HYPERTROPHY

Hypertrophy is the increase in the volume of an organ or tissue due to the enlargement of its component cells. OR

Hypertrophy is an increase in the size of an organ caused by an increase in the size of the cells rather than the number of cells. The cells of the heart and kidney are particularly prone to hypertrophy. **Hypertrophy** is also called overgrowth.

Muscle hypertrophy involves an increase in size of skeletal muscle through a growth in size of its component cells. Two factors contribute to hypertrophy: sarcoplasmic hypertrophy, which focuses more on increased muscle glycogen storage; and myofibrillar hypertrophy, which focuses more on increased myofibril size.

A range of stimuli can increase the volume of muscle cells. These changes occur as an adaptive response that serves to increase the ability to generate force or resist fatigue in anaerobic conditions.

Pathogenesis

- The hypertrophied organ has no new cells, just larger cells. The increased size of the cells is due not to cellular swelling but to the synthesis of more structural components.
- Cells capable of division may respond to stress by undergoing both hyperplasia and hypertrophy, whereas in nondividing cells (e.g., myocardial fibers), hypertrophy occurs.
- Nuclei in hypertrophied cells may have a higher DNA content than in normal cells, probably because the cells arrest in the cell cycle without undergoing mitosis.
- Hypertrophy can be physiologic or pathologic and is caused by increased functional demand or by specific hormonal stimulation.

Muscular hypertrophy

- The striated muscle cells in both the heart and the skeletal muscles are capable of tremendous hypertrophy.
- The most common stimulus for hypertrophy of muscle is increased workload. For example, the bulging muscles of bodybuilders engaged in "pumping iron" result from an increase in size of the individual muscle fibers in response to increased demand.
- The workload is thus shared by a greater mass of cellular components, and each muscle fiber is spared excess work and so escapes injury.
- The enlarged muscle cell achieves a new equilibrium, permitting it to function at a higher level of activity.

- In the heart, the stimulus for hypertrophy is usually chronic hemodynamic overload, resulting from either hypertension or faulty valves. Synthesis of more proteins and filaments occurs, achieving a balance between the demand and the cell's functional capacity.

Endometrial mucosa in pregnancy

- The massive physiologic growth of the uterus during pregnancy is a good example of hormone-induced increase in the size of an organ that results from both hypertrophy and hyperplasia.
- The cellular hypertrophy is stimulated by estrogenic hormones acting on smooth muscle estrogen receptors, eventually resulting in increased synthesis of smooth muscle proteins and an increase in cell size.
- Similarly, prolactin and estrogen cause hypertrophy of the breasts during lactation. These are examples of physiologic hypertrophy induced by hormonal stimulation.

NEOPLASIA

Neoplasia is new, uncontrolled growth of cells that is not under physiologic control.

Neoplasm is an abnormal growth of tissue, and when also forming a mass is commonly referred to as a **tumor** or **tumour**. This abnormal growth (neoplasia) not always forms a mass.

Types

A neoplasm can be benign, potentially malignant (pre-cancer), or malignant (cancer).

Benign tumors are localized and do not transform into cancer.

Potentially-malignant neoplasms include carcinoma in situ. They are localised, do not invade and destroy but in time, may transform into a cancer.

Malignant neoplasms are commonly called cancer. They invade and destroy the surrounding tissue, may form metastases and, if untreated or unresponsive to treatment, will prove fatal.

Secondary neoplasm refers to any of a class of cancerous tumor that is either a metastatic offshoot of a primary tumor, or an apparently unrelated tumor that increases in frequency following certain cancer treatments such as chemotherapy or radiotherapy.

Rarely there can be a metastatic neoplasm with no known site of the primary cancer and this is classed as a cancer of unknown primary origin

Causes

A neoplasm can be caused by an abnormal proliferation of tissues, which can be caused by genetic mutations. Not all types of neoplasms cause a tumorous overgrowth of tissue.

Benign conditions that are *not* associated with an abnormal proliferation of tissue (such as sebaceous cysts) can also present as tumors, however, but have no malignant potential. Breast cysts (as occur commonly during pregnancy and at other times) are another example, as are other encapsulated glandular swellings (thyroid, adrenal gland, pancreas).

Encapsulated hematomas, encapsulated necrotic tissue (from an insect bite, foreign body, or other noxious mechanism), keloids (discrete overgrowths of scar tissue) and granulomas may also present as tumors.

Discrete localized enlargements of normal structures (ureters, blood vessels, intrahepatic or extrahepatic biliary ducts, pulmonary inclusions, or gastrointestinal duplications) due to outflow obstructions or narrowings, or abnormal connections, may also present as a tumor. It can be dangerous to biopsy a number of types of tumor in which the leakage of their contents would potentially be catastrophic. The nature of a tumor is determined by imaging, by surgical

exploration, and/or by a pathologist after examination of the tissue from a biopsy or a surgical specimen.

Cancers may be classified by their primary site of origin or by their histological or tissue types.

Classification by site of origin

By primary site of origin, cancers may be of specific types like breast cancer, lung cancer, prostate cancer, liver cancer renal cell carcinoma (kidney cancer), oral cancer, brain cancer etc.

Classification by tissue types

Based on tissue types cancers may be classified into six major categories:

1. Carcinoma

This type of cancer originates from the epithelial layer of cells that form the lining of external parts of the body or the internal linings of organs within the body.

Carcinomas usually affect organs or glands capable of secretion including breast, lungs, bladder, colon and prostate.

Carcinomas are of two types – adenocarcinoma and squamous cell carcinoma. Adenocarcinoma develops in an organ or gland and squamous cell carcinoma originates in squamous epithelium. Adenocarcinomas may affect mucus membranes and are first seen as a thickened plaque-like white mucosa. These are rapidly spreading cancers.

2. Sarcoma

These cancers originate in connective and supportive tissues including muscles, bones, cartilage and fat. Bone cancer is one of the sarcomas termed osteosarcoma

3. Myeloma

These originate in the plasma cells of bone marrow. Plasma cells are capable of producing various antibodies in response to infections. Myeloma is a type of blood cancer.

4. Leukemia

This group of cancer is blood cancers. These cancers affect the bone marrow which is the site for blood cell production. When cancerous, the bone marrow begins to produce excessive immature white blood cells that fail to perform their usual actions and the patient is often prone to infection.

Types of leukemia include:

Acute myelocytic leukemia (AML) – these are malignancy of the myeloid and granulocytic white blood cell series seen in childhood.

Chronic myelocytic leukemia (CML) – this is seen in adulthood.

Acute Lymphatic, lymphocytic, or lymphoblastic leukemia (ALL) – these are malignancy of the lymphoid and lymphocytic blood cell series seen in childhood and young adults.

Chronic Lymphatic, lymphocytic, or lymphoblastic leukemia (CLL) – this is seen in the elderly.

Polycythemia vera or erythremia – this is cancer of various blood cell products with a predominance of red blood cells.

5. Lymphoma

These are cancers of the lymphatic system. Unlike the leukemias, which affect the blood and are called “liquid cancers”, lymphomas are “solid cancers”. These may affect lymph nodes at specific sites like stomach, brain, intestines etc. These lymphomas are referred to as extranodal lymphomas.

Lymphomas may be of two types – Hodgkin’s lymphoma and Non-Hodgkin’s lymphomas. In Hodgkin lymphoma there is characteristic presence of Reed-Sternberg cells in the tissue samples which are not present in Non-Hodgkin lymphoma.

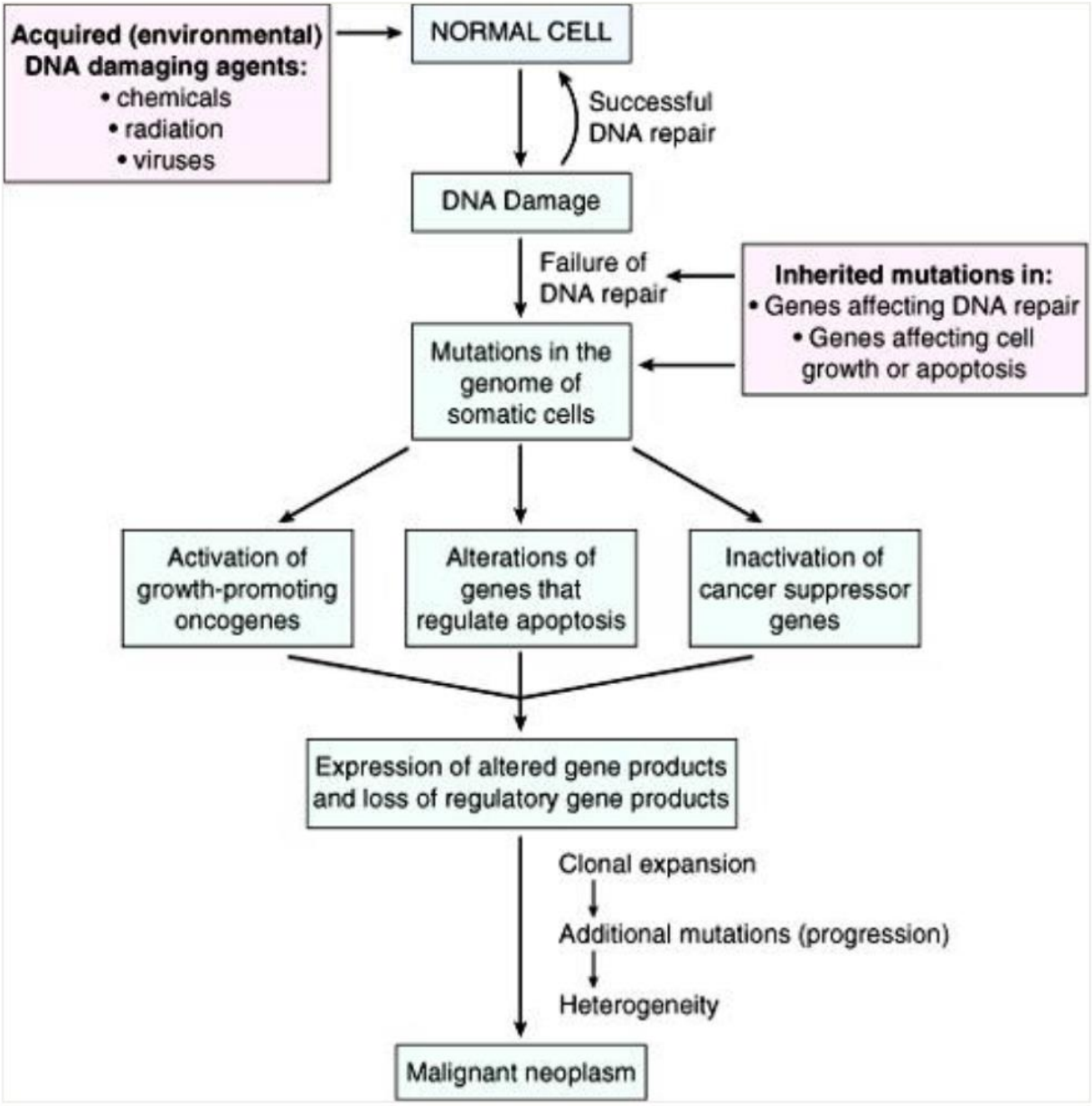
6. Mixed types

These have two or more components of the cancer. Some of the examples include mixed mesodermal tumor, carcinosarcoma, adenosquamous carcinoma and teratocarcinoma. Blastomas are another type that involves embryonic tissues.

Differences between Benign and Malignant Tumors

- ***Rate of growth*** - In general, malignant tumors grow much more rapidly than benign tumors.
- ***Ability to metastasize*** - Benign tumors expand locally, whereas malignant tumors can spread (metastasize) to other parts of the body by way of the bloodstream and lymphatic channels.
- ***Site of recurrence*** - While benign tumors may recur locally — that is, near the site of the original tumor — malignant tumors may recur at distant sites, such as the brain, lungs, bones and liver, depending on the type of cancer.
- ***"Stickiness"*** - The cells in benign tumors manufacture chemicals (adhesion molecules) that cause them to stick together. Malignant tumor cells do not produce these molecules and can break off and "float away" to other regions of the body.
- ***Tissue invasion*** - In general, malignant tumors tend to invade nearby tissues, whereas benign tumors do not. In contrast, envision cancer as having "fingers" or "tentacles" that can reach into nearby tissues. In fact, the Latin word cancer derives from the word crab, used to describe the crablike, or fingerlike, projections of cancerous tumors.
- ***Cellular appearance*** - Under a microscope, cells that are benign often look much different from those that are malignant. One of these differences is that the cell nucleus of cancer cells is often larger and appears darker due to an abundance of DNA.
- ***Effective treatments*** - Benign tumors can usually be removed with surgery alone, while cancerous (malignant) tumors will often require chemotherapy and radiation therapy.
- ***Likelihood of recurrence*** - Benign tumors do not recur after surgery, whereas malignant tumors recur much more commonly. Surgery to remove a malignant tumor is more difficult than surgery for a benign tumor. If cells are left over from these, the tumor is more likely to come back.
- ***Systemic effects*** - Malignant tumors are more likely to have systemic or total body, effects than benign tumors. Due to the nature of these tumors, symptoms such as fatigue and weight loss are common. Several types of malignant tumors also secrete substances that cause effects on the body beyond those caused by the original tumor.
- ***Death toll*** - Benign tumors cause around 13,000 deaths per year in the United States. The number of deaths that can be blamed on malignant (cancerous) tumors is over 575,000.

General Etiology and Pathogenesis



Environmental Carcinogens

- **A cancer-causing agent**
- **Three main types:**

Chemical

Direct-acting

Nitrogen mustard, Nitrosomethylurea, Benzyl chloride

Indirect-acting (must be metabolized to activated metabolic forms)

- **Polycyclic aromatic hydrocarbons (PAH)**
- **Produced by incomplete combustion of organic materials**

- **Present in chimney soot, charcoal-grilled meats, auto exhaust, cigarette smoke**

Physical (radiation)

Ultraviolet light, Ionizing radiation (X-rays), Asbestos

Biological (viruses and Bacteria)

- **Viral infections account for an estimated one in seven human cancers worldwide**
- **Majority of these are due to infection with two DNA viruses**
  - **HBV - linked to hepatocellular carcinoma**
  - **HPV - linked to cervical carcinoma**
- **Human papillomaviruses - HPV**
- **Epstein-Barr Virus (EBV)**
- **Human herpesvirus 8 (HHV8)**
- **Hepatitis B virus - HBV**
- **Hepatitis C virus - HCV**

Helicobacter pylori

- **Gastric infection linked to gastric lymphomas and adenocarcinomas**
- **Detection of H pylori in majority of cases of gastric lymphomas**
- **Antibiotic treatment results in gastric lymphoma regression in most cases**

Spread of tumors

Metastasis, or **metastatic disease**, is the spread of a cancer or other disease from one organ or part to another not directly connected with it. The new occurrences of disease thus generated are referred to as **metastases.**

Metastasis is a Greek word meaning "displacement", from, *meta*, "next", and *stasis*, "placement".

Routes of metastasis

Primary cancers are denoted by "*...cancer*" and their main metastasis sites are denoted by "*...metastases*".

Metastasis occurs by following four routes:

1. Transcoelomic

The spread of a malignancy into body cavities can occur via penetrating the surface of the peritoneal, pleural, pericardial, or subarachnoid spaces. For example, ovarian tumors can spread transperitoneally to the surface of the liver.

2. Lymphatic spread

Lymphatic spread allows the transport of tumor cells to lymph nodes and ultimately, to other parts of the body. This is the most common route of metastasis for carcinomas. Lymph node with almost complete replacement by metastatic melanoma.

3. Hematogenous spread

This is typical route of metastasis for sarcomas, but it is also the favored route for certain types of carcinoma, such as those originating in the kidney (renal cell carcinoma).

4. Transplantation or implantation

Cancer cells may spread to lymph nodes (regional lymph nodes) near the primary tumor. This is called nodal involvement, positive nodes, or regional disease. Localized spread to regional lymph nodes near the primary tumor is not normally counted as metastasis, although this is a sign of worse prognosis. Transport through lymphatics is the most common pathway for the initial dissemination of carcinomas.

Cellular and Molecular Basis of Cancer

Cellular Kinetics

Generation time is the time required for a quiescent cell to complete a cycle in cell division and give rise to 2 daughter cells. Malignant cells, particularly those arising from the bone marrow or lymphatic system, may have a short generation time, and there usually are a smaller percentage of cells in G_0 (resting phase). Initial exponential tumor growth is followed by a plateau phase when cell death nearly equals the rate of formation of daughter cells. The slowing in growth rate may be related to exhaustion of the supply of nutrients and O_2 for the rapidly expanding tumor. Small tumors have a greater percentage of actively dividing cells than do large tumors.

A subpopulation within many tumors, identified by surface proteins, may have the properties of primitive "normal" stem cells, as found in the early embryo. Thus, these cells are capable of entering a proliferative state. They are less susceptible to injury by drugs or irradiation. They are believed to repopulate tumors after surgical, chemical, or radiation treatment.

Cellular kinetics of particular tumors is an important consideration in the design of antineoplastic drug regimens and may influence the dosing schedules and timing intervals of treatment. Many antineoplastic drugs, such as antimetabolites, are most effective if cells are actively dividing, and some drugs work only during a specific phase of the cell cycle and thus require prolonged administration to catch dividing cells during the phase of maximal sensitivity.

Tumor Growth and Metastasis

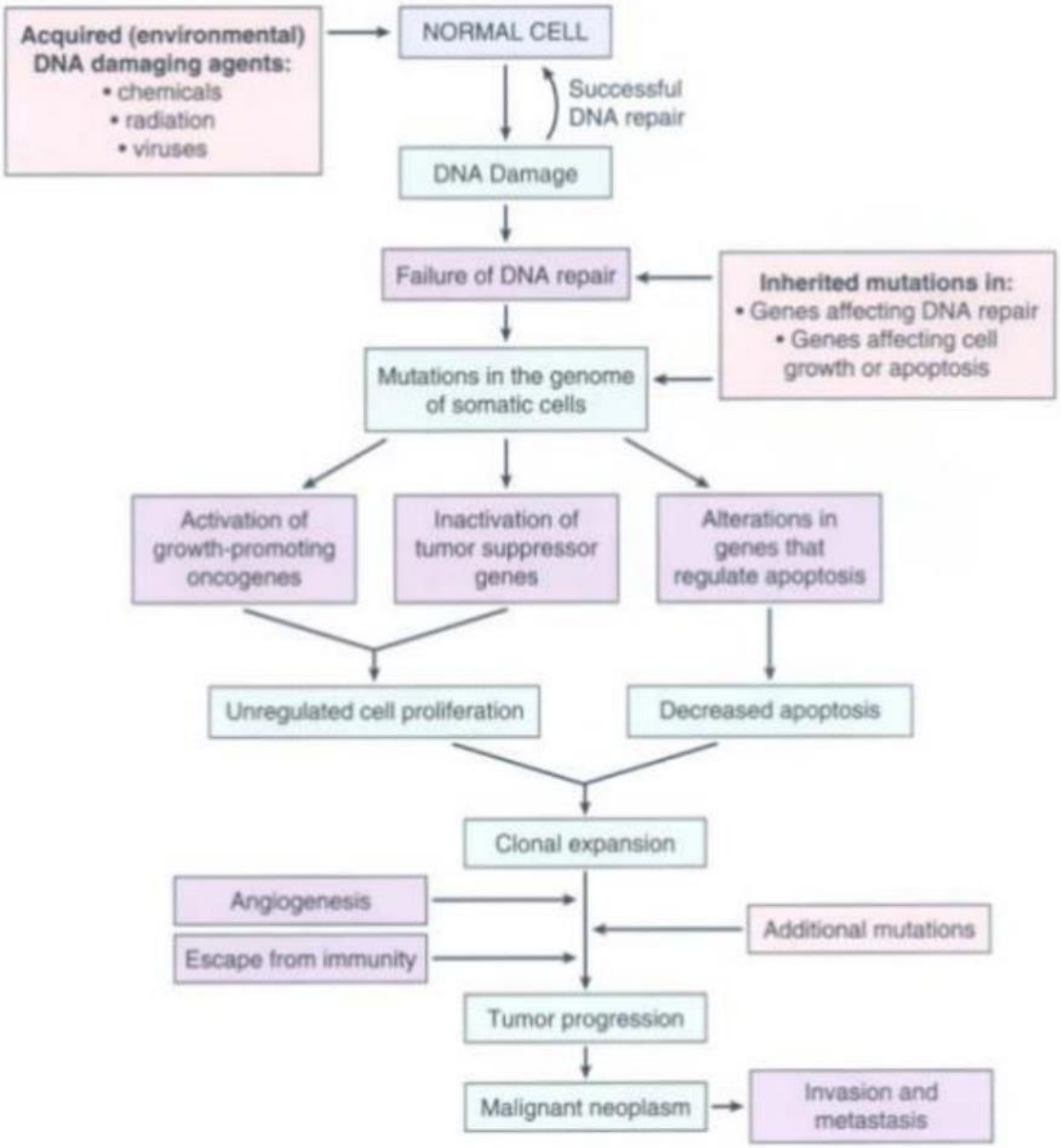
As a tumor grows, nutrients are provided by direct diffusion from the circulation. Local growth is facilitated by enzymes (eg, proteases) that destroy adjacent tissues. As tumor volume increases, tumor angiogenesis factors, such as vascular endothelial growth factor (VEGF), are produced by tumors to promote formation of the vascular supply required for further tumor growth.

Almost from inception, a tumor may shed cells into the circulation. From animal models, it is estimated that a 1-cm tumor sheds > 1 million cells/24 h into the venous circulation. Circulating tumor cells are present in many patients with advanced cancer and even in some with localized disease. Although most circulating tumor cells die in the intravascular space, an occasional cell may adhere to the vascular endothelium and penetrate into surrounding tissues, generating independent tumors (metastases) at distant sites. Metastatic tumors grow in much the same manner as primary tumors and may subsequently give rise to other metastases.

Experiments suggest that the ability to invade, migrate, and successfully implant and stimulate new blood vessel growth are all important properties of metastatic cells, which likely represent a subset of cells in the primary tumor.

Molecular Abnormalities

Genetic mutations are responsible for the generation of cancer cells and are thus present in all cancers. These mutations alter the quantity or function of protein products that regulate cell growth and division and DNA repair. Two major categories of mutated genes are oncogenes and tumor suppressor genes.



Flow chart depicting a simplified scheme of the molecular basis of cancer.

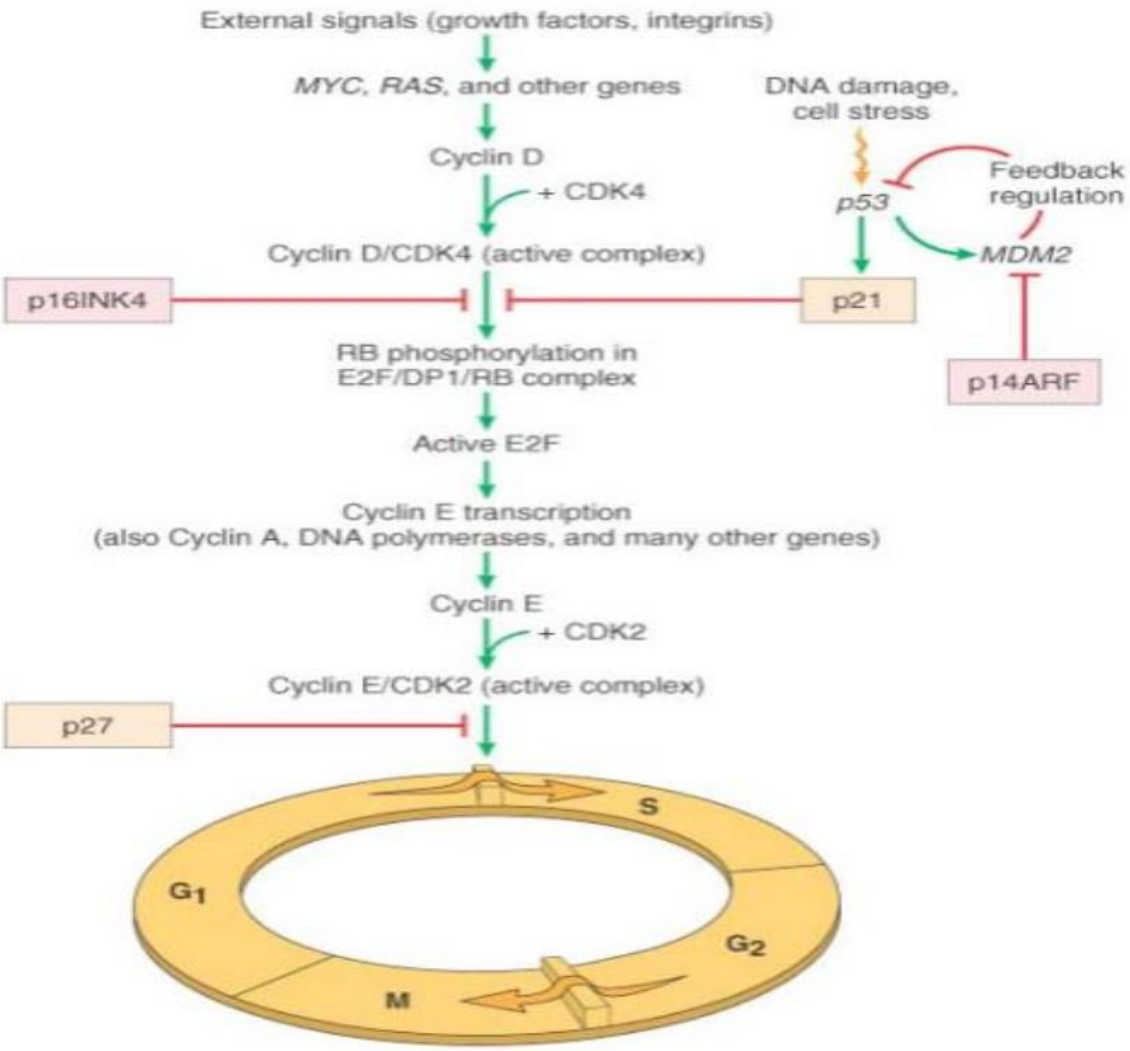


Figure 7-29 Schematic illustration of the role of cyclins, CDKs, and cyclin-dependent kinase inhibitors in regulating the G_1/S cell-cycle transition. External signals activate multiple signal transduction pathways, including those involving the *MYC* and *RAS* genes, which lead to synthesis and stabilization of cyclin D (there are several D cyclins, but, for simplification, we refer to them as "cyclin D"). Cyclin D binds to CDK4, forming a complex with enzymatic activity (cyclin D can also bind to CDK6, which appears to have a similar role as CDK4). The cyclin D-CDK4 complex phosphorylates RB, located in the E2F/DP1/RB complex in the nucleus, activating the transcriptional activity of E2F (E2F is a family of transcription factors, which we refer to as "E2F"), which leads to transcription of cyclin E, cyclin A and other proteins needed for the cell to go through the late G_1 restriction point. The cell cycle can be blocked by the Cip/Kip inhibitors p21 and p27 *(red boxes)* and the INK4A/ARF inhibitors p16INK4A and p14ARF *(green boxes)*. Cell-cycle arrest in response to DNA damage and other cellular stresses is mediated through p53. The levels of p53 are under negative regulation by MDM2, through a feedback loop that is inhibited by p14ARF.

Oncogenes

These are abnormal forms of normal genes (proto-oncogenes) that regulate various aspects of cell growth. Mutation of these genes may result in direct and continuous stimulation of the pathways (eg, cell surface growth factor receptors, intracellular signal transduction pathways, transcription factors, secreted growth factors) that control cellular growth and division, DNA repair, angiogenesis, and other physiologic processes.

There are > 100 known oncogenes that may contribute to human neoplastic transformation. For example, the*RAS* gene encodes the ras protein, which carries signals from membrane bound receptors down the RAS-MAPKinase pathway to the cell nucleus, and thereby regulates cell division. Mutations may result in the inappropriate activation of the ras protein, leading to uncontrolled cell growth. In fact, the ras protein is abnormal in about 25% of human cancers. Other oncogenes have been implicated in specific cancers. These include

- *HER2-NEU* (amplified but not mutated in breast cancer)
- *BCR-ABL* (a translocation of 2 genes that underlies chronic myelocytic leukemia and some B-cell acute lymphocytic leukemias)
- *C-MYC* (Burkitt lymphoma)
- *N-MYC* (small cell lung cancer, neuroblastoma)
- Mutated *EGFR* (adenocarcinoma of the lung)
- *EML4-ALK* (a translocation that activates the ALK tyrosine kinase and causes a unique form of adenocarcinoma of the lung)

Specific oncogenes may have important implications for diagnosis, therapy, and prognosis (see individual discussions under the specific cancer type).

Oncogenes typically result from acquired somatic cell mutations secondary to point mutations (eg, from chemical carcinogens), gene amplification (eg, an increase in the number of copies of a normal gene), or translocations (in which pieces of different genes merge to form a unique sequence). These changes may either increase the activity of the gene product (protein) or change its function. Occasionally, mutation of genes results in inheritance of a cancer predisposition, as in the inherited cancer syndrome associated with mutation and loss of function of *BRCA1* , *BRCA2* , or *p53* .

Tumor suppressor genes

Genes such as the *p53* gene play a role in normal cell division and DNA repair and are critical for detecting inappropriate growth signals or DNA damage in cells. If these genes, as a result of inherited or acquired mutations, become unable to function, the system for monitoring DNA integration becomes inefficient, cells with spontaneous genetic mutations persist and proliferate, and tumors result.

As with most genes, 2 alleles are present that encode for each tumor suppressor gene. A defective copy of one gene may be inherited, leaving only one functional allele for the individual tumor suppressor gene. If a mutation is acquired in the other allele, the normal protective mechanism of the 2nd normal tumor suppressor gene is lost. For example, the retinoblastoma (*RB*) gene encodes for the protein Rb, which regulates the cell cycle by stopping DNA replication. Mutations in the *RB* gene family occur in many human cancers, allowing affected cells to divide continuously.

Another important regulatory protein, p53, prevents replication of damaged DNA in normal cells and promotes cell death (apoptosis) in cells with abnormal DNA. Inactive or altered p53 allows cells with abnormal DNA to survive and divide. Mutations are passed to daughter cells, conferring a high probability of replicating error-prone DNA, and neoplastic transformation results. The *p53* gene is defective in many human cancers. As with oncogenes, mutation of tumor suppressor genes such as *p53* or *RB* in germ cell lines may result in vertical transmission and a higher incidence of cancer in offspring.