Lectures 1-4

Neoplasia Overview

- **Neoplasia** refers to new, uncontrolled growth of cells (tumors). It can be benign or malignant.
- Cancer is primarily a **genetic disorder** caused by DNA mutations and epigenetic changes, either:
  - Induced by mutagens (e.g., radiation, chemicals).
  - Spontaneous due to aging.

Key Characteristics of Neoplasia

1. **Genetic Alterations**: Heritable changes that lead to tumor progression and dominance of aggressive clones.
2. **Autonomy**: Tumor cells grow independently of normal regulatory signals.
3. **Tumor Composition**:
   - **Parenchyma**: Neoplastic cells.
   - **Stroma**: Connective tissue, blood vessels, and inflammatory cells supporting the tumor.

Tumor Classification

1. **Benign Tumors**:
   - Non-invasive, localized, and removable by surgery.
   - Naming: Suffix "-oma" (e.g., fibroma, chondroma).
   - Examples: Adenomas, papillomas, cystadenomas.
2. **Malignant Tumors**:
   - Invade adjacent tissues and metastasize to distant sites.
   - Naming:
     - **Sarcomas**: From mesenchymal tissues.
     - **Carcinomas**: From epithelial cells (e.g., adenocarcinoma, squamous cell carcinoma).

Special Tumors

1. **Mixed Tumors**: Derived from a single cell capable of differentiating into multiple tissue types.
   - Example: **Pleomorphic adenoma** of salivary glands.
2. **Teratomas**: Contain tissues from all three germ layers; originate from **totipotent cells**.
   - Sites: Gonads, embryonic rests.

Benign vs. Malignant Neoplasms

1. **Differentiation and Anaplasia**:
   - Benign: Well-differentiated, resembling original tissue.
   - Malignant: Poorly differentiated; exhibit **anaplasia** (loss of structural/functional differentiation).
2. **Local Invasion**:
   - Benign: Encapsulated and non-invasive.

- Malignant: Poorly demarcated; infiltrative growth.

3. **Metastasis**:
   - Benign: Does not metastasize.
   - Malignant: Spreads via seeding, lymphatics, or blood (e.g., liver, lungs).

Cancer Epidemiology

1. Environmental factors (e.g., diet, smoking, alcohol) and infections contribute significantly to cancer risk.
2. **Age**: Incidence increases with age due to accumulated mutations and declining immune function.
3. **Familial Cancers**:
   - Inherited predispositions (e.g., breast, ovarian, pancreatic cancers).
   - Features: Early onset, multiple relatives affected, and bilateral/multiple tumors.

Hallmarks of Cancer

1. **Self-sufficiency in growth signals**: Activation of oncogenes (e.g., RAS, ABL).
2. **Insensitivity to inhibitory signals**: Loss of tumor suppressors (e.g., TP53, RB).
3. **Evasion of apoptosis**: Altered expression of pro- and anti-apoptotic genes.
4. **Limitless replication**: Activation of telomerase.
5. **Sustained angiogenesis**: New blood vessel formation to support growth.
6. **Invasion and metastasis**: Ability to spread to distant sites.
7. **Altered metabolism**: Shift to glycolysis (Warburg effect).
8. **Immune evasion**: Avoidance of immune detection and destruction.

Molecular Basis of Cancer

1. **Oncogenes**:
   - Derived from proto-oncogenes via mutations or overexpression.
   - Examples:
     - RAS: Mutations trap RAS in its active state.
     - ABL: BCR-ABL fusion in **chronic myeloid leukemia** (CML) promotes uncontrolled growth (treated with **imatinib**).
2. **Tumor Suppressor Genes**:
   - Normally inhibit cell growth or promote apoptosis.
   - Examples:
     - TP53: Guardian of the genome; mutated in >50% of cancers.
     - RB: Governs cell cycle checkpoints.
3. **CDKs and Cyclins**:
   - Drive the cell cycle; dysregulation (e.g., overexpression of cyclin D or loss of CDK inhibitors like p16) promotes cancer.
   - CDK inhibitors (p21, p27) act as brakes; their mutations are seen in many cancers.

Genetic Lesions in Cancer

1. **Point Mutations**:
   - Common in RAS (oncogene) and TP53 (tumor suppressor).
2. **Gene Rearrangements**:
   - Examples:
     - **Philadelphia chromosome** in CML (BCR-ABL fusion).
     - MYC translocation (8;14) in Burkitt lymphoma.
3. **Gene Amplifications**:
   - NMYC in neuroblastoma, HER2 in breast cancer.
4. **Aneuploidy**:
   - Imbalance in chromosomes leads to oncogene overexpression and tumor suppressor loss.

Pathways of Metastasis

1. **Seeding**: Spread into body cavities (e.g., peritoneal carcinomatosis).
2. **Lymphatic Spread**: Common in carcinomas (e.g., breast cancer to axillary nodes).
3. **Hematogenous Spread**: Common in sarcomas (e.g., lung and liver metastases).

Key Tumor Examples

- **Breast Cancer**: Amplification of HER2 or cyclin D.
- **Melanoma**: Mutations in CDKN2A or BRAF.
- **Glioblastoma**: Overexpression of PDGF and receptor.

Neoplasia 5: Insensitivity to Growth-Inhibitory Signals

1. **Tumor Suppressor Genes:**
   - Act to prevent cell proliferation.
   - Mechanisms:
     1. Cause dividing cells to enter G0 (quiescence).
     2. Push cells into a postmitotic, differentiated state, losing replicative potential.
2. **Retinoblastoma (RB) Gene – Governor of the Cell Cycle:**
   - Key negative regulator of the cell cycle; often inactivated in cancers.
   - Discovered as the first cancer suppressor gene.
   - Associated with **retinoblastoma**, a rare childhood tumor (60% sporadic, 40% familial).
   - Familial cases follow autosomal dominant inheritance. Sporadic cases require two somatic mutations.
   - RB controls the G1/S checkpoint. Mutation leads to unchecked cell cycle progression.
3. **Knudson's Two-Hit Hypothesis:**
   - Two mutations in the RB gene are required for retinoblastoma.

- Familial cases inherit one defective allele; the second mutation occurs somatically.
- Sporadic cases require two somatic mutations.
- Loss of RB contributes to other cancers like breast, lung, and bladder cancers.

4. **RB Protein Function in the Cell Cycle:**
   - Exists in hypophosphorylated (active) and hyperphosphorylated (inactive) forms.
   - Active RB halts cells in G1, allowing exit into quiescence or senescence if required.
   - RB binds to E2F transcription factors, blocking transcription of genes like cyclin E.
   - Growth factor signaling phosphorylates RB, releasing E2F, enabling DNA replication.
5. **Mutations Affecting RB Function:**
   - Mutations in cyclins (e.g., overexpression of cyclin D) or CDKs (activation of CDK4) mimic RB loss.
   - Viral oncoproteins (e.g., HPV E7) bind to and inactivate hypophosphorylated RB, bypassing growth inhibition.
6. **p53 Gene – Guardian of the Genome:**
   - The most frequently mutated tumor suppressor gene in human cancers.
   - Responds to DNA damage, anoxia, or oncogene activation.
   - Functions:
     1. Temporary cell cycle arrest (quiescence).
     2. Permanent arrest (senescence).
     3. Programmed cell death (apoptosis).
   - Activated by stresses (e.g., DNA damage) via kinases like ATM/ATR.
   - Regulates transcription of genes for cell cycle arrest (e.g., p21) or apoptosis (e.g., GADD45).
   - Mutations in p53 are found in over 70% of cancers; loss leads to uncontrolled growth.
7. **Li-Fraumeni Syndrome:**
   - Inherited mutation in one p53 allele.
   - Predisposes individuals to multiple cancers (e.g., sarcomas, breast cancer) due to the second "hit."

Neoplasia 6: Tumor Biology and Pathways

1. **Transforming Growth Factor-β (TGF-β) Pathway:**
   - TGF-β inhibits proliferation in normal epithelial, endothelial, and hematopoietic cells.
   - Activates CDK inhibitors while repressing MYC and CDK4.
   - Mutations in TGF-β signaling (e.g., SMAD4 in pancreatic cancer) impair this inhibition.
   - Tumor cells may co-opt TGF-β to suppress immunity or promote angiogenesis.
2. **Contact Inhibition and E-Cadherin:**
   - Normal cells stop dividing upon contact with neighbors, mediated by E-cadherin.
   - Cancer cells lose contact inhibition due to:
     1. **NF2 (merlin):** Tumor suppressor downstream of E-cadherin. Loss leads to neurofibromatosis type 2.
     2. **β-Catenin:** Regulated by APC; promotes proliferation when dysregulated.

3. **Adenomatous Polyposis Coli (APC) Pathway:**
   - APC regulates β-catenin degradation, preventing its nuclear translocation.
   - Loss of APC or β-catenin mutations activates growth-promoting genes (e.g., cyclin D).
   - Found in 70-80% of colon cancers; associated with familial adenomatous polyposis.
4. **Evasion of Apoptosis:**
   - Apoptosis pathways:
     1. **Extrinsic Pathway (CD95/Fas):** Initiated by death receptor activation, leading to caspase 8 and downstream caspase activation.
     2. **Intrinsic Pathway:** Triggered by mitochondrial permeabilization, releasing cytochrome c to activate caspase 9.
   - Malignant cells evade apoptosis via:
     - Reduced CD95 expression or high FLIP levels.
     - Overexpression of anti-apoptotic BCL2.
     - Loss of pro-apoptotic regulators (e.g., BAX, APAF-1).
5. **Role of BCL2:**
   - BCL2 translocation (t(14;18)) in B-cell lymphomas prevents apoptosis.
   - Lymphomas with BCL2 overexpression are slow-growing due to reduced cell death.
6. **Limitless Replicative Potential:**
   - Normal cells undergo senescence after ~60-70 doublings due to telomere shortening.
   - Tumor cells bypass this by reactivating **telomerase** (active in 85-95% of cancers).
   - Telomere dysfunction leads to bridge-fusion-breakage cycles, causing genomic instability.
   - Reactivation of telomerase stabilizes chromosomal ends, enabling cancer progression.

Lecture 7

1. Sustained Angiogenesis

- Tumors cannot grow beyond **1-2 mm** unless vascularized.
- **Mechanisms**:
  1. **Neoangiogenesis**: New vessels sprout from existing capillaries.
  2. **Vasculogenesis**: Endothelial cells are recruited from the bone marrow.
- **Effects of Neovascularization**:
  1. Provides nutrients and oxygen.
  2. Endothelial cells stimulate tumor growth by secreting growth factors (e.g., IGFs and PDGF).
- Tumor vasculature is **abnormal, leaky, and haphazard**.

Regulation of Angiogenesis:

- Controlled by a balance of **promoters (e.g., VEGF)** and **inhibitors (e.g., angiostatin, endostatin)**.
- **Hypoxia** activates **HIF1α**, increasing VEGF production.

- Mutations (e.g., VHL, p53) and oncogenes (e.g., RAS, MYC) tilt the balance towards angiogenesis.
- Anti-VEGF therapies are used to treat cancers.

2. Invasion and Metastasis

- Responsible for most cancer-related morbidity and mortality.

Steps of Metastasis:

1. **Local invasion**:
   - **Loosening of tumor cells**: Loss of **E-cadherins**, which normally keep cells together by binding **β-catenin** and transmitting antigrowth signals.
   - Activation of oncogenes (e.g., SNAIL, TWIST) promotes **epithelial-to-mesenchymal transition (EMT)**, aiding migration.
2. **Degradation of ECM**: Tumor cells or stromal cells secrete **proteases** (e.g., MMPs, cathepsins) to break down ECM.
3. **Attachment to ECM components**: Tumor cells bind to exposed sites (e.g., collagen, laminin) to migrate.
4. **Migration**: Guided by factors like **HGF/SCF** and growth factors.

- **Proteases** (e.g., MMP-9) remodel ECM, releasing VEGF and creating new binding sites for migration.
- **Stromal cells** produce **HGF/SCF**, aiding motility, especially in tumors like glioblastoma.

Vascular Dissemination and Homing:

- Tumor cells can travel as single cells or form emboli with platelets.
- **Site of metastasis** depends on:
  1. **Vascular drainage** of the primary tumor.
  2. Expression of **chemokine receptors** (e.g., CXCR4) matching organ-specific chemokines (e.g., CXCL12).
- **Non-permissive environments** may prevent metastasis even if tumor cells reach an organ.

Key Molecular Players:

- **E-cadherin**: Loss promotes cell detachment and invasion.
- **HIF1α**: Hypoxia stabilizes HIF1α, promoting VEGF transcription.
- **p53**: Loss removes inhibition of angiogenesis and allows VEGF expression.
- **SNAIL/TWIST**: Promote EMT, aiding invasion and migration.

Lec 8 & 9

Etiology of Cancer: Carcinogenic Agents

1. **Carcinogenic agents inflict genetic damage**, a key aspect of carcinogenesis.
2. **Classes of Carcinogens**:
   - **Chemical Carcinogens**:
     - **Direct-acting agents**: Do not require metabolic activation (e.g., alkylating agents such as cyclophosphamide, β-Propiolactone).
     - **Indirect-acting agents (Procarcinogens)**: Require metabolic activation (e.g., polycyclic aromatic hydrocarbons like Benzo(a)pyrene, 7,12-dimethylbenz(a)anthracene).
   - **Radiation**: UV and ionizing radiation cause mutations (e.g., pyrimidine dimers and double-stranded DNA breaks).
   - **Microbial products**:
     - **Oncogenic RNA viruses**: HTLV-1 causes adult T-cell leukemia/lymphoma.
     - **Oncogenic DNA viruses**: HPV, EBV, HBV, HCV, etc.
     - **Bacteria**: Helicobacter pylori is associated with gastric adenocarcinoma and MALT lymphoma.

Mechanisms of Action of Carcinogens

1. **Chemical Carcinogens**:
   - Form adducts with DNA, RNA, and proteins.
   - Target key genes like **RAS** and **p53**.
   - Require an **initiator** (mutates DNA) and **promoters** (induce proliferation).
2. **Radiation**:
   - Ionizing radiation induces chromosomal damage.
   - UV radiation causes **pyrimidine dimers**, repaired by nucleotide excision repair (defective in xeroderma pigmentosum).
3. **Viruses and Microbes**:
   - HTLV-1 Tax protein disrupts cell cycle regulation and enhances genomic instability.
   - EBV promotes oncogenesis via **LMP1** (activates NF-κB) and **EBNA-2** (activates cyclin D).
   - H. pylori induces inflammation, DNA damage, and growth factor stimulation.

Laboratory Diagnosis of Cancer

1. **Morphologic Methods**:
   - **H&E Stain**: Basic stain for cellular morphology.
   - Techniques: **Biopsy, Fine-needle aspiration, Cytologic smears (e.g., Pap test), Frozen sections.**
2. **Immunohistochemistry**:
   - Uses antibody markers (e.g., **PSA for prostate cancer**, **ER for breast cancer**).

3. **Molecular Diagnosis**:
   - Identifies genetic abnormalities (e.g., HER2, NMYC, BRCA1).
   - Detects residual disease and hereditary predispositions.
4. **Flow Cytometry**:
   - Classifies leukemias and lymphomas by analyzing cell surface markers.
5. **Tumor Markers**:
   - **PSA**: Elevated in prostate cancer but lacks specificity.
   - **CEA**: Elevated in colon, pancreas, stomach, and breast cancers.
   - **AFP**: Associated with hepatocellular carcinoma, yolk sac tumors, teratocarcinomas, and fetal neural tube defects.

Grading and Staging of Cancer

1. **Grading**:
   - Measures tumor cell differentiation and mitotic activity.
   - Categories: Low-grade (I) to high-grade (IV).
2. **Staging**:
   - **TNM System**:
     - **T** (Tumor size): T1-T4, T0 for in situ lesions.
     - **N** (Lymph nodes): N0 (no nodes), N1-N3 (increasing involvement).
     - **M** (Metastasis): M0 (none), M1/M2 (presence of metastases).

Key Viral Oncogenesis

1. **Epstein-Barr Virus (EBV)**:
   - Associated with **Burkitt lymphoma, Hodgkin lymphoma, and nasopharyngeal carcinoma**.
   - Mechanism:
     - **LMP1** activates NF-κB and prevents apoptosis via BCL-2.
     - **EBNA-2** activates cyclin D.
   - Endemic in malaria regions due to immune suppression.
2. **HPV**:
   - High-risk strains (16, 18) inactivate **p53** and **RB**, promoting cervical cancer.