chemotherapy and radiation therapy (Ouyang et al., 2012).

MicroRNAs (miRNAs) have been found to have both oncogenic (e.g., miRNA21) and tumor suppressor capabilities with the ability to promote apoptosis. Some miRNAs (e.g.,

Figure 1-9. Autophagy

Stress signal from the cell

↓

Formation of membrane from the cytoplasm to become phagosome

↓

Fusion of phagosome with lysosome

↓

Autophagy

Note. Based on information from Mizushima, 2014.

Figure 1-10. Apoptosis

Cell shrinkage

↓

Chromatin condensation

↓

Membrane blebbing

↓

Nuclear collapse and DNA fragmentation

↓

Apoptosis

↓

Phagocytosis of apoptotic cells and fragments

Note. Based on information from Ouyang et al., 2012.

Figure 1-11. Programmed Necrosis/ Necroptosis

Organelle dysfunction

↓

Formation of necrosome

+

Cell swelling

↓

Packaging of poorly or nonfunctioning organelles

↓

Increased reactive oxygen species production

↓

Permeability of the mitochondrial membrane

↓

Programmed necrosis/necroptosis

Note. Based on information from Su et al., 2015.

miR15a–miR16-1) act as tumor suppressors to target *BCL2*, influence Bax and Bak, and ultimately promote apoptosis (Lin & Gregory, 2015; Ouyang et al., 2012). (See also Chapter 10 for a discussion of miRNAs in targeted therapies.)

Cells that lose their ability to signal apoptosis contribute to early tumorigenesis because they are unable to repair problems in the DNA to eliminate genetically damaged cells. Without repair, damaged cells survive, ultimately leading to tumorigenesis (Venkatanarayanan, Keyes, & Forster, 2013). Inactivation of the *TP53* gene leads to decreased apoptosis and rapid tumor progression. The loss of *TP53* function may indirectly contribute to tumor development by permitting the proliferation of mutated cells (Hanahan & Weinberg, 2011; Venkatanarayanan et al., 2013).

Follicular lymphoma, a type of indolent (slow-growing) non-Hodgkin lymphoma, is an example of the loss of apoptosis. This slow-growing lymphoma accounts for approximately 20% of all non-Hodgkin lymphomas and commonly has a rearrangement of the *BCL2* gene. The overexpression of the BCL-2 protein inhibits apoptosis, allowing continued cellular proliferation and making destruction of this lymphoma difficult (NCI, 2016). It is hypothesized that restoration of apoptosis may provide an approach to cancer therapy.

Programmed Necrosis (Necroptosis)

The third type of programmed cell death associated with cancer is programmed necrosis, or necroptosis. Programmed necrosis is caused by activation of the TNF receptor family, T-cell receptors, interferon receptors, Toll-like receptors, cellular metabolic and genotoxic stress, or multiple types of anticancer agents (Su, Yang, Xu, Chen, & Yu, 2015). The first step in programmed necrosis is formation of the necrosome. This can be blocked or initiated at three checkpoints (Su et al., 2015). Caspases are not part of programmed necrosis. Morphologic features include cell swelling, organelle dysfunction, and cell lysis (Ouyang et al., 2012). This type of cell death is associated with packaging of poorly functioning or nonfunctioning organelles and engages the formation of a cascade of molecules to interact with specialized enzymes that enhance metabolism. Production of reactive oxygen species increases, leading to permeability of the mitochondrial membrane and programmed necrosis. Other molecules, such as PARP1, modulate this complicated process and ultimately programmed necrosis (Ouyang et al., 2012). Impaired programmed necrosis has been associated with chronic lymphocytic leukemia and non-Hodgkin lymphoma (Su et al., 2015).

Sustained Angiogenesis

Tumor cells have limitations in oxygen supply that cause areas of hypoxia. This boosts the need for glucose uptake and glycolysis to generate energy, resulting in lactate production. Although this supports the use of positron-emission tomography in nuclear medicine to identify increased metabolism, it also can result in decreased adenosine triphosphate production and ultimately contribute to the fatigue experienced by patients with a malignancy (Goel & Mercurio, 2013). This lack of oxygen also curtails the proliferation of malignant cells (Hanahan & Folkman, 1996). For tumors to grow to a larger size, they need to develop a microcirculatory system through the process of angiogenesis (Hanahan & Weinberg, 2011).

VEGF causes the growth of new vessels, forming a microcirculatory system in a tumor (i.e., angiogenesis). Tumor cells induce hypoxia, leading to the transcription of VEGF-α, which binds to cell surface receptors and ultimately causes increased blood vessel permeability, angiogenesis, and the proliferation of cells (Goel & Mercurio, 2013). Multiple malignan-

cies, including metastatic breast and colorectal cancers, overexpress VEGF.

Tissue Invasion and Metastasis

Altered Cytoskeletal Control

Cells have a skeleton with interior and exterior functions. The cell's shape and ability to move are included in the external function of the cytoskeleton. The internal function of the cytoskeleton permits substances to move within the cell. On the exterior membrane, microtubules evoke a rigidity to add strength to the membrane surface. Internally, they promote movement of organelles within the cytoplasm. During mitosis, the microtubules are arranged in a centriole as nine bundles of three microtubules each. These form the spindle fibers, which are responsible for separation of the chromosomes prior to the actual splitting of the cell (McCance, 2014). With a malignancy, the cell loses external cytoskeleton control. This causes it to lose rigidity and become more amenable to continued cellular division. In addition, the cytoskeleton is needed for spindle microtubule formation, mitosis, and cellular growth. Multiple protein types participate in these changes associated with malignant transformation (Hanahan & Weinberg, 2011; Liaw, Chang, & Kavallaris, 2007).

Altered Mobility of Membrane Components

Proteins, glycoproteins, and glycolipids are known to have altered mobility on the membrane of a malignant cell. One outcome of this change enables the cancer to avoid immune surveillance. Other outcomes could promote spread and metastasis (Hanahan & Weinberg, 2011; Wallach, 1968).

Modified Contact Adhesion and Inhibition of Movement

After replication, normal cells contact the adjacent cell membrane and are inhibited from growing. Malignant cells lose this characteristic and continue to proliferate even though they are touching the cell next to them. This contributes to the lack of control in malignant cells (Hanahan & Weinberg, 2011; McCance, 2014).

Altered Surface Charge Density

Malignant cell membranes have a lower level of electrical potential than that of normal cells. This is because of the increased amounts of negatively charged phospholipids in the cell membrane (Venkatanarayanan et al., 2013). Positively charged sodium and calcium channels contribute to apoptosis (Williams & Djamgoz, 2005). Changes in the charge of the cell membrane inhibit apoptosis and contribute to the longevity of malignant cells.

Increased Lectin Agglutinability

Alterations in lectin binding enable leukocytes to adhere to and cover malignant cells. This change allows malignant cells to escape surveillance and travel to distant sites in the body as a bolus of normal and abnormal cells (Hanahan & Weinberg, 2011; McCance, 2014).

Limitless Replicative Potential

One factor allowing for limitless replicative potential is the expression of telomerase. This enzyme prevents destruction of the telomere. Because telomeres protect chromosomes, cells with increased telomerase are associated with longer telomeres and longevity of cell life. Short telomeres are associated with a shorter life span. Cancer stem cells have increased levels of telomerase and thus have an extended life enhanced by the protected telomeres at the ends of the chromosome. This also protects the cell from apoptosis (Hanahan & Weinberg, 2011).

Conclusion

The curricula in undergraduate nursing programs do not typically include molecular biology. With completion of the sequencing of the human genome in 2003, many diagnostics and treatments have been developed that require an understanding of certain characteristics of cells, the central dogma, and how cell signaling and communication occur. This knowledge is important for oncology nurses and helps them to anticipate the symptoms of cancer in their patients, to be aware of how the treatments work, and to have a basic foundation when developing teaching plans related to individualized treatment plans for their patients. This chapter has provided a description of how malignancies develop and some of the molecular biology used for diagnostics and treatment in oncology. These include self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, sustained angiogenesis, tissue invasion and metastasis, and limitless replicative potential (Hanahan & Weinberg, 2011). For people new to oncology or for those who simply want to review and close some gaps in their knowledge, an understanding of the biology of cancer will be useful as they care for patients and their families.

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Key Points

- Cancer is a heterogenic disease because of diverse cell types and genetic and epigenetic differences between cancer cells.
- Several models have been developed to explain the heterogeneity seen in cancer, such as the clonal model, the cancer stem cell model, the plasticity model, and the inflammatory model.
- A genetic change present in at least 1% of the population is termed a *polymorphism* and is likely benign, whereas a genetic change present in less than 1% of the population is termed a *mutation* and is more likely to have negative effects.
- Germ-line mutations occur in the ova or sperm and are present in every cell in the body, whereas somatic mutations are not inherited and can be present in any cell in the body except the sex cells.
- Epigenetic changes are chemical modifications to the DNA molecule that are not inherited and do not alter the sequence of the cellular DNA.
- Driver mutations are those that provide the cell with a selective growth advantage and help to establish the malignancy. Passenger mutations do not contribute to the malignant phenotype and seem to be "along for the ride."
- Cancer cells have many characteristics associated with malignancy, including self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, sustained angiogenesis, tissue invasion and metastasis, and limitless replicative potential.

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Chapter 1 Study Questions

1. A patient's tumor has a mutation in a copy of her *p53* gene. The mutation results in a shortened, nonfunctional protein. What type of mutation does the patient most likely have?
   A. Point mutation
   B. Missense mutation
   C. Nonsense mutation
   D. Insertion

2. A new tumor suppressor protein has recently been discovered. What could be a possible function of this new protein?
   A. A transcription factor for epidermal growth factor
   B. A tyrosine kinase in the RAS–RAF pathway
   C. An inhibitor of *NF1* function
   D. An upregulator of *BAX* expression

3. Which of the following procancer traits is associated with increased inflammation?
   A. Upregulation of growth factors
   B. Enzymes that alter the extracellular matrix
   C. Promotion of apoptosis evasion
   D. All of the above

4. The use of positron-emission tomography scans in identifying cancer is based on what characteristic of malignancy?
   A. Cytoskeletal changes
   B. Changes to cellular metabolism
   C. Increased angiogenesis
   D. Evasion of apoptosis

5. Loss of heterozygosity refers to which of the following?
   A. Loss of the second allele (gene)
   B. Wild type of the allele (gene)
   C. Mutation of many zygotes
   D. Shift of the DNA base pair sequences