Cancer is a genetic disorder caused by DNA mutations (heritable). /increases in DNA methylation and alterations in histone modifications.

Neoplastic cells: they continue to replicate/ autonomy/ depend on the host for their nutrition and blood supply.

***Neoplasms derived from hormone responsive tissues often also require endocrine support.

benign tumor: relatively innocent, localized and is amenable to local surgical removal.

Malignant: the lesion can invade and destroy adjacent structures and spread to distant sites (metastasize) to cause death.

All tumors have two basic components: 1. the parenchyma (determines its biologic behavior): transformed or neoplastic cells/ 2. Stroma (crucial to the growth of the neoplasm): connective tissue, blood vessels, and host-derived inflammatory cells.

Benign Tumors (suffix -oma): fibroma/ chondroma (cartilaginous)/ **adenoma**: benign epithelial neoplasms that 1. produce glandlike structures or 2. derived from glands but lack a glandular growth pattern. / Papilloma: benign epithelial neoplasms that produce macroscopic fingerlike fronds. / polyp is a mass that projects above a mucosal surface (usually benign, maybe malignant, whereas nasal polyps not neoplastic but inflammatory in origin). / Cystadenomas: are hollow cystic masses that typically arise in the ovary.

Malignant Tumors: **sarcomas**: arising in solid mesenchymal tissues/ **leukemias or lymphomas**: arising from the mesenchymal cells of the blood. E.g.: Liposarcoma: fat-like cells. / chondrosarcoma: chondrocyte-like cells.

carcinomas: malignant neoplasms of epithelial cells. E.g.: renal tubular epithelium (mesoderm), the skin (ectoderm), and lining epithelium of the gut (endoderm).

Carcinomas are subdivided further: 1. **Adenocarcinomas:** Carcinomas that grow in a glandular pattern. /2. **squamous cell carcinomas:** produce squamous cells.

Mixed tumors (pleomorphic adenoma): are still of **monoclonal origin**, but the progenitor cell in such tumors has the capacity to differentiate down more than one lineage (have 1. epithelial components 2. fibromyxoid stroma 3. cartilage or bone). E.g.: mixed tumor of salivary gland / Fibroadenoma of the female breast.

Teratoma: mixed tumor that contains recognizable mature or immature cells or tissues derived from **more than one germ** cell layer. (Originate in ovary and testis). (have bone, epithelium, muscle, fat, nerve, and other tissues).

lymphoma, mesothelioma, melanoma, and seminoma are malignant tumors and they are exceptions in their naming.

benign and malignant tumors can be distinguished by: differentiation and anaplasia, local invasion, and metastasis.

Differentiation: extent to which neoplasms resemble their parenchymal cells of origin, both morphologically and functionally.

Anaplasia: lack of differentiation (always malignancy)

benign neoplasms: well-differentiated cells. / mitoses are usually rare and are of normal configuration/ retain the functional capabilities.

malignant neoplasms: exhibit morphologic alterations that betray their malignant nature.

scirrhous tumors: dense, abundant fibrous stroma.

Anaplastic cells often display the following morphologic features: Pleomorphism/ Nuclear abnormalities: hyperchromatism (dark-staining), variation in nuclear size and shape, prominent single or multiple nucleoli, nuclear-to-cytoplasmic ratio that approaches 1:1 / Tumor giant cells may be formed/ Atypical mitoses/ Loss of polarity / much less likely to have specialized functional activities.

ectopic hormones: Cancer's of nonendocrine origin hormones. (paraneoplastic phenomena)

dysplasia: disorderly proliferation / Mitotic figures are more abundant.

carcinoma in situ: severe dysplastic changes and involve the entire thickness of the epithelium/ preinvasive stage of cancer.

Dysplasia often noted to malignant neoplasms. Not always cancerous (could be reversable)

Local Invasion: progressive infiltration, invasion, and destruction of surrounding tissues (malignant). **most benign tumors grow remain localized/ they develop a capsule.

Encapsulation makes the tumor discrete, moveable

not all benign neoplasms are encapsulated: the leiomyoma of the uterus (discretely defined)/ vascular neoplasms such as hemangiomas (lack of demarcation).

Metastasis: the spread of a tumor to sites differ from the primary tumor. (malignant)

30% of patients with newly diagnosed solid tumors present with clinically evident metastases additional 20% have occult (hidden) metastases at the time of diagnosis.

all malignant tumors can metastasize. basal cell carcinomas and most primary tumors of the central nervous system rarely metastasize. leukemias and lymphomas always malignant.

Malignant neoplasms disseminate by one of three pathways: (1) seeding within body cavities, (2) lymphatic spread, (3) hematogenous spread.

seeding within body cavities: cancers of the ovary cover the peritoneal surfaces widely/ Neoplasms of the central nervous system, such as a medulloblastoma or ependymoma.

Lymphatic spread favored by: carcinomas, whereas hematogenous spread: sarcomas.

Lung carcinomas metastasize to: the regional bronchial lymph nodes → tracheobronchial and hilar nodes

upper outer quadrant and first Carcinoma of the breast usually spreads to the axillary nodes.

medial breast lesions drain through the chest wall to the nodes along the internal mammary artery. **in both instances, the supraclavicular and infraclavicular nodes may be seeded.

sentinel lymph nodes: the first regional lymph node that receives lymph flow from a primary tumor/ identified by injection of blue dyes or radiolabeled tracers near the primary tumor

enlargement of nodes near a primary neoplasm maybe metastatic spread or immunologic responses

the liver and lungs are the most frequently involved secondary sites in hematogenous dissemination.

Exceptions to anatomic localization of a neoplasm: 1. prostatic carcinoma spreads to: 2. bone, bronchogenic carcinoma: adrenal glands and brain, 3. neuroblastoma: liver and bones.

Prostate cancer is the most common cancer in men then lung/ breast in women then lung

Lung cancer is the most cause of death in men and women.

EPIDEMIOLOGY

Papanicolaou (PAP) smear test for early detection of cervical cancer decrease death rates from it. The deployment of the human papillomavirus (HPV) vaccine may nearly eliminate this cancer in coming years

Environmental Factors: Diet/ Smoking/ Alcohol consumption/ Reproductive history/ Infectious agents

Age and Cancer: cancer increases with age

Acquired Predisposing Conditions: include disorders associated with chronic inflammation, immunodeficiency states, and precursor lesions

Tumors arising in the context of chronic inflammation are mostly carcinomas, but also include mesothelioma and several kinds of lymphoma. By contrast, immunodeficiency states mainly predispose to virus-induced cancers, including specific types of lymphoma and carcinoma and some sarcoma-like proliferations.

Precursor lesions are localized disturbances of epithelial differentiation that are associated with an elevated risk for developing carcinoma. E.g.: Squamous metaplasia and dysplasia of bronchial mucosa/ Endometrial hyperplasia and dysplasia/ Leukoplakia of the oral cavity, vulva, and penis/ Villous adenoma of the colon

In general, benign tumors are not precancers

CANCER GENES:

Proto-oncogenes: normal cellular genes whose products promote cell proliferation

• **Oncogenes**: mutant or overexpressed versions of protooncogenes that function autonomously without a requirement for normal growth-promoting signals

Tumor suppressor genes: prevent uncontrolled growth and, when mutated or lost from a cell, allow the transformed phenotype to develop. both normal alleles of tumor suppressor genes must be damaged for transformation to occur.

Tumor suppressor genes can be placed into two general groups:

Governors: act as important brakes on cellular proliferation

Guardians: responsible for sensing genomic damage, leading to the cessation of proliferation or, if the damage is too great to be repaired, or induce apoptosis.

Genes that regulate apoptosis: enhancing cell survival, rather than stimulating proliferation

genes that regulate interactions between tumor cells and host cells: enhance or inhibit recognition of tumors cells by the host immune system.

Driver mutations: are mutations that alter the function of cancer genes and thereby directly contribute to the development or progression of a given cancer. Directly cause cancer.

passenger mutations: are acquired mutations that are neutral in terms of fitness and do not affect cellular behavior. Have proven to be important in several ways: most genomic damage is directly caused by the carcinogen in question. they create genetic variants that may provide tumor cells with a selective advantage in the setting of therapy.

Point Mutations

Point mutations convert proto-oncogenes into oncogenes. e.g.: convert the RAS gene into a cancer gene. in tumor suppressor genes it reduce or disable the function of the encoded protein e.g.: TP53

Gene Rearrangements: These rearrangements can activate proto-oncogenes in two ways:

1. overexpression of proto-oncogenes by removing them from their normal regulatory elements and placing them under control of an inappropriate, highly active promoter or

enhancer. E.g.: Burkitt lymphoma: translocation between chromosomes 8 and 14, leads to overexpression of the MYC gene on chromosome 8.
follicular lymphoma: between chromosomes 14 and 18 leads to overexpression of the anti-apoptotic gene, BCL2, on chromosome 18.

2. create fusion genes encoding novel chimeric proteins. E.g.: chronic myeloid leukemia: Philadelphia (Ph) chromosome between chromosomes 9 and 22 lead to BCR-ABL fusion gene.
   Ewing sarcoma: (11;22)(q24;q12) translocation, oncoprotein composed of EWS and FLI1.

Deletions: Deletion of specific regions of chromosomes lead to Deletion of specific regions of chromosomes

Tumor suppressors generally require inactivation of both alleles in order to contribute to carcinogenesis. A common mechanism for this is an inactivating point mutation in one allele, followed by deletion of the other, nonmutated allele.

e.g.: Retinoblastoma: deletions involving 13q14, the site of the RB gene. / deletion of 17p is associated with loss of TP53.

Gene Amplifications: Proto-oncogenes may be converted to oncogenes by gene amplification, with consequent overexpression and hyperactivity of otherwise normal proteins

Two clinically important examples of amplification involve the NMYC gene in neuroblastoma and the HER2 gene in breast cancers.

Aneuploidy is defined as a number of chromosomes that is not a multiple of 23.

Aneuploidy frequently results from errors of the mitotic checkpoint.

chromosome 8 have MYC gene (never lost in tumor cells)

chromosome 17 have TP53 gene (often lost)

MicroRNAs: negative regulators of genes / They inhibit gene expression by repressing translation or by messenger RNA (mRNA) cleavage. miRNAs also can contribute to carcinogenesis by reduce the tumor suppressor protein (oncomIRs) or by reduction in the quantity or function of that miRNA that inhibits the translation of an oncogene.

Epigenetics: refers to reversible, heritable changes in gene expression that occur without mutation

cancer cells are characterized by a global DNA hypomethylation and selective promoter-localized hypermethylation

NOTCH1 gene has an oncogenic role in T-cell leukemia, yet acts as a tumor suppressor in squamous cell carcinomas.

all cancers display eight fundamental changes in cell physiology, which are considered the hallmarks of cancer:

Self-sufficiency in growth signals • Insensitivity to growth-inhibitory signals • Altered cellular metabolism • Evasion of apoptosis • Limitless replicative potential (immortality) • Sustained angiogenesis • Invasion and metastasis • Evasion of immune surveillance

Self-Sufficiency in Growth Signals: gain-of-function mutations that convert proto-oncogenes to oncogenes. / oncoproteins: Oncogenes encode proteins that promote cell growth, even in the absence of normal growth-promoting signals.

Growth Factors: Cancers may secrete their own growth factors or induce stromal cells to produce growth factors in the tumor microenvironment

Growth Factor Receptors: Many of the myriad growth factor receptors function as oncoproteins when they are mutated or if they overexpressed.

ERBB1, the EGF receptor, is overexpressed in many squamous and epithelial tumors. / HER2 (ERBB2) in breast cancer.

tyrosine kinase activity is stimulated by point mutations or small indels that create fusion genes encoding chimeric receptors. most common in leukemias, lymphomas, and sarcoma.

Downstream Signal-Transducing Proteins: 1. **RAS:** the most commonly mutated oncogene in human tumors. 30% of all human tumors contain mutated RAS genes.

GTPase-activating proteins (GAPs) act as molecular brakes that prevent uncontrolled RAS activation by favoring hydrolysis of GTP to GDP.

Activated RAS alter the expression of genes that regulate growth, such as MYC

Mutations of phosphatidyl inositol-3 kinase (PI3 kinase) in the PI3K/AKT pathway also occur with high frequency in some tumor types, with similar consequences.

RAS most commonly is activated by point mutations interfere with breakdown of GTP.

loss-of function mutations in GAPs mimic the activating mutations in RAS

PTEN is a negative inhibitor of PI3 kinase and is frequently mutated

2.ABL: The ABL proto-oncoprotein has tyrosine kinase activity that is dampened by internal negative regulatory domains.

BCR-ABL hybrid protein (mentioned earlier) that contains the ABL tyrosine kinase domain and a BCR domain that self-associates, an event that unleashes a constitutive tyrosine kinase activity. / activates all the signals that are downstream of RAS→ stimulator of cell growth.

Nuclear Transcription Factors: mutations affecting genes that regulate DNA transcription.

host of oncoproteins, including products of the MYC, MYB, JUN, FOS, and REL oncogenes, function as transcription factors that regulate the expression of growth-promoting genes, such as cyclins.

Dysregulation of MYC promotes tumorigenesis

MYC primarily functions by activating the transcription of other genes

Genes activated by MYC include several growth-promoting genes like cyclin-dependent kinases (CDKs)

cell cycle is orchestrated by (CDKs), which are activated by binding to cyclins

The CDK-cyclin complexes phosphorylate crucial target proteins that drive cells forward through the cell cycle.

cyclins arouse the CDKs, CDK inhibitors (CDKIs) silence the CDKs

There are two main cell cycle checkpoints, one at the G1/S transition and the other at the G2/M transition. each of which is regulated by a balance of growth promoting and growth-suppressing factors, as well as by sensors of DNA damage.

Once cells pass through the G1/S checkpoint, they are committed to undergo cell division.

all cancers appear to have genetic lesions that disable the G1/S checkpoint. The causes:

1. Gain-of-function mutations involving CDK4, D cyclins increasing the expression of them.
2. Loss-of-function mutations involving CDKIs e.g.: mutations or deletion of CDKN2A

Insensitivity to Growth Inhibitory Signals: Tumor Suppressor Genes:

anti-growth signals can prevent cell proliferation by: 1. The signal may cause dividing cells to enter G0 (quiescence), where they remain until external cues prod their reentry into the proliferative pool. / 2. the cells may enter a postmitotic, differentiated pool and lose replicative potential. 3. Nonreplicative senescence 4. programmed for death by apoptosis.

RB: Governor of the Cell Cycle

60% of retinoblastomas are sporadic, 40% are familial.

Two mutations (hits) are required to produce retinoblastoma →Both of the normal alleles of the RB locus must be inactivated →a retinal cell that has lost both normal copies of the RB gene becomes cancerous.

in retinoblastoma families is inherited as a dominant trait, at the level of the cell, one intact RB gene is all that is needed for normal function.

The function of the RB protein is to regulate the G1/S checkpoint

signals that promote cell cycle lead to the phosphorylation and inactivation of RB, while those that block cell cycle act by maintaining RB in an active hypophosphorylated state.

The initiation of DNA replication (S phase) requires the activity of cyclin E/CDK2.

cyclin E is dependent on the E2F

Early in G1, RB is in its hypophosphorylated active form, and it binds to and inhibits the E2F preventing transcription of cyclin E

Growth factor signaling leads to cyclin D expression and activation of cyclin D–CDK4/6 complexes→ phosphorylate RB, inactivating the protein and releasing E2F to induce target genes such as cyclin E/ D-CDK4/6 activity is tempered by antagonists such as p16, regulated by growth inhibitors such as TGFβ./ During the ensuing M phase, the phosphate groups are removed from RB by cellular phosphatases

one of the four key regulators of the cell cycle (p16, cyclin D, CDK4, RB) is mutated in most human cancers

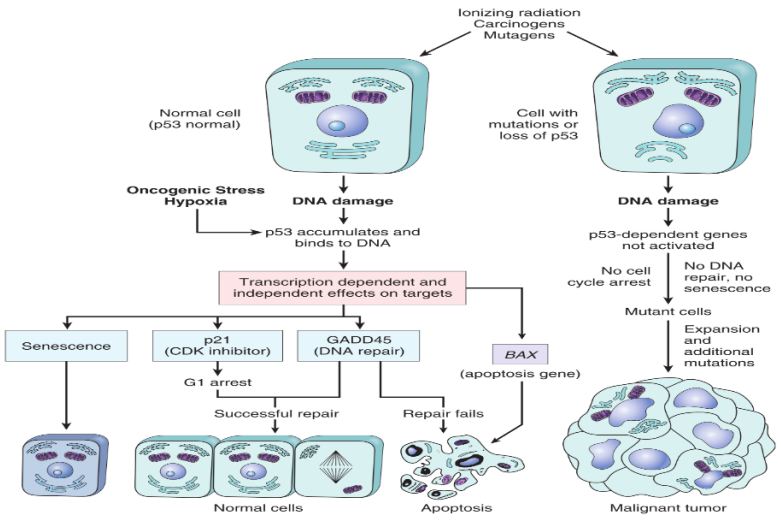
HPV encode proteins (e.g., E7) that bind RB and render it nonfunctional.

TP53: Guardian of the Genome

TP53, is the most commonly mutated gene in human cancer. It can:

activation of temporary cell cycle arrest (quiescence), induction of permanent cell cycle arrest (senescence), or triggering apoptosis

In nonstressed, healthy cells, p53 has a short half-life (20minutes) because of its association with MDM2, a protein that targets p53 for destruction. When the cell is stressed (anoxia, inappropriate pro-growth stimuli, DNA damage) sensors that include protein kinases such as ATM (ataxia telangiectasia mutated) are activated. These activated sensors catalyze posttranslational modifications in p53 release it from MDM2, increasing its half-life.



more than 70% of human cancers have a defect in this gene. the remaining malignant neoplasms often have defects in genes upstream or downstream of TP53

mutations affecting both TP53 alleles are acquired in somatic cells

patients inherit a mutant TP53 allele; is called the Li-Fraumeni syndrome. (25-fold greater chance of developing a malignant tumor)

Have predisposes like RB. oncogenic HPVs, polyoma viruses, hepatitis B virus bind to p53.

Transforming Growth Factor-β Pathway

TGF-β is a potent inhibitor of proliferation/ regulates cellular processes by binding to a complex composed of TGF-β receptors I and II. / activation of CDKIs, as well as repression of growth-promoting genes such as MYC and CDK4.

mutations may alter the type II TGF-β receptor (cancers of the colon, stomach, and endometrium) or SMAD (pancreatic cancers) molecules. loss of p21 expression and/or overexpression of MYC

TGF-β–induced program, including immune system suppression or promotion of angiogenesis, to facilitate tumor progression. Thus, TGF-β can function to prevent or promote tumor growth

Contact Inhibition, NF2, and APC

Cell–cell contacts in many tissues are mediated by cadherins. ** E-cadherin (E for epithelial)

Two mechanisms have been proposed:

1. tumor suppressor gene NF2: Its product, neurofibromin-2 (merlin) acts downstream of E-cadherin in a signaling pathway that helps maintain contact inhibition.

Homozygous loss of NF2 is known to cause certain neural tumors, and germ line mutations in NF2 are associated with a tumor-prone hereditary condition called neurofibromatosis type 2.

2. E-cadherin bind β-catenin, another signaling protein. β-catenin is a key component of the WNT signaling pathway

adenomatous polyposis coli (APC): This disorder is characterized by the development of numerous adenomatous polyps in the colon that have a very high incidence of transformation into colonic cancers. ** loss of a tumor suppressor gene called APC. Lead to inappropriately activated even in the absence of WNT factors

APC promote the degradation of β-catenin. cytoplasmic β-catenin is degraded by a destruction complex, of which APC is an integral part

β-catenin also is a key component of the WNT that prevent the APC-mediated degradation of β-catenin, allowing it to translocate to the nucleus

In colonic epithelium APC disorder leads to increased transcription of growth-promoting genes, such as cyclin D1 and MYC, as well as transcriptional regulators, such as TWIST and SLUG, which repress E-cadherin expression and thus reduce contact inhibition.

Somatic loss of both alleles of the APC gene is seen in approximately 70% of sporadic colon cancers.

Altered Cellular Metabolism

high levels of glucose uptake and increased conversion of glucose to lactose (fermentation) via the glycolytic pathway.

This phenomenon, called the **Warburg effect** also known as aerobic glycolysis

visualize tumors via positron emission tomography (PET) in which patients are injected with 18 F-fluorodeoxyglucose. Most tumors are PET-positive

rapidly proliferating normal cells, such as in embryonic tissues and lymphocytes during immune responses, also rely on aerobic fermentation Thus, “Warburg metabolism” is not cancer specific.

Aerobic glycolysis provides rapidly dividing tumor cells with metabolic intermediates that are needed for the synthesis of cellular components, whereas mitochondrial oxidative phosphorylation does not.

average each molecule of glucose metabolized produces approximately four molecules of ATP (small fraction of oxidative phosphorylation pathway)

upregulating glucose uptake and inhibiting the activity of pyruvate kinase/ upstream glycolytic intermediates, which are siphoned off for synthesis of DNA, RNA, and protein.

RAS signaling: upregulate the activity of glucose transporters and multiple glycolytic enzymes.

MYC: regulated genes are those for several glycolytic enzymes and glutaminase.

tumor suppressors that induce growth arrest suppress the Warburg effect.

Autophagy

Tumor cells often seem to be able to grow under marginal environmental conditions without triggering autophagy. genes that promote autophagy are tumor suppressors

tumor cells may use autophagy to become “dormant,” a state of metabolic hibernation that allows cells to survive hard times for long periods. Such cells are believed to be resistant to therapies that kill actively dividing cells.

Oncometabolism: mutations in enzymes that participate in the Krebs cycle.

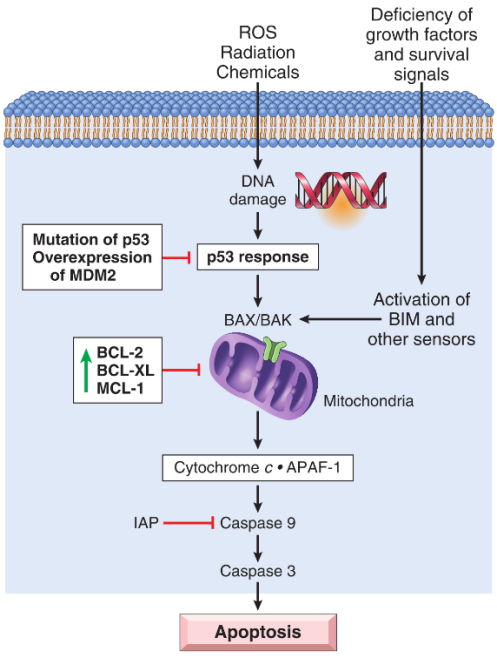
e.g.: socitrate dehydrogenase (IDH): the mutated protein loses its normal ability and acquires a new enzymatic activity that catalyzes the production of 2-hydroxglutarate (2-HG). 2-HG in turn acts as an inhibitor of TET family, including TET2. TET2 is one of several factors that regulate DNA methylation. According to the model, loss of TET2 activity leads to abnormal patterns of DNA methylation which leads to cancer.

Evasion of Cell Death

apoptosis: the extrinsic pathway, triggered by the death receptors FAS and FAS-ligand; and the intrinsic pathway (also known as the mitochondrial pathway)

chemotherapy or radiation therapy kill tumor cells by activating the intrinsic pathway of apoptosis

evasion of apoptosis by cancer cells occurs mainly by way of acquired mutations and changes in gene expression that disable key components of the intrinsic pathway, or that reset the balance of regulatory factors so as to favor cell survival in the face of intrinsic stresses



BH3-only proteins," which include BAD, BID, and PUMA, shift the balance between the pro-apoptotic and anti-apoptotic family members by neutralizing the actions of anti-apoptotic proteins like BCL2 and BCL-XL, thereby promoting apoptosis

Another group of factors that function as negative regulators of the intrinsic pathway is known as inhibitor of apoptosis proteins (IAPs), which bind caspase-9 and prevent apoptosis.

loss of p53 increased expression of anti-apoptotic members of the

BCL2 family by PUMA. Overexpression of anti-apoptotic members of the BCL2 family (follicular type Bcell lymphomas, resulting from characteristic t(14;18) (q32; q21).)

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