Section I. Cancer Basics

CHAPTER

1 Genomics of Cancer

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Introduction

Today, nurses in the oncology clinical setting recognize they need more than a generalized medical–surgical knowledge of cancer to provide personalized care for a patient being treated for a malignancy. The plan of care for a patient with cancer is based on a nurse's specialized knowledge and ability to anticipate signs and symptoms of the emerging and changing biology of a cancer diagnosis. This includes the provision of rationale for transformations occurring in the patient. Other knowledge is comprised of an understanding of the initiation and progression of cancer, inflammation and its role in carcinogenesis, the multiple types of cancer, the implications of that specific disease diagnosis for the patient's assessment, diagnosis of a problem to be addressed by a nurse, how to develop a specialized plan of care, identification of appropriate interventions with personalized goals for effectiveness, and how to evaluate the outcomes. To emphasize, this long list of information needs to be anticipated and implemented by the knowledgeable nurse in oncology.

A cancer diagnosis was once believed to be a single disorder. Today, it is known to be a complex diagnosis, with the potential to include multiple different diseases (some authors quote as few as 100 and as many as 277), many interactive causes, and occurrence at different ages throughout the life span. The different types of cancer may also have unique rates of growth, an assortment of undifferentiated or differentiated cells in the same tumor, a mixture of the cells' sensitivities to detection, different capacities to spread or metastasize, use of a variety of treatments or treatment types, therapy responses, and finally multiple prognoses over time due to transition of cancer cells, such as estrogen receptor–positive biomarkers in breast cancer to triple-negative biomarkers (Hassanpour & Dehghani, 2017; MedicineNet, 2021).

This chapter will describe the malignant changes of a cell and the resultant new biology of cancer compared to a healthy cell. This information will provide nurses new to oncology with a foundation for understanding the development and growth of cancer and its treatment and the basis to provide education to patients and families.

Background

Even though the same labels can describe the characteristics and function of both healthy and abnormal cells with cancer (malignancy), wide variation exists in how they appear and function (see Table 1-1).

Knowledge of cancer as a disease has evolved from a characterization of six hallmarks identified from studies in mouse models and cultured cells. These are *self-sufficiency in growth signals*, *insensitivity to antigrowth signals*, *evasion of apoptosis with limit-*

TABLE 1-1
COMPARISON OF HEALTHY CELLS AND CANCER CELLS

Characteristics	Healthy Cell	Cancer Cell
Shape	Regular	Irregular
Nucleus	Proportionate size	Larger, darker
Growth	In control, systematic	Out of control
Death	Apoptosis or cell suicide	–
Maturation	Mature (cell differentiation)	Immature, does not mature
Communication	Communicates	Does not communicate
Visibility	Invisible to immune cells, cell surface identification	Invisible to immune cells
Blood supply	Angiogenesis during repair	Tumor angiogenesis
Oxygen	Requires oxygen	Does not like or require oxygen (anaerobic)
Glucose	Requires some glucose	Craves glucose
Energy efficiency	Very high (95%)	Very low (5%)
Amount of adenosine triphosphate	38 units	2 units
Cell environment	Alkaline	Acidic
Nutrient preference	Fat, ketone, glucose	Glucose

less replicative potential, *sustained angiogenesis*, *tissue invasion*, and *metastasis* (Fouad & Aanei, 2017). In 2011, more hallmarks were added to make a total of 11. These included *reprogramming energy metabolism* and *evasion of the immune response.* Two enabling traits of *genome instability* and *mutation plus tumor-promoting inflammation* were also added (Zhong et al., 2020).

Genetic alterations of cancer could be caused by nurture. This concept includes *obesity, lack of exercise, poor diet,* and *social habits,* such as smoking. All of these changes found in the microenvironment of cancer led to the decision that malignant growth results from changes in DNA, gene transcription, or gene translation. The resultant defective protein or proteins transform healthy cell components, with the cell developing uncontrolled proliferation, spread, or metastasis (Sapienza & Issa, 2016).

Carcinogens are chemical substances, or a mixture of chemical substances, which can induce cancer after inhalation, ingestion, dermal application, or injection. These substances can increase cancer incidence or shorten time to tumor occurrence by any dosage level, by any route, in any species of animals, compared to controls (Bordonaro, 2019; Calabrese et al., 2021). Environmental and chemical human carcinogens include aflatoxins, asbestos, nitrosamines, alcohol, and tobacco (Fishbein et al., 2021).

Studies on anti-inflammation have identified a new superfamily of endogenous and specialized cells, known as pro–resolving lipid mediators or resolvins. They have a strong novel inflammation

clearing activity without being immunosuppressive (Fishbein et al., 2021). This is unlike most anti-inflammatory agents, including nonsteroidal anti-inflammatory drugs ibuprofen and celecoxib, that directly suppress cyclooxygenase enzyme activity. The pro-resolving lipid mediators serve as brake signals to turn off inflammation and act by clearing up cellular debris supervised by immune cells (e.g., macrophage) (Fishbein et al., 2021). Resolvins have reduced localized proinflammatory cytokine levels during resolution. Failure of resolution via these cells is important in pathogenesis and a unifying component of many underlying chronic inflammatory diseases, obesity, infection, asthma, wound healing, Alzheimer disease, sepsis, aging, cardiovascular diseases, and various ocular disorders (Serhan & Levy, 2018).

Terms and Concepts

Pathology Reports

Tumors typically grow and progress stepwise from healthy to very abnormal or undifferentiated (see Table 1-2). If cells divide too much but appear healthy, they are labeled hyperplasia. Dysplasia describes tumor cells and tissue that appear abnormal. If a tumor contains primarily altered cells, grows larger, and has not left the site of origin, it is labeled as a carcinoma in situ. A malignant tissue has begun to invade nearby or distant tissues. If tissue becomes malignant, it is named based on the location and type of original tissue (see Chapter 6).

Benign tissue does not spread from its initial locations and may have abnormal features. This tissue may enlarge, causing pressure on adjacent tissue. Benign tissue can transform to malignant tissue, such as with colon polyps.

Theories and Models Describing Cancer

A model visualizes the "pattern or figure of something to be made" (Merriam-Webster, n.d.-a). Models of carcinogenesis theories are included to depict the transformation of cells. Theories and models that describe carcinogenesis as a genetic disease include somatic mutation theory, multistage models, two-hit theory, and evolutionary models.

Theories describe the development of cancer or unregulated cell division. A theory is "a plausible or scientifically acceptable general principle or body of principles offered to explain phenomena" (Merriam-Webster, n.d.-b). Multiple theories related to malignant transformation have developed over the past 250 years, as morphological traits of tumors for pathologic diagnosis have been identified and classified. In addition, acknowledgment of the ability of cells to live forever with autonomy has been established as a necessary condition (Dou et al., 2020).

Somatic Mutation Theory

Somatic mutation theory considers cancer to be a genetic disease. Multistate models view variant phenotypes and healthy cellular populations as able to coexist. This theory has been the predominant cancer model for more than 50 years. Its principals include the following (Brücher & Jamall, 2016):

- Cancer is a disease of genetic variants.
- Cancer is derived from a single somatic cell.
- Initiation and carcinogenesis are irreversible.

Multistep Theory of Carcinogenesis

Another popular theory of carcinogenesis includes its three development stages: initiation, promotion, and progression. Metastasis is the fourth stage (see Figure 1-1).

During initiation, a permanent and irreversible change, a variant, occurs to the cell's genetic material, where the cell is primed to become malignant. Future generations of daughter cells will also carry the variant. Many initiators are specific to particular tissue types and must be metabolized before they can cause a permanent change to the gene. The greater the dosage of the initiator, the higher the risk for the development of tumors. In addition, cancer initiators need to be applied as a linear relationship in the right

TABLE 1-2
BIOMARKERS

Biomarker	Cancer Type or Cancer-Like Conditions	Substance Analyzed	How Used
ALK gene rearrangements and overexpression	Non-small cell lung cancer, anaplastic lung cancer, histiocyte	Tumor	To help determine treatment and prognosis
Alpha-fetoprotein (AFP)	Liver cancer and germ cell tumors	Blood	To help diagnose liver cancer and follow response to treatment; to assess stage, prognosis, and response to treatment of germ cell tumors
B-cell immunoglobulin gene rearrangement	B-cell lymphoma	Blood, bone marrow, or tumor tissue	To help in diagnosis, to evaluate effectiveness of treatment, and to check for recurrence
BCL2 gene rearrangement	Lymphomas and leukemias	Blood, bone marrow, or tumor tissue	For diagnosis and planning treatment, and to check for recurrence
Beta-2-microimmunoglobulin (B2M)	Multiple myeloma, chronic lymphoblastic leukemia, and some lymphomas	Blood, urine, or cerebrospinal fluid	To determine prognosis and follow response to treatment
Bladder tumor antigen (BTA)	Bladder cancer and cancer of the kidney or ureter	Urine	As surveillance with cytology and cystoscopy of patients already known to have bladder cancer
BRCA1 and *BRCA2* gene mutations	Ovarian and breast cancers	Blood and/or tumor	To help determine treatment
BCR-ABL fusion gene (Philadelphia chromosome)	Chronic myeloid leukemia, acute lymphoblastic leukemia, and acute myelogenous leukemia	Blood or bone marrow	To confirm diagnosis, predict response to targeted therapy, help determine treatment, and monitor disease status
BRAF V600 mutations	Cutaneous melanoma, Erdheim-Chester disease, Langerhans cell histiocytosis, colorectal cancer, and non-small cell lung cancer	Tumor	To help determine treatment
C-kit/CD117	Gastrointestinal stromal tumor, mucosal melanoma, acute myeloid leukemia, and mast cell disease	Tumor, blood, or bone marrow	To help in diagnosis and to help determine treatment

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TABLE 1-2
BIOMARKERS *(CONTINUED)*

Biomarker	Cancer Type or Cancer-Like Conditions	Substance Analyzed	How Used
CA15-3/CA 27.29	Breast cancer	Blood	To assess whether treatment is working or if the cancer has recurred
CA19-9	Pancreatic, gallbladder, bile duct, and gastric cancers	Blood	To assess whether treatment is working
CA-125	Ovarian cancer	Blood	To help in diagnosis, assessment of response to treatment, and evaluation of recurrence
CA 27.29	Breast cancer	Blood	To detect metastasis or recurrence
Calcitonin	Medullary thyroid cancer	Blood	To aid in diagnosis, check whether treatment is working, and assess recurrence
Carcinoembryonic antigen (CEA)	Colorectal cancer and some other cancers	Blood	To keep track of how well cancer treatments are working and check if cancer has come back or spread
Cluster of differentiation 19 (CD19)	B-cell lymphomas and leukemias	Blood and bone marrow	To help in diagnosis and to help determine treatment
CD20	Non-Hodgkin lymphoma	Blood	To help determine treatment
CD22	B-cell lymphomas and leukemias	Blood and bone marrow	To help in diagnosis and to help determine treatment
CD25	Non-Hodgkin (T-cell) lymphoma	Blood	To help determine treatment
CD30	Classic Hodgkin lymphoma, B-cell and T-cell lymphomas	Tumor	To help determine treatment
CD33	Acute myeloid leukemia	Blood	To help determine treatment
Chromogranin A (CgA)	Neuroendocrine tumors	Blood	To help in diagnosis, assessment of treatment response, and evaluation of recurrence
Chromosome 17p deletion	Chronic lymphoblastic leukemia	Blood	To help determine treatment

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TABLE 1-2
BIOMARKERS *(CONTINUED)*

Biomarker	Cancer Type or Cancer-Like Conditions	Substance Analyzed	How Used
Chromosomes 3, 7, 17, and 9p21	Bladder cancer	Urine	To help in monitoring for tumor recurrence
Circulating tumor cells of epithelial origin (CELLSEARCH)	Metastatic breast, prostate, and colorectal cancers	Blood	To inform clinical decision-making and assess prognosis
Cytokeratin fragment 21-1	Lung cancer	Blood	To help in monitoring for recurrence
Cyclin D1 (*CCND1*) gene rearrangement or expression	Lymphoma, myeloma	Tumor	To help in diagnosis
Des-gamma-carboxy prothrombin (DCP)	Hepatocellular carcinoma	Blood	To monitor the effectiveness of treatment and to detect recurrence
DPD gene mutation	Breast, colorectal, gastric, and pancreatic cancers	Blood	To predict the risk of a toxic reaction to 5-fluorouracil therapy
EGFR gene mutation	Non-small cell lung cancer	Tumor	To help determine treatment and prognosis
Estrogen receptor (ER)/ progesterone receptor (PR)	Breast cancer	Tumor	To help determine treatment
FGFR2 and *FGFR3* gene mutations	Bladder	Tumor	To help determine treatment
Fibrin/fibrinogen	Bladder	Urine	To monitor progression and response to treatment
FLT3 gene mutations	Acute myeloid leukemia	Blood	To help determine treatment
Gastrin	Gastrin-producing tumor (gastrinoma)	Blood	To help in diagnosis, to monitor the effectiveness of treatment, and to detect recurrence
HE4	Ovarian cancer	Blood	To plan cancer treatment, assess disease progression, and monitor for recurrence
HER2/neu gene amplification or protein overexpression	Breast, ovarian, bladder, pancreatic, and stomach cancers	Tumor	To help determine treatment

(Continued on next page)

TABLE 1-2
BIOMARKERS *(CONTINUED)*

Biomarker	Cancer Type or Cancer-Like Conditions	Substance Analyzed	How Used
5-HIAA	Carcinoid tumors	Urine	To help in diagnosis and to monitor disease
IDH1 and *IDH2* gene mutations	Acute myeloid leukemia	Bone marrow and blood	To help determine treatment
Immunoglobulins	Multiple myeloma and Waldenström macroglobulinemia	Blood and urine	To help diagnose disease, assess response to treatment, and look for recurrence
IRF4 gene rearrangement	Lymphoma	Tumor	To help in diagnosis
JAK2 gene mutation	Certain types of leukemia	Blood and bone marrow	To help in diagnosis
KRAS gene mutation	Colorectal cancer and non-small cell lung cancer	Tumor	To help determine treatment
Lactate dehydrogenase	Germ cell tumors, lymphoma, leukemia, melanoma, and neuroblastoma	Blood	To assess stage, prognosis, and response to treatment
Microsatellite instability (MSI) and/or mismatch repair deficient (dMMR)	Colorectal cancer and other solid tumors	Tumor	To guide treatment and to identify those at high risk of certain cancer-predisposing syndromes
MYC gene expression	Lymphomas, leukemias	Tumor	To help in diagnosis and to help determine treatment
MYD88 gene mutation	Lymphoma, Waldenström macroglobulinemia	Tumor	To help in diagnosis and to help determine treatment
Myeloperoxidase (MPO)	Leukemia	Blood	To help in diagnosis
Neuron-specific enolase (NSE)	Small cell lung cancer and neuroblastoma	Blood	To help in diagnosis and to assess response to treatment
NTRK gene fusion	Any solid tumor	Tumor	To help determine treatment
Nuclear matrix protein 22	Bladder cancer	Urine	To monitor response to treatment
PCA3 mRNA	Prostate cancer	Urine (collected after digital rectal exam)	To determine need for repeat biopsy after negative biopsy

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TABLE 1-2
BIOMARKERS *(CONTINUED)*

Biomarker	Cancer Type or Cancer-Like Conditions	Substance Analyzed	How Used
PML/RARα fusion gene	Acute promyelocytic leukemia (APL)	Blood and bone marrow	To diagnose APL, to predict response to all-trans-retinoic acid or arsenic trioxide therapy, to assess effectiveness of therapy, to monitor minimal residual disease, and to predict early relapse
Prostatic acid phosphatase (PAP)	Metastatic prostate cancer	Blood	To help in diagnosing poorly differentiated carcinomas
Programmed death ligand 1 (PD-L1)	Non-small cell lung cancer, breast cancer, liver cancer, stomach cancer, gastroesophageal junction cancer, classical Hodgkin lymphoma, and other aggressive lymphoma subtypes	Tumor	To help determine treatment
Prostate-specific antigen (PSA)	Prostate cancer	Blood	To help in diagnosis, to assess response to treatment, and to look for recurrence
ROS1 gene rearrangement	Non-small cell lung cancer	Tumor	To help determine treatment
Soluble mesothelin-related peptides (SMRP)	Mesothelioma	Blood	To monitor progression or recurrence
Somatostatin receptor	Neuroendocrine tumors affecting the pancreas or gastrointestinal tract (GEP-NETs)	Tumor (by diagnostic imaging)	To help determine treatment
T-cell receptor gene rearrangement	T-cell lymphoma	Bone marrow, tissue, body fluid, blood	To help in diagnosis; sometimes to detect and evaluate residual disease
Terminal transferase (TdT)	Leukemia, lymphoma	Tumor, blood	To help in diagnosis
Thiopurine S-methyltransferase (TPMT) enzyme activity or *TPMT* genetic test	Acute lymphoblastic leukemia	Blood and buccal (cheek) swab	To predict the risk of severe bone marrow toxicity (myelosuppression) with thiopurine treatment
Thyroglobulin	Thyroid cancer	Blood	To evaluate response to treatment and to look for recurrence

(Continued on next page)

TABLE 1-2
BIOMARKERS *(CONTINUED)*

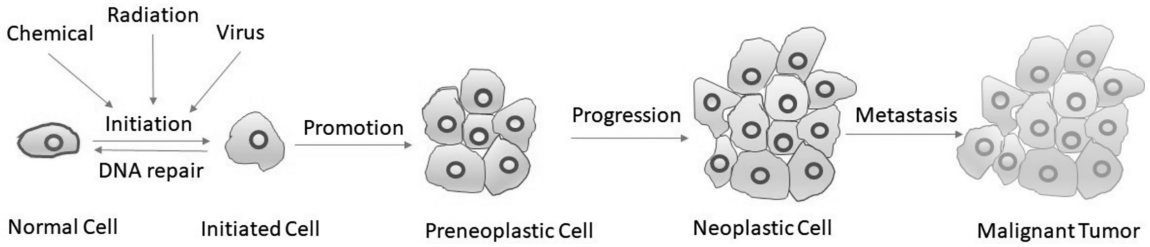
Biomarker	Cancer Type or Cancer-Like Conditions	Substance Analyzed	How Used
UGT1A1*28 variant homozygosity	Colorectal cancer	Blood and buccal (cheek) swab	To predict toxicity from irinotecan therapy
Urine catecholamines: VMA and HVA	Neuroblastoma	Urine	To help in diagnosis
Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor (PAI-1)	Breast cancer	Tumor	To determine aggressiveness of cancer and guide treatment
FoundationOne CDx (F1CDx) genomic test	Any solid tumor	Tumor, blood	As a companion diagnostic test to determine treatment
Guardant360 CDx genomic test	Any solid tumor	Blood	As a companion diagnostic test to determine treatment and for general tumor mutation profiling
5-Protein signature (OVA1)	Ovarian cancer	Blood	To pre-operatively assess pelvic mass for suspected ovarian cancer
17-Gene signature (Oncotype DX GPS test)	Prostate cancer	Tumor	To predict the aggressiveness of prostate cancer and to help manage treatment
21-Gene signature (Oncotype DX)	Breast cancer	Tumor	To evaluate risk of distant recurrence and to help plan treatment
46-Gene signature (Prolaris)	Prostate cancer	Tumor	To predict the aggressiveness of prostate cancer and to help manage treatment
70-Gene signature (Mammaprint)	Breast cancer	Tumor	To evaluate risk of recurrence

Note. From *Tumor Markers in Common Use*, by National Cancer Institute, 2021 (https://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis/tumor-markers-list). In the public domain.

amounts, in the right order, and at the right time. Examples of initiators include tobacco smoke, radon, ultraviolet light, asbestos, medical radiation, certain viruses, and air pollution. Some may require high, low, or multiple doses over time or doses in the right order at the right time with other initiators.

When a nonreactive compound stimulates tumor development, it is called a promoter and is involved in the second stage of malignancy development. Promoters are not typically mutagenic in this stage but accelerate to becoming cancer. Examples include nitrites, alcohol, high estrogen levels, dietary fat, ultraviolet light, and saccharin (Libre Texts, 2020).

FIGURE 1-1
MULTISTEP CARCINOGENESIS



Note. From "Carcinogenesis," by LibreTexts, 2020 (https://med.libretexts.org/Courses/American_Public_University/APUS%3A_An_Introduction_to_Nutrition_(Byerley)/Text/07%3A_Nutrition_and_Cancer/7.02%3A_Carcinogenesis), licensed under CC BY-SA 3.0 (https://creativecommons.org/licenses/by-sa/3.0/deed.en).

The third stage is progression of the malignancy, with movement into surrounding tissue and dissemination throughout the organs and skeletal system. This can include large pieces of tumor breaking off from the main tumor or one cell hiding in the resting phase (G_0). The cell remains in this phase until a stimulus causes it to move into the active cell cycle, with maturation leading to generalized metastasis (see Figure 1-2).

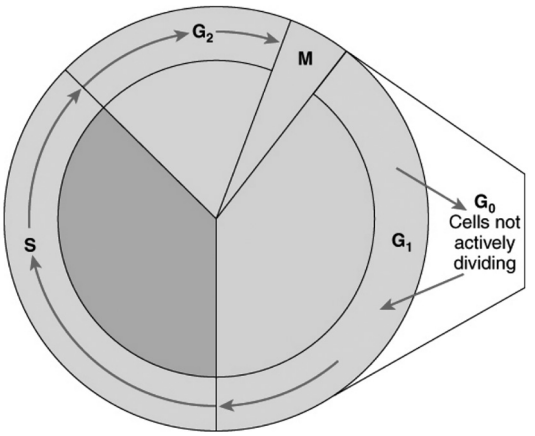
Stochastic Modeling

Two additional models represent how a theory might work and how cancer might develop in the real world. The first is stochastic modeling, which includes the two-hit theory (see Figure 1-3). This model suggests that each cancer cell can multiply and form new tumors. The malignant cells have a selective advantage over healthy neighbors and proliferate rapidly, accumulating genetic damage with each generation. As the damage accumulates, the most aggressive characteristics promote immortalized growth and the formation of a tumor (Oduola & Li, 2018).

The individual cancer stem cell is the focus of the second model and is supported by most cancer researchers. According to the Cancer Stem Cell Model, many different types of cancer cells exist in addition to endothelial, hematopoietic, stromal, and other types of healthy cells to meet the functioning needs of the tumor and demonstrate heterogeneity. With proliferation, cell division occurs. All cells can multiply, but only the cancer stem cell can become a new tumor (Werbowetski-Ogilivie, 2021).

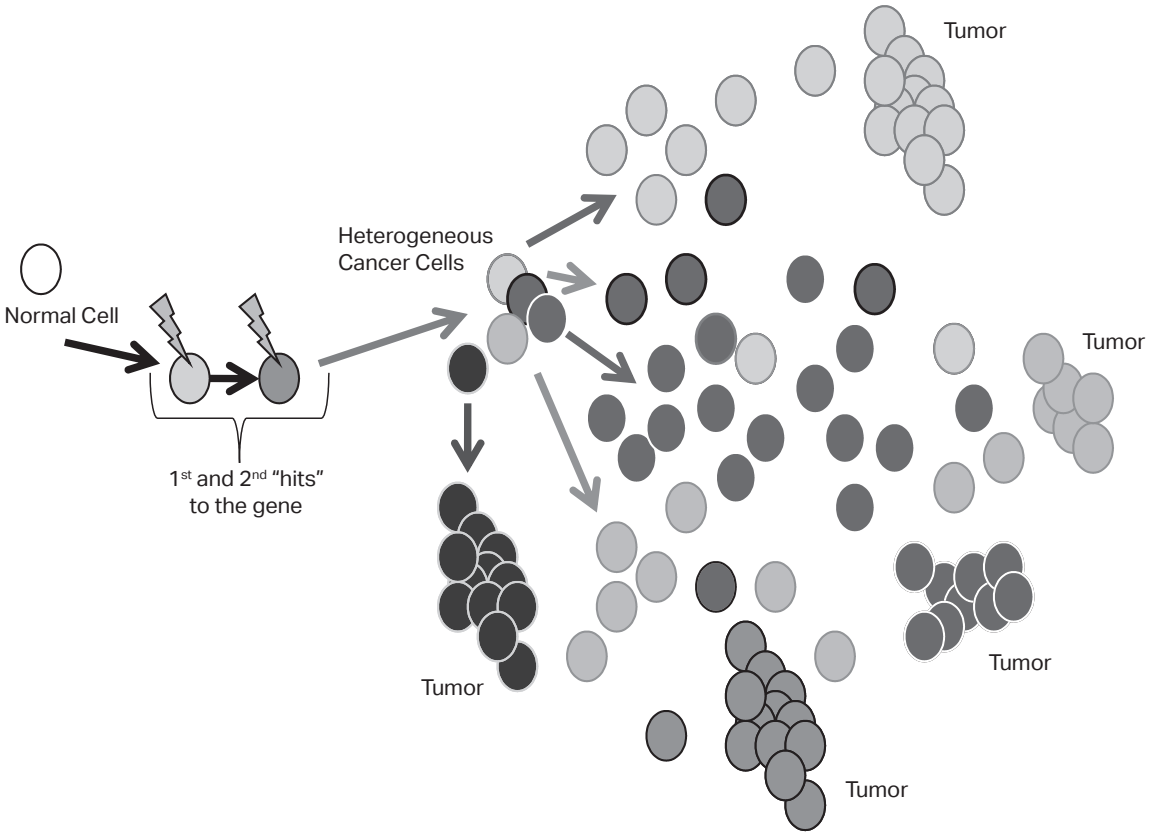
The heterogeneous cells proliferate once the new tumor is established, allowing the tumor to enlarge. The cancer stem cell then moves into the resting phase (G_0) (see Figure 1-4). Cells in this phase are resistant to treatment and remain as one surviving cancer cell while treatment destroys the other

FIGURE 1-2
CELL CYCLE WITH RESTING PHASE



Note. From "Cell cycle," by OpenStax, 2016 (https://commons.wikimedia.org/wiki/File:0329_Cell_Cycle.jpg), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/deed.en).

FIGURE 1-3
KNUDSON'S "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.

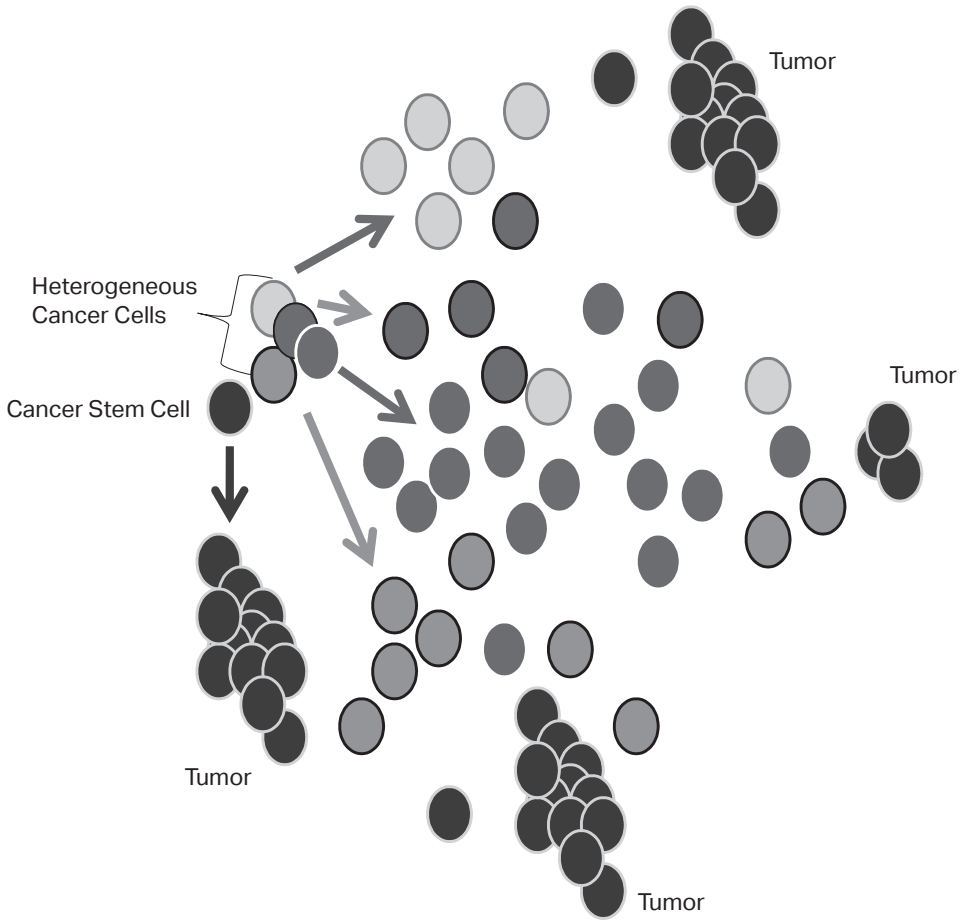
rapidly dividing stem cells (Werbowetski-Ogilivie, 2021). Thus, months or years later, the resting cancer stem cell could move into the active phases of the cell cycle, proliferate, and cause exacerbation of once-dormant cancer believed to be destroyed (Werbowetski-Ogilivie, 2021).

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 cell's life) allows cancer stem cells to become heterogeneous with the ability to come out of remission and become metastatic. Noncancer stem cells have meager potential to become tumorigenic, develop more tumors, and metastasize (Walcher et al., 2020).

Structure and Function of DNA and Chromosomes

Within the nucleus of each healthy human cell, 23 pairs of chromosomes are present. These con-

FIGURE 1-4
CANCER STEM CELL THEORY OF CANCER DEVELOPMENT



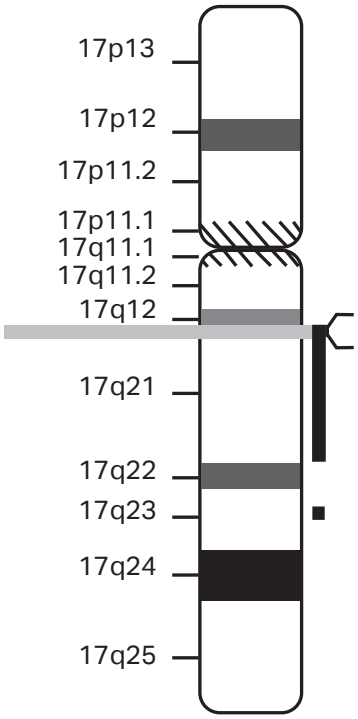
Theory: Cancer stem cells are the only type of heterogeneous cancer cells to develop into tumors.

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

sist of 22 pairs of nonsex chromosomes (autosomes) and one pair of sex chromosomes (XX for female, XY for male). A person inherits one sex chromosome from the father and the other from the mother. A chromosome has a short arm (*p* for petite) and a long arm (*q* to follow *p* in the alphabet), with a unique banding pattern to identify specific regions. These regions are numbered from the centromere to the end of each arm (Genetics Home Reference, 2021c). For example, the breast cancer gene (*BRCA1*) is found on chromosome 17, with a band position of q21 on the long arm (see Figure 1-5). If the position of a gene is uncertain, a range might be noted, such as 17q21–24 (Genetics Home Reference, 2021a, 2021b). *BRCA2* is located on chromosome 13 at band position 13.2 on the *q* arm (see Figure 1-6).

Each chromosome is a single double-helix DNA molecule with millions of base pairs connected in a long, unbroken string that intricately coils back on

FIGURE 1-5
BRCA1 GENE LOCATION



Note. From "Ideogram: Breast Cancer 1 (BRCA1)," by NCBI Map Viewer, n.d. 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.

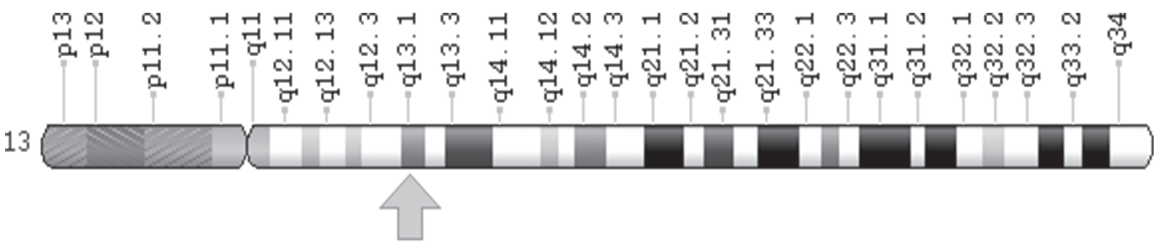
itself and is scattered with proteins called histones (see Figure 1-7).

The central dogma of molecular biology states that DNA (adenine [A], cytosine [C], guanine [G], and thymine [T]) is transcribed to RNA (A, C, G, and uracil [U]) and then translated into proteins (Saw et al., 2021; Yi et al., 2020; see Figure 1-8).

For example, a string of 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 acid to protein. This is important 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, allowing several mistakes without creating a problem protein. However, tryptophan has one spelling (Algorithmic Arts, 2006). Any error in this codon spelling would cause a dysfunctional or nonfunctional protein (Ding et al., 2019).

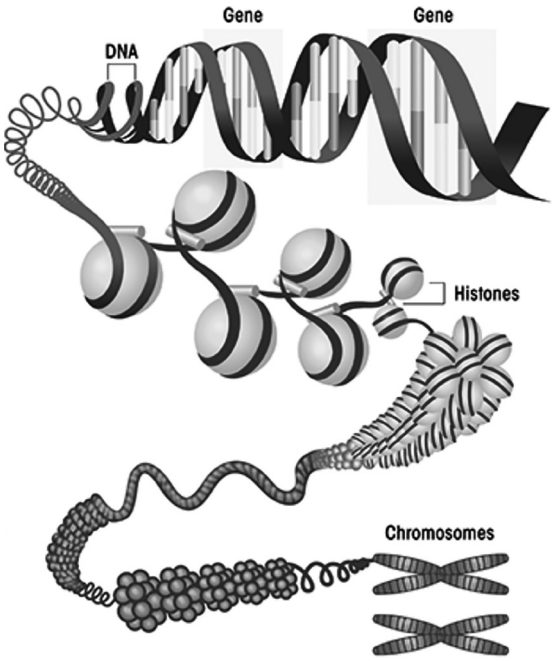
Changes in DNA nucleotides can be a variant or a polymorphism, depending on the frequency in the general population. The change is called a polymorphism if it occurs in at least 1% of the population and a variant if it occurs in less than 1%. To further explain, a normal length of DNA is similar to a recipe for an ordinary chocolate cake. Although this is the most common, other cakes exist, including strawberry, white, spice, pineapple upside-down,

FIGURE 1-6
BRCA2 GENE LOCATION



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

FIGURE 1-7
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, 2013, *Alcohol Alert, 86,* p. 2. http://pubs.niaaa.nih.gov/publications/aa86/aa86.htm.

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 1-9). This is a variant and not the desired outcome.

Several types of variants exist. The most common type is the point variant, in which only one nucleotide base is altered. A nonsense variant occurs with premature termination of the protein. The stop codon, which signals termination of the length of amino acids, has been misspelled and gives an early or late signal to end the compilation of amino acids into a protein (National Cancer Institute [NCI], 2021b; Palma & Lejeune 2021).

Variants that occur within cells are somatic. They accumulate over a lifetime and cause sporadic cancers, typically after an individual has reached age 50 years. Variants in the ova or sperm are germline and associated with inherited cancers, typically in people aged younger than 50 years (see Figure 1-10). The results of this genomic instability affect all future generations, depending on the pattern of inheritance (NCI, 2021b; Palma & Lejeune 2021).

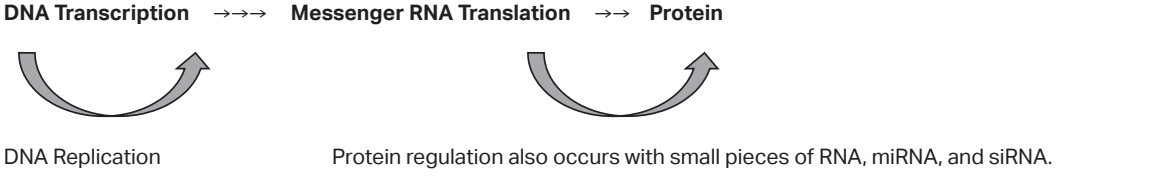
Most patterns of inheritance follow the dominant or recessive model developed by Gregor Mendel (Saw et al., 2021). Each individual typically has two sets of chromosomes. On each chromosome is a gene, or allele, for a particular characteristic. Although an allele may have a collection of many different traits (such as blue, green, hazel, or brown eyes), each chromosome can only exhibit one of these. So, one chromosome may have the blue eyes allele, and the second chromosome could have the brown eyes allele. All other eye colors are still allelic options but are not displayed by this set of chromosomes. Each allele is either a dominant or recessive type. For example, the brown eyes allele is dominant over the recessive blue eyes allele. If the dominant allele is inactivated or lost, the recessive allele will become active (Saw et al., 2021).

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 caught in a cloud of fog. The house is still standing but is not visible because of the denseness of the low-lying cloud cover. Age, modifier genes, carcinogens, repair enzymes, and hormone or reproductive factors affect penetrance (Saw et al., 2021).

DNA Changes and Cancer

Descriptions of variants associated with cancer include drivers and passengers. Driver variants, such

FIGURE 1-8
MODIFIED CENTRAL DOGMA OF DNA MODEL



miRNA—microRNA; siRNA—small interfering RNA

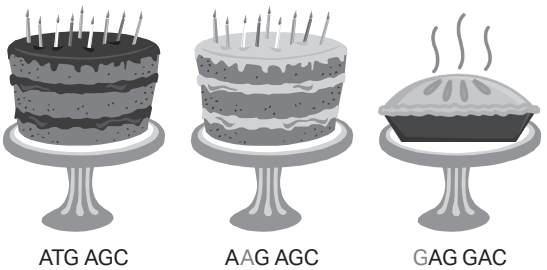
Note. Based on information from Crick, 1970; Hayes et al., 2014.

as *TP53*, are commonly associated with the development of cancer (oncogenesis) and offer a clonal advantage in the microenvironment of the evolving cancer cell (Porta-Pardo et al., 2020). Within the same tumor, passenger variants are found but do not offer growth advantage and have no known contribution to the development of the cancer type. They seem to be along for the ride (Skvortsova et al., 2019). Different cancers may have different driver and passenger variations but appear with similar phenotypes. The drivers in this group of variant gene sets are targeted for treatment individually or in a staggered approach (Skvortsova et al., 2019; Stratton et al., 2020).

In healthy cells, driver and passenger variants can be restored to pre-damage level by healthy DNA repair mechanisms 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 (Skvortsova et al., 2019).

Much of the scientific evidence about the development of cancer and its progression suggests that genomic instability is a precursor to changes associated with the 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 the 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 *TP53* or retinoblastoma protein tumor suppressor proteins cause cell cycle arrest for repair or apoptosis (programmed cell

FIGURE 1-9
POLYMORPHISMS VERSUS VARIANTS



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).

FIGURE 1-10
SOMATIC VERSUS GERMLINE VARIANTS

Somatic Cell	Germline Cell (Egg or Sperm)
• Variant occurs in only one cell. • DNA damage may occur in one cell (not an egg or sperm) and accumulate over an extended period after conception. • Variant is not inheritable.	• DNA in egg or sperm already has variant at conception. • DNA damage is replicated in cell lineage, and a tumor develops in one organ or tissue type. • As cells duplicate, DNA damage is incorporated into every body cell and tissue type of the offspring. • The potential for malignancy exists in multiple tissue types over time. • Variant is passed to future generations.

Note. Based on information from National Cancer Institute, 2021b.

death) (Skvortsova et al., 2019; Strasser & Vaux, 2020).

Much research has confirmed that most human cancers lose function in the *TP53* tumor suppressor pathway. Other genes involved in targeting and repairing DNA damage have also been found to lose function in multiple cancers (Skvortsova et al., 2019). 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 (Strasser & Vaux, 2020).

Epigenetics

Healthy Structure and Function

Changes that occur to DNA activity beyond the actual sequence of the base pairs are termed *epigenetics* (Strasser & Vaux, 2020). These changes occur above and over the DNA, so there is no effect on the basic sequence, and the genotype is not changed; however, the phenotypic outcome may be altered. These phenotypic changes occur through loosening or altering the tightly wound chromatin by binding the different chemicals in such a way that can determine when and where genes might be expressed or turned on (Strasser & Vaux, 2020).

Chromatin consists of proteins and DNA as part of the chromosomes (Skvortsova et al., 2019). 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. Similar to sewing bobbins, histones organize and control the long threads of DNA, wrapping them into a tight coil so that the DNA can fit neatly packaged inside the nucleus of a cell. The coiling is necessary because the strands of DNA in the body would stretch about five feet but would be only 50 trillionths of an inch (2 nanometers [nm]) wide. For comparison, the membrane of a brightly colored soap bubble is between 100 and 400 nm wide (UCSB ScienceLine, 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 1-7. These chromatids enable the chromosomes to be visualized for karyotyping during the metaphase of cell division (McCance & Huether, 2019).

These continuous strands of DNA and histones appear like beads on a string (euchromatin). Multiple histones wrapped tightly together (heterochromatin) prevent transcription and contain inactive genes. The nucleosome comprises eight separate histone molecules with two loops of DNA wrapped around each group of eight histones (Skvortsova et al., 2019; Strasser & Vaux, 2020).

Epigenetic Modifications and Cancer

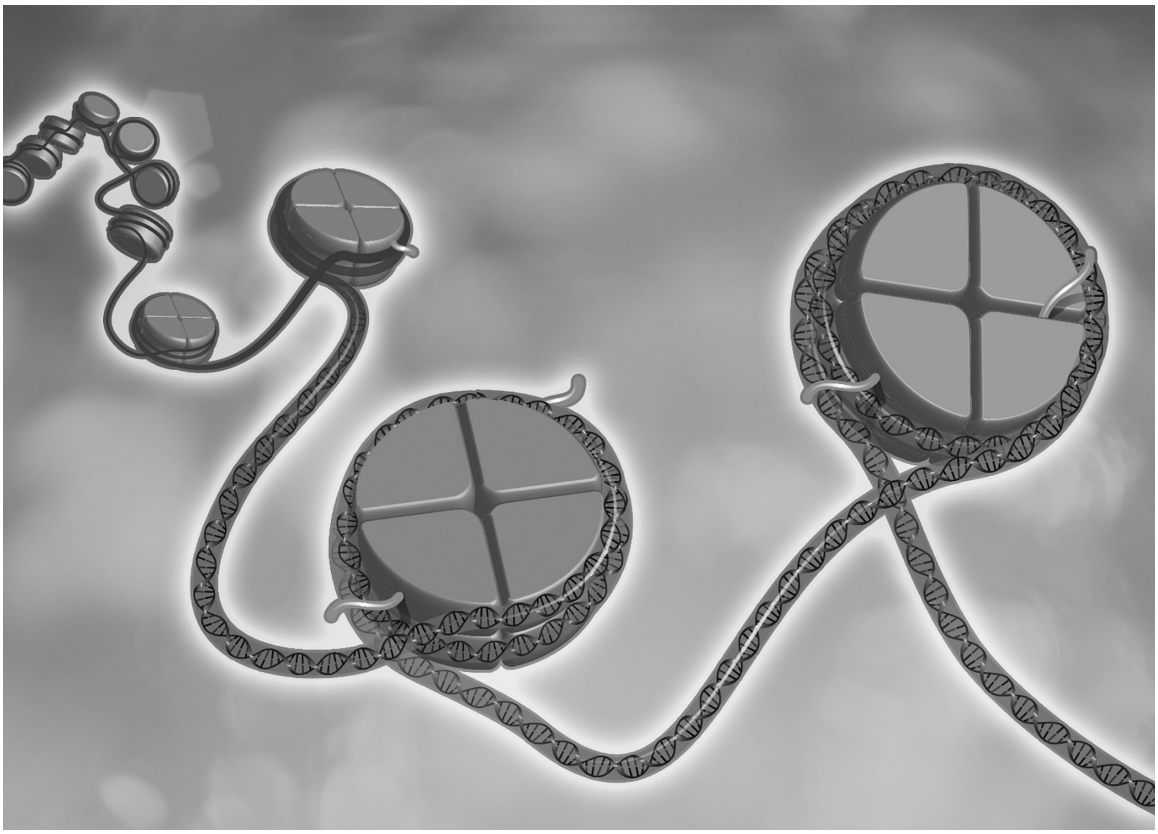
The changes associated with epigenetics are caused when the DNA and the histone proteins

become modified with the addition or removal of chemical groups (tags) (see Figure 1-11). 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.

Because histones are proteins, they can be modified after translation by attaching acetyl, phosphate, or ubiquitin groups (Thakur & Fei, 2019; Uckelmann & Sixma, 2017; Zhang et al., 2020). During nontranscription, the genome tightly wraps genes to make them unreadable. During transcription, the active genes are easily accessible when the genome is relaxed.

Collections of enzymes have been identified to have functioned as readers, writers, and erasers in the epigenome. Epigenetic readers are 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.

FIGURE 1-11
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 courtesy of Darryl Leja and National Human Genome Research Institute. https://www.genome.gov/dmd/img.cfm?node=Photos/Graphics/Illustrations&id=97352.

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 for gene expression. Erasers are collections of enzymes that remove (erase) histone modifiers (Skvortsova et al., 2019; Strasser & Vaux, 2020).

Epigenetics and Cancer

Although increased DNA methylation is associated with certain genes, the methylation levels are overall lower in malignant cells than healthy cells. Different types of cancer with similar characteristics can have varied DNA methylation patterns (Thakur & Fei, 2019; Zhang et al. 2020).

Epigenetic-based tests have been developed and used with other diagnostic screening tests to identify colorectal cancers with increased methylation at the *SEPT9* gene. For example, the Epi proColon test is used to detect methylated Septin 9 DNA in EDTA plasma derived from the whole blood specimen of a patient. Patients with positive test results should be referred for a diagnostic colonoscopy. This test does not replace colorectal cancer screening tests recommended by appropriate guidelines (Thakur & Fei, 2019; Zhang et al., 2020).

Healthy Versus Abnormal Cell Division

Healthy cells cease to multiply once all available intracellular space to grow has been overtaken by tumor cells. Therapeutic agents that destroy cancer cells can use cytoskeletal control to destroy.

Proteins, glycoproteins, and glycolipids are known to have altered mobility on the outside membrane of a malignant cell. This mobility enables cancer to change its surface to avoid immunosurveillance. Other outcomes could promote spread and metastasis (Skvortsova et al., 2019; Strasser & Vaux, 2020).

After replication, healthy cells contact the adjacent cell membrane and inhibit growth. Malignant cells lose this inhibition and continue to proliferate, even though they have contact or are touching the cell next to them. This modification or loss of contact inhibition contributes to cell division, persistent overgrowth of adjacent cells, and a lack of growth control by malignant cells. This is considered a hallmark of cancer (McCance & Huether, 2019).

Malignant cell membranes have a lower level of electrical potential than healthy cells because of the increased amounts of negatively charged phospholipids in the cell membrane (Skvortsova et al., 2019; Strasser & Vaux, 2020). Positively charged sodium and calcium channels contribute to apoptosis. Changes in the charge of the cell membrane inhibit apoptosis and contribute to the longevity of malignant cells.

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 healthy and abnormal cells (McCance & Huether, 2019).

Self-Sufficiency in Growth Signals

Growth Factors

Cell behavior is controlled by circulating proteins known as growth factors (ligands) that can act as chemical signals. They direct cell growth, differentiation, and survival and determine tissue architecture and morphology. Growth factors must interact with their particular receptor to accomplish signaling (Erdogan & Webb, 2017).

Growth factors associated with cancer development include epidermal growth factor, transforming growth factor, and colony-stimulating factor. Other growth factors exist that are overproduced and associated with different cancer types. For example, platelet-derived growth factor is associated with sarcomas and glioblastomas (Erdogan & Webb, 2017).

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 the transmission of a message to the cell nucleus. The message causes a change in the expression of specific genes that help usher the cell through its growth cycle (Erdogan & Webb, 2017). Overproduction of some growth factors causes altered cellular communication and is associated with cancers. One of these, vascular endothelial growth factor, has an important role in tumor neoangiogenesis (new growth of vessels on a tumor).

Lack of oxygen leads to the vascular endothelial growth factor-alpha protein transcription by binding to its designated cell surface receptors. The binding trips a signal, indicating the need for increased blood vessel permeability and resulting in angiogenesis with even more proliferation of cells (Erdogan & Webb, 2017). Vascular endothelial growth factor 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. Proliferative signals are sent into the cytoplasm once they are bound by a ligand that causes activation. Most growth factor receptors possess tyrosine kinase activity, which leads to reactions that stimulate mitotic cell division, allowing rapid growth of the malignant cell (Erdogan & Webb, 2017).

Examples of growth factor receptors that are cancer-causing (oncogenic) when overexpressed include HER2, epidermal growth factor receptor, and transforming growth factor-beta. A variety of cancers express epidermal growth factor receptors, including non-small cell lung, breast, ovarian, and colorectal cancer. Approximately 80%–100% of head and neck cancers overexpress epidermal growth factor receptors, which also is associated with lower survival. Increased HER2 expression corresponds with more aggressive cancers, including ovarian and breast cancers. When epidermal growth factor receptor and transforming growth factor-beta are expressed, it is a prognostic marker for tumor relapse and decreased survival (Erdogan & Webb, 2017).

Nonreceptor Tyrosine Kinases

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

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 enzymatic protein produced by the *RAF1* gene (GeneCards, n.d.-a). In the cytoplasm, tyrosine kinase 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 (Erdogan & Webb, 2017; GeneCards, n.d.-a).

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, beginning the signaling cascade inside the cell (Arang & Gutkind, 2020).

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 in the cell cytoplasm. Normal *RAS* genes wait for prompting to send stimulatory signals from growth factor receptors to other proteins. Variant *RAS* genes activate signaling pathways even when unprompted. Variant *RAS* is found in virtually all types of human cancer and occurs in approximately two-thirds of all malignant tumors. G proteins act at the cell membrane to cause malignant transformation (Arang & Gutkind, 2020).

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. Variant 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 transcription factor–induced cancers are characterized by translocation of chromosomes (Donehower et al., 2019). 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 (Donehower et al., 2019).

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. Cell growth is the accelerator. The tumor suppressor genes are the brakes, which can prevent cellular proliferation or suppress malignant transformation. At the cellular level, variations in the cell cause tumor suppressor genes to lose function of both alleles. In other words, the loss of function or variant 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 variant of a tumor suppressor gene, it is considered heterozygous because the alleles are different. The gene's function and protein product are maintained because a healthy allele is present. Once the remaining allele becomes a variant, the gene and its product will lose healthy functioning and *heterozygosity*. Cells can experience loss of heterozygosity with entire chromosome loss, translocation of a part of the chromosome, reduplication of a part of the chromosome that already has an abnormal gene, or the development of a point variation in the second functioning allele. Loss of heterozygosity is associated with cancer susceptibility genes, such as oncogenes and tumor suppressor genes (e.g., *TP53*). Research is identifying an increasing number of tumor suppressor genes that, when variants, are closely associated with the development and progression of human cancers (NCI, 2021a, 2021b).

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

different leukemias (Genetics Home Reference, 2020a; NCBI, n.d.).

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 *TP53* gene can halt cell division and induce apoptosis (NCBI, n.d.).

Tumor suppressor genes also can encode proteins in the cytoplasm. The *NF1* (neurofibromatosis) gene encodes a protein similar to those modulating *RAS* oncogene function (Genetics Home Reference, 2020b). Loss of *NF1* may keep *RAS* activated and prolong the signal for cell proliferation (Erdogan & Webb, 2017). Loss of other tumor suppressor genes, such as *NF2* and *APC* (adenomatous polyposis coli), may cause cellular disorganization and lead to abnormal cell proliferation.

Insensitivity to Antigrowth Signals

Antigrowth signals move the healthy cell from the cell cycle growth phases into the resting phase. The *transforming growth factor*-beta pathway is the best example of a signaling mechanism that causes inhibition of cell growth and proliferation. This occurs in two ways in the healthy pathway. First, transforming growth factor-beta prevents inactivation of retinoblastoma protein, a tumor suppressor protein, and synthesis of the proteins from the tumor suppressor genes *p15INK4α* and *p21*. Second, cells cannot move into and through the cell cycle if cyclins are blocked. If the p15 protein is not synthesized, cyclins are not blocked, allowing cells to continuously move into the active cell cycle with growth and proliferation. Finally, retinoblastoma protein tumor suppressor function is lost. These interfering mechanisms, alone or in combination, allow continued cell growth and proliferation (Genetics Home Reference, 2020c).

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

If the Hedgehog, Notch, or Wnt pathways overexpress the wild-type signaling molecules or have activated variants, malignant conversion of adult stem cells to cancer stem cells occurs (Strasser & Vaux, 2020). Variation of *BRCA1* can prevent DNA repair. If *PTEN* is mutated or deleted, it can increase expression of genes that promote continuous movement through the cell cycle (Strasser & Vaux, 2020). New therapies target some of these and other signaling pathways, potentially initiating programmed cell death.

Limitless Potential for Replication

One factor allowing for limitless replicative potential is expression of telomerase. Telomeres are nucleoprotein structures found at the end of each chromosome arm to maintain geonomic stability (Turner et al., 2019).

- Telomeres protect the end of chromosomes from damage with repetitive sequences of noncoding DNA.
- Telomerase added to the end of a telomere prevents its destruction.
- Cells with increased telomerase are associated with longer telomeres and longevity of cell life.
- Short telomeres are associated with a shorter life span.
- Each cell division causes telomeres to become shorter.
- Cancer stem cells have increased levels of telomerase, leading to extended life enhanced by the protected telomeres at the ends of the chromosome.
- Increased telomerase also protects the cancer cell from apoptosis.

Nursing Implications

Today, a nurse in the specialized oncology clinical setting needs to have more than just a general knowledge of caring for patients with a cancer diagnosis. Nurses need to understand the initiation and progression of cancer, inflammation and its role in carcinogenesis, the types of cancer, and implications of specific disease diagnoses for patient assessment. Oncology nurses must develop a specialized plan of care, identify appropriate interventions with personalized goals for effectiveness, and be educated on evaluating outcomes.

Summary

The curricula in undergraduate nursing programs do not typically include molecular biology. With the completion of human genome sequencing 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 essential for oncology nurses. It helps them anticipate cancer symptoms in patients and understand how treatments work, and provides a basic foundation for developing individualized

Key Points

- Eight hallmarks have been identified to assist caregivers and providers in understanding how cancer develops. These include self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis with limitless replicative potential, sustained angiogenesis, tissue invasion, metastasis, reprogramming energy metabolism, and evasion of the immune response. Two enabling traits, genome instability and mutation plus tumor-promoting inflammation, were also added. Nurture is now included because it can cause genetic alterations of cancer. These nurture sources include obesity, lack of exercise, poor diet, and social habits.
- Carcinogenesis occurs in three stages: initiation, promotion, and progression. Some sources suggest a fourth state, malignant conversion.
- Some environmental and chemical human carcinogens are so strong that they can disrupt inflammation resolution and contribute as a hit, contributing to the two-hit theory of DNA damage.
- The central dogma is the backbone of molecular biology and includes the three core processes of DNA replication, transcription, and translation.
- Driver variants, like those found in *TP53*, are commonly associated with cancer development. Passenger variants are found with cancer but do not offer growth advantage and seem to be only along for the ride. Checkpoint gatekeepers function at specific points in the active phases of the cell cycle before the S phase and M phase to guarantee the accuracy of the genome and cell processes. If an error is present, the TP53 retinoblastoma tumor suppressor protein will cause cell cycle arrest for repair or programmed cell death (apoptosis) if too much damage has occurred.
- An oncogene is a variant form of a gene from a healthy cell that can cause cancer. Oncogenes can be inherited or caused by exposure to cancer-causing substances in the environment.
- Phenotypic changes occur through loosening or tightening the chromatin.
- Visualized chromosomes seen during karyotyping are sister chromatids.
- Epigenetic modifications occur along a splice of DNA and histones using chemical tags. Methyl groups can be added at the C and G nucleotides (CpG islands) to cause silencing or stopping of transcription. Other chemical tags can be added and close the gaps to all transcription.

Key Points

- Methylation levels are lower in malignant cells than in healthy cells.
- Physiologic changes found in healthy cells changed to malignant cells include altered mobility of outside membrane components, modified contact adhesion and inhibition of movement, altered surface charge density, and the ability of cancer cells to hide due to increased lectin agglutinability (stickiness) of leukocytes.
- Failure of resolution, via pro-resolving lipid mediators, is essential in pathogenesis and a unifying component of many underlying chronic inflammatory diseases such as obesity.
- Carcinogens are chemical substances, or a mixture of chemical substances, that induce cancer after inhalation, ingestion, dermal application, or injection.

treatment plans. Understanding the biology of cancer is integral for people new to oncology or those who want to review and close some gaps in knowledge.

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Chapter 1 Study Questions

1. Which type of cancer cell is the only one with the ability to establish a new tumor?
   A. Cancer endothelial cell
   B. Cancer hematopoietic cell
   C. Cancer stem cell
   D. Cancer stromal cell

2. Which of the phases in the central dogma includes designation of a new protein?
   A. Translation
   B. Replication
   C. Transcription
   D. All of the above

3. 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

4. An example of incomplete penetrance is which of the following?
   A. A small boy alone on a playground without his mother
   B. Three adults and two small children playing football in the fog and rain
   C. Two teenagers playing football who cannot make a touchdown in the rain
   D. Children who can be heard in the fog but cannot be seen

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