OVERVIEW OF CANCER PATHOPHYSIOLOGY

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A Few Definitions to Get Us Started...

**Physiology**
- A science that deals with the ways that living things function
- The ways that living things or any of their parts function
- A branch of biology that deals with functions & activities of life or of living matter (as organs, tissues, or cells) & of physical / chemical phenomena
- Organic processes & phenomena of an organism or any of its parts or of a particular bodily process

**Pathophysiology**
- The physiology of abnormal states; specifically: the functional changes that accompany a particular syndrome or disease

**Cancer**
- Northern zodiacal constellation between Gemini & Leo: 4th zodiac sign in astrology. From Latin, crab, cancer
- Malignant tumor of potentially unlimited growth: expands locally by invasion and systemically by metastasis; abnormal body state marked by such tumors
- Evil / malignant thing spreads destructively, e.g. cancer of hidden resentment

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**Definition: Cancer**

- A large group of diseases characterized by
  - cells growing out of control
  - Spreading throughout the body
  - Malignant cell have been altered genetically to look and function differently than normal cells
- Disease of the cell and involves
  - Mutations/changes in genetic makeup or DNA of the cell

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**Defining Targeted Molecular Therapy**

- Targeted molecular therapy uses drugs or substances to interfere with specific molecules so can block tumor growth and proliferation
- These drugs or substances work by disrupting or blocking cell communication signals 1 of 2 locations:  
  - From the outside of the cell to the inside of the cell
  - Inside the cell so that signals do not reach the nucleus to instruct the cell to divide, or make proteins
- Targeted therapies can be categorized according to effects on cancer hallmarks. Are divided into 2 broad categories: small molecule (suffix “ib”or“tib”) & monoclonal antibodies (suffix “mab”)

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Setting the Stage: Why is Cancer Pathophysiology / Biology Important?

- Aids clinicians in planning a patient's treatment
- Provides prognostic information
- Evaluates the results of treatment
- Facilitates the exchange of information between treatment centers
- Contributing to and advancing research on cancer

Classification of Cancer Biomarkers by Function

<table>
<thead>
<tr>
<th>Function</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Most tumor markers are not useful for screening; only one tumor marker (prostate-specific antigen [PSA]) is used for screening, and its value in detecting prostate cancer has been heavily debated.</td>
</tr>
<tr>
<td>Diagnostic aid</td>
<td>Tumor markers can add to the information about the molecular features of a tumor, helping to define its molecular subtype.</td>
</tr>
<tr>
<td>Determine disease</td>
<td>Some tumor markers are factors considered when determining prognosis, or a prediction of the outcome.</td>
</tr>
<tr>
<td>Guide therapy</td>
<td>Some tumor markers can provide information about what types of treatment are more or less likely to be effective.</td>
</tr>
<tr>
<td>Monitor response to treatment</td>
<td>Tumor markers can monitor the effectiveness of treatment, especially for advanced cancers.</td>
</tr>
<tr>
<td>Detect recurrence or progression</td>
<td>Some tumor markers can indicate that cancer has recurred or progressed; if the level of a tumor marker is elevated before treatment, is low after treatment, and then begins to increase after treatment, it is likely that cancer is recurring or progressing.</td>
</tr>
</tbody>
</table>

Personalized Medicine: Genetic Biomarkers

- Advanced tests analyze tumor samples, other tissue for abnormal gene feature (allow cancer to develop or spread)
- May look at single gene OR entire chromosome. With tests, researchers look for genetic mutations / alterations in some tumors to help guide treatment decisions, e.g. look for genetic profile or fingerprint.
- Limited to breast and colorectal cancer. Tests improve care as the right person is matched to the right treatment plan
- OncotypeDX – calculates recurrence score. Measures activity 16 cancer genes, 5 control genes

Personalized Medicine: Protein Biomarker

- Include substances that are either produced by cancer cells themselves or by other cells in response to cancer.
- Most protein biomarkers related to cancer are used to monitor response and/or detect recurrence or progression during follow-up after treatment.
- Some biomarkers used to predict outcome or prognosis
Protein Biomarkers for Cancer Types

Objectives. By the end of this presentation, participants will be able to:

- Describe 3 parts of a cell’s anatomy & list 3 normal functions
- Review angiogenesis in normal cell functioning
- Explain how cell signaling affects normal cell function
- Explore theories of carcinogenesis
- State how cell signaling influences the cell cycle in a cancer cell.
- Identify steps in malignant angiogenesis and metastases
- Describe the common signal transduction pathways identified in the development of new therapeutic cancer agents
- Identify several therapeutic agents approved to target the signal transduction pathways commonly associated with malignancy

Normal Cell Anatomy and Function

Cell Anatomy:
- Cell Membrane
- Receptors: Extracytoplasmic, transmembrane, intracytoplasmic
- Organelles: Mitochondria, smooth / rough endoplasmic reticulum, lysosomes, proteosomes
- Nucleus: RNA (messenger, translation, & transcription), DNA, chromosomes, genes, nucleolus, nucleotides (base pairs)

Cell Function:
- Signaling pathways – activate or inhibit genetic signals
- Protein production unique to cell type (surfactant, insulin)
- Produce energy (ATP): aerobic (Kreb’s cycle) Anaerobic glycolysis (lactic acid)
- Cell replication / Programmed cell death (apoptosis)
**Structure / Function of DNA and Chromosomes**

- DNA is copied during cell division.
  - The DNA "parent" strands pull apart.
  - Complementary bases are added: (A-T, C-G).
  - The result is two complete DNA molecules that are an exact copy of the original molecule.
  - Each cell gets a complete copy.


**DNA Packaging**

Genetic Mutations

Mutated cell may:
- Die from damage or by initiating programmed cellular suicide (apoptosis)
- Recognize damage and repair itself
- Survive and pass on damage


Genetic mutations: Acquired or hereditary?

Genes can become mutated, or abnormal, if the DNA sequence is changed. Changes in DNA sequences occur often, mostly during cell division, but DNA can fix these errors (p53 tumor suppressor gene / DNA repair gene). Sometimes, repair method fails & the genetic mutation passes on to future copies of changed cell.

The most common types of mutations in cancer involve four abnormalities:
1) AMPLIFICATION: Increase in # copies of a specific DNA fragment DNA
2) DELETION: Loss of genetic material, ranging from small (a single missing DNA base pair) to large (a piece of a chromosome)
3) INACTIVATION: Loss of the biologic function of the gene
4) TRANSLOCATION: A broken chromosome reattaches to a different one

BCR-ABL inhibitors used to treat CML: Dasatinib, Imatinib, Nilotinib, Ponatinib
Genetic Mutations: Somatic (Acquired) vs. Germline (Inherited)

- Somatic mutations
  - Multifactorial
  - Majority of cancers
- Germline mutations
  - Inherited/familial
  - Minority of cancer


Genes important in Carcinogenesis

1. Apoptosis Gene (programmed cell death) – this gene is shut down / inactivated in cancer
2. DNA Repair Gene (repair abnormal copy / signal cell if can’t)
3. Proto-oncogene (signals cell to begin replicating, enter cell cycle). Mutations to gene transform it, making gene oncogenic. Continuous signals to divide
4. Tumor suppressor gene (instructs cell – stop dividing). Mutations here are like losing car brakes; cell never receives signal to stop dividing

Table 1. Cancers with strong hereditary links

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Major gene(s)</th>
<th>Risk of developing cancer (risk in general population)</th>
<th>Risk for other cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast and ovarian cancer</td>
<td>BRCA1 and BRCA2</td>
<td>Breast cancer: 50% to 95% (12%) Ovarian cancer: 15% to 40% (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>APC</td>
<td>Almost 100% (6%)</td>
<td>Small bowel cancer: 4 to 12% Pancreatic cancer: 2% Papillary thyroid cancer: 2%</td>
</tr>
<tr>
<td>Familial adenomatous polyposis (FAP)</td>
<td>APC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary non-polyposis colorectal cancer (Lynch Syndrome)</td>
<td>MSH2, MSH6, MSH4, PMS2</td>
<td>80% (8%)</td>
<td>Endometrial cancer: 20 to 50% Gastric (stomach) cancer: 11 to 15% Ovarian cancer: 9 to 12% Urinary tract: 4 to 5%</td>
</tr>
<tr>
<td>Kidney (renal) cancer (clear cell)</td>
<td>VHL</td>
<td>40% (less than 1%)</td>
<td></td>
</tr>
<tr>
<td>Metastatic thyroid cancer (familial)</td>
<td>RET</td>
<td>95% to 100% (less than 1%)</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>CYP102A</td>
<td>70% (22%)</td>
<td>Pancreatic cancer: up to 17%</td>
</tr>
</tbody>
</table>

* Associated with multiple endocrine neoplasia (MEN) 2 syndrome
† Genetic testing not recommended outside of a research study.
Angiogenesis

- Normally only present if require wound healing or during pregnancy when gene is activated
- Recruit elements to build new vasculature, capillaries:
  - Endothelial cells
  - Fibroblasts
  - Epidermal cells
- Respond to messages / signaling of vascular endothelial growth factor (VEG-F), fibroblast growth factor (FBG-F), & epidermal growth factor
- Malignant angiogenesis: tumor makes VEG-F, FBG-F in conditions of hypoxia, need for nutrients, waste disposal, promote metastases
- Therapeutic Anti-angiogenic agents: Thalidomide (Thaladomid®, Cetuximab (Erbitux®) – Blocks VEG-R receptor on endothelial cell)
  - Bevacizamb (Avastin®) – Binds with VEG ligand prior to VEGF-R

Steps in Angiogenesis

- Modulated by a number of factors:
  - Vascular Endothelial Growth Factor (VEGF)
  - Fibroblast Growth Factor
  - Epidermal Growth Factor


So What Causes Cancer?

- Age
- Hereditary factors
- Lifestyle choices (tobacco/alcohol use and diet)
- Occupational hazards (asbestos, chemicals, metals)
- Environmental exposure (radiation, sun and viruses)
- Combination of factors
New Research: Stress & Inflammation Combine to Fuel Cancer Growth

**Definitions**

- **Stress**: Experience of significant or negative life event or an event without effective coping. Psychological / physiologic response to body perceives as a threat.

- **Inflammation**: Cellular manifestation stress. “Acute”, i.e. innate immunity activates immune system to ward off infection or “Chronic”, i.e. lingering inflammation can predispose individuals to illness such as cancer.

- Stress & inflammation probably mediate cancer development & progressions. 25% of cancers are associated with chronic inflammation of broad origin.

Psycho-Oncology Interventions for Managing Stress and Inflammation in Cancer

- Mind-body techniques
- Meditation
- Acupressure
- Natural Products
- Botanicals
- Probiotics
- Walking
- Bicycling

- Yoga
- Cognitive / Behavioral therapy
- Energy-Based Techniques
- Acupuncture
- Meridian tapping
- Vitamins and minerals
- Fish Oils
- Exercise
- Swimming / Hiking
- Zumba / Dance Fitness


Theories of Cancer Development

- Multistep
- Mutagenesis
- Epigenetics
- Oncogene hypothesis
- Tumor suppressor gene
- Knudson's "two hit"
- Cancer stem cell hypothesis
- Immunosurveillance


Knudson 2 Hit Theory of Cancer Development


Cancer Stem Cell Theory

Many Cancer Types Caused by “Bad Luck” of Random Mutations  
(Source: Science 1-2-15)

- Cancer often strikes individuals without any type of known risk factors; new research says many cancer types due to “bad luck”

- With statistical model measuring proportion of cancer incidence across 31 tissue types, Johns Hopkins Univ. School of Medicine researchers found that 22 cancers, (2/3’s of the total reviewed), could be largely explained by “bad luck” or random mutations during DNA replication in normal, non-cancerous stem cells.

- The remaining 9 cancer types were more attributable to environmental, lifestyle, and hereditary factors.

- Focus on stem cell division—the more divisions taking place e.g. stem cell turn-over, the more prone tissue is to develop cancer

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The Metastatic Process

The spread of tumor cells  
Blood or lymph system  
Primary tumor to distant sites

Overall most common sites of metastases  
- Bone  
- Brain  
- Liver  
- Lungs  
- Lymph nodes

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Pathologic Diagnosis of Cancer

- Pathologist key to determining extent of cancer
  - Identifies and grades biopsy
  - Examine sentinel lymph nodes
  - Examine regional lymph nodes
  - Examine tissue from distant sites
Pathologic Diagnosis of Cancer

- Mitotic activity
  - Presence of dividing cells
- Pleomorphism
  - Variation in size and shape of cells
- Hyperchromatism
  - Nucleoli that stain darker than normal
- Abnormal chromosome arrangements
  - Aneuploidy

Grading and Differentiation

**Grade:** Degree to which tumor cells resemble parent tissue

- **GX** Grade can not be assessed
- **G1** Well-differentiated (Low grade)
- **G2** Moderately-differentiated
- **G3** Poorly-differentiated
- **G4** Undifferentiated (High grade)

Tumor Grade

- Internationally developed grading systems
  - Gleason
  - Scarff-Bloom-Richardson (Nottingham)
- Uses more specific and objective criteria based on
  - Nuclear grade may be assigned
  - Mitotic count
**TMN Staging**

- **T = TUMOR**  
  Local involvement, invasion  
  e.g. extent of primary tumor

- **N = NODES**  
  Lymph node involvement, e.g.  
  presence / absence of regional  
  lymph node metastases

- **M = METASTASIS**  
  Distant location(s), e.g.  
  presence or absence of distant  
  metastases

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**TMN Staging for Lung Cancer**

**LUNG STAGING FORM**

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Stage Category Definitions</th>
<th>Prognostic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1</strong> Primary tumor cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T2</strong> Clinical evidence of primary tumor in situ</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **T3** Tumor c.1cm or greatest dimension, concomitant by (lung or distant) sites,  
  without bronchoscopic evidence of invasion more proximal than the lobar  
  bronchus(s), e.g. cartilaginous  
  branch? | | |
| **T3a** Tumor c.1cm or greatest dimension | | |
| **T3b** Tumor > 2 cm but < 3 cm in greatest dimension | | |
| **T3c** Tumor > 3 cm but < 7 cm in greatest dimension | | |
| **T4** Tumor > 7 cm or any that directly invade any of the following structures:  
  heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebra(s),  
  bone, superior vena cava (SVC) or anastomosis | | |

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**Regional Lymph Nodes (N)**

- **N0** No regional lymph node metastases
- **N1** Metastases in ipsilateral hilar and/or paratracheal lymph nodes
- **N2** Metastases in ipsilateral mediastinal lymph nodes and/or in ipsilateral bronchial lymph nodes
- **N3** Metastases in contralateral mediastinal, contralateral hilar, ipsilateral or  
  contralateral subcarinal, supraclavicular lymph nodes

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**Distant Metastases (M)**

- **M0** No distant metastases
- **M1a** Distant metastases limited to a single organ (e.g. bone, liver, brain,  
  or lungs)  
  with no pleural or pericardial effusion
- **M1b** Distant metastases limited to all organs (e.g. bone, liver, brain,  
  or lungs)  
  with pleural or pericardial effusion

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These elements and clinical judgment dictate that the classification of distant  
metastases is not related to the primary tumor. The classification should be  
categorized as either stage I, II, III, or IV.
**Advances in Cancer Therapy**

- Oncogenes, when mutated or expressed aberrantly, disrupt normal signaling pathways to allow cells to divide continuously and invade adjacent tissues & metastasize to distant body organs.

- Thriving cancer cells must continually divide, evade tumor suppressors & immune system, an environment conducive to growth, an adequate blood supply, avoid programmed cell death, & use cellular energy (glycolysis).

- Newer trial designs such as “umbrella” or “basket” trials are being used to speed evaluation of targeted therapies.

- Molecular targeted therapy blocks signals that stimulate cancer cells to grow and proliferate, to invade, and to metastasize.

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**Types of targeted molecular therapy:**

- Angiogenesis inhibitors
- BCR-ABL inhibitors
- BRAF and MEK inhibitors
- BTK inhibitors
- EGFR inhibitors
- HDAC inhibitors
- Multikinase inhibitors
- PARP inhibitors
- PI3K inhibitors
- Proteasome inhibitors
- Cyclin-dependent kinase inhibitors
- Hedgehog pathway inhibitors
- Mammalian target of rapamycin (mTOR) inhibitors

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**National Cancer Institute “MATCH” trial**

- **NCI-Molecular Analysis for Therapy Choice (NCI-MATCH)** is a clinical trial to analyze tumors to see whether they contain genetic abnormalities for which a targeted drug exists (i.e., “actionable mutations”). Treatment assigned based on abnormality.

- Trial seeks to determine whether treating cancers according to their molecular abnormalities will show evidence of effectiveness.

- Trial opened for enrollment in Aug. 2015 with 10 arms. Each arm to enroll adults ≥18 y.o. with advanced solid tumors & lymphomas that no longer respond (or never responded) to standard therapy & are growing. Accrual goal each arm-1000. Trial endpoint ORR (CR, PR)

- Plan to obtain tumor biopsy specimens (3000) for DNA sequencing to identify those with genetic abnormalities that may respond to the targeted drugs on trial. Testing 20 FDA-approved targeted agents.
**Targeted Therapy**

- Targeted therapy is selective to specific proteins, antigens, pathways, or processes, and associated with fever and less-severe side effects.
- Side effects from targeted therapy are specific to the drug, class of agents, or the cellular target.
- Targeted therapy is dosed at the biologically active dose.
- Small molecule–targeted therapies are able to pass through cell membrane to interfere with normal cell functions and processes.
- Small molecule therapies are given orally but monoclonal antibodies (large molecules) are administered intravenously.


**Communication**

- **Identifying the Target**
  - Cells are instructed by messages from outside the cell, which pass through cell surface receptors (cell signaling).
  - These messages, and other messages from inside the cell are delivered to the cell nucleus by a process called **signal transduction**.
  - Receptor tyrosine kinases and non–receptor tyrosine kinases are proteins that carry the message.

- **Signal Transduction**
  - A receptor tyrosine kinase (RTK) is made of extracellular (outside cell), transmembrane (across membrane) & cytoplasmic parts.
  - When a ligand attaches to a receptor, dimerization occurs; this activates phosphorylation & sends message through the cell membrane to activate the cytoplasmic tyrosine kinase.
  - Cell’s energy moves message “downstream” towards cell nucleus.
  - Communication from outside cell to nucleus is signal **transduction**.
Cellular Communication

- Nonreceptor Tyrosine Kinases
  - nRTKs regulate differentiation, growth, division, adhesion, and survival
  - Mutation of nRTK genes can alter the transmission of messages to the cell nucleus allowing uncontrolled and continuous growth and proliferation
  - Therapeutic targets include mTOR, and within the MAPK pathway, RAS, RAF, MEK, ERK and c-Kit

- Cancer and Signal Transduction
  - In cancer cells, components of signal transduction pathways are often mutated (eg, RAS, BRAF), enabling cell nucleus to receive continuous signals to proliferate, grow & not respond to programmed cell death
  - Continual genetic mutation within tumor cells can lead to the development of alternate pathways and subsequent drug resistance

Biology Application: Checkpoint inhibitors for Advanced Melanoma

New drugs act as PD-1 receptors; are monoclonal antibodies
1) First drug – ipilimumab (Yervoy™) approved in 2011
2) Second drug - pembrolizumab (Ketruda™) approved in 2014
3) Third drug - nivolumab (Opdivo™) approved in 2014

• Immune system uses feedback loop to regulate self; at check-points, receives signals telling it to slow down or turn off. Goal: to prevent over-activation or attack of body's own cells. Tumors express such signals with the end result the body's natural cancer defenses are limited.

• Checkpoint inhibitor drugs block the tumor's signals; thus, immune system is up-regulated & body's natural defense against cancer cells is enhanced.

Biology Application: Co-treating Hairy Cell Leukemia and Melanoma with BRAF Inhibitor, Dabrafenib and MEK Inhibitor, Trametinib

• The activating BRAF mutation has been identified in many cancers, including: colon & lung adenocarcinomas, papillary thyroid cancer, malignant melanoma & hairy cell leukemia.

• Malignant melanoma & HCL are of particular interest because of both the high proportion of cases harboring the mutation and the dramatic responses to BRAF inhibitor therapy reported in the literature.

• Patients with Hairy Cell Leukemia & malignant melanoma present with the BRAF p.V600E mutation, but may be successfully treated for both cancers with the BRAF inhibitor dabrafenib (Tafinlar).

• Source: http://www.jnccn.org/content/13/1/9

Are you beginning to appreciate why understanding cancer biology is critical?

• Cancer Moonshot Initiative: Vice-President Joe Biden – Research funding for cure
• Personalized medicine / Molecular profiling
• Genetic mutations and actionable targets
• Biosimilars
• New side effect profiles and management
• Patient / family / provider education needed
• Cancer as a chronic disease: 20 million survivors by 2020 (NCCS)