BIOLOGY OF CANCER

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Why is it Important to Understand the Biology of Cancer?

- 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

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

DNA Packaging

Structure / Function of DNA and Chromosomes

Regulation of the Cell Cycle
- Cyclins D, E, A, B
- Inhibitors
- Restriction point

Schematic of Cell: Normal or Malignant

Differences between malignant & normal cells
- Normal Cells
  - Controlled growth and division
  - Contact Inhibition
  - Anchorage dependent
  - Noninvasive
  - Not immortal
- Cancer cells
  - Uncontrolled cell division
  - Lack contact inhibition
  - Tend to invade other tissues
  - Have potential to spread
  - Lack of differentiation

Causes of Carcinogenesis

**Individual factors:**
- Immune function, genetic predisposition

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.

New Research: Stress & Inflammation Combine to Fuel Cancer Growth

- Many cancer-related deaths caused by treatment resistant metastases. Stress & inflammation drive metastatic process.
- Body produces pro-inflammatory markers such as cytokines in response to stress. Cytokines regulate immune responses and inflammation. Two pro-inflammatory cytokines are interleukins & tumor necrosis factor; these turn on various transcription factors.
- Inflammation changes tissue homeostasis; this leads to chronic response promoting tumor growth, angiogenesis, invasion and metastasis through activation of surrounding stromal cells and recruitment of inflammatory cells (e.g. mast cells, natural killer cells, neutrophils, and leukocytes).
- Inflammatory cells create reactive O2 & Nitrogen species, turn on oncogenes, and silence tumor suppressor genes

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


Carcinogenesis

- The process by which cancer arises
  - Initiation
    - Carcinogens damage DNA
    - Irreversible change in DNA
  - Promotion
    - Further carcinogen exposure
    - May be reversible
  - Progression
    - Detectable symptomatic disease > 1 cm mass


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

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

Genetic Mutations: Somatic (Acquired) versus Germline (Inherited)

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

Cancer Genetics

Testing available:
- Hereditary breast and ovarian cancer
- Hereditary nonpolyposis colorectal cancer
- Familial adenosis polyposis syndromes
- Hereditary melanoma
- Li-Fraumeni syndrome
- Hereditary retinoblastoma
Genetic Influences Associated with Cancer

- Genes play two major roles in cancer
  - Cause cancer - Oncogenes
  - Suppress cancer - Tumor Suppressor Genes

What genes are important in carcinogenesis?
1. Apoptosis Gene (programmed cell death)-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
4. Tumor suppressor gene (instructs cell - stop dividing)
5. Mutated gene examples:
   - BRCA1, BRCA2 (Breast, ovarian)
   - FAP, HNPCC, APC (Colorectal)
   - Alk Phos, EGF Receptor, VEGF receptor, KRAS (Lung)
   - BRAF (Gastric, Colon, Lung, Hairy Cell Leukemia, thyroid, melanoma)
   - KRAS (Oncogene)
   - TP53 (Tumor Suppressor gene) – Found in nearly 50% of cancer
   - ABL translocation in CML i.e. “Philadelphia Chromosome”

Biology Application: Downstream KRAS Oncogene Pathway target in Lung Adenocarcinoma

Genetic Mutations

- **Proto-Oncogenes**
  - Oncogenes
  - K-Ras

- **Tumor suppressor genes**
  - P53
  - Apoptosis

**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 August 2015 with 10 arms. Each arm will enroll adults ≥ 18 years of age with advanced solid tumors and lymphomas that no longer respond (or never responded) to standard therapy & are growing. Accrual goal of each arm = 1000. Trial endpoint -Objective Response Rate-either complete or partial response

- 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.

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

Angiogenesis

Growth of new blood vessels
- Normal in embryo
- Quiet in adults in most tissues
Angiogenesis

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

The Metastatic Process

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

Extracellular Receptor Inhibition via Monoclonal Antibody Mechanism of Action

- Detachment
- Invasion
- Survival
- Arrest
- Establishment of secondary tumor
The Metastatic Process

Overall most common sites of metastases

- Bone
- Brain
- Liver
- Lungs
- Lymph nodes
### 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

### 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

- **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
Diagnostic Biomarkers for Staging and Monitoring

- α-fetoprotein
- Human chorionic gonadotropin-β
- CA 19-9:
- CA 125:
- CEA
- CA 15-3, CA 27-29, HER2/NEU
- Fibrin / FDP, BTA, High molecular weight CEA & mucin, chromosomes 3, 7, 9, 17
- Thyroglobulin
- PSA

Testicular cancer (nonseminatous)
Testicular cancer
Pancreatic cancer
Ovarian cancer
Colon cancer
Breast cancer
Bladder cancer
Thyroid cancer
Prostate cancer

Four Different Types of Staging

- Clinical Staging
- Pathologic Staging
- Post-Therapy or Post-Neoadjuvant Therapy Staging
- Re-staging

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

TNM System

- Primary Tumor (T)
  - TX – Primary tumor cannot be evaluated
  - To – No evidence of primary tumor
  - Tis – Carcinoma in situ
  - T1, T2, T3, T4 – Size and/or extent of the primary tumor

  - The size and extent of spread are specifically defined for each cancer site

AJCC Cancer Staging Manual, 7th Ed., 2010
TNM System

- **Regional Lymph Nodes (N)**
  - NX – Regional lymph nodes cannot be evaluated
  - No – No regional lymph node involvement
  - N₁, N₂, N₃, N₄ – Involvement of regional lymph nodes (number and/or extent of spread)
- Categorized by
  - Number of positive nodes
  - Involvement of specific regional node groups

- **Distant Metastasis (M)**
  - Mo – No distant metastasis
  - M₁ – Distant metastasis present
  - To areas where cancer spreads by
    - Vascular channels
    - Lymphatic
  - Beyond the “regional” nodes

Typical TNM Staging

- Stage I: T₁, N₀, M₀
- Stage II: T₂, N₁, M₀
- Stage III: T₃, N₂, M₀
- Stage IV: T₄, N₃, M₁

TMN Staging for Lung Cancer

### Lung Staging Form

**Stage Category Definitions**

- **T** indicates the primary tumor.
- **N** indicates the regional lymph nodes.
- **M** indicates distant metastasis.

#### T Stage

| T1 | Tumor less than 3 cm in greatest dimension, not involving regional lymph nodes. |
| T2 | Tumor 3 cm or greater, not involving regional lymph nodes. |
| T3 | Tumor greater than 3 cm or involving regional lymph nodes. |
| T4 | Tumor involving major blood vessels or visceral pleura. |

#### N Stage

| N0 | No regional lymph node involvement. |
| N1 | Regional lymph node involvement. |

#### M Stage

| M0 | No distant metastasis. |
| M1 | Distant metastasis. |

### Other Classification Systems

- **Colon cancer:** Dukes
- **Lymphoma:** Ann Arbor, Working formulation, Rappaport Classification
- **Leukemia:** French-American-British (FAB) criteria
- **World Health Organization (WHO)**
- **Lung Cancer:** SCLC versus NSCLC

Questions?