Cellular & Molecular Biology of Cancer Course
PATHG4500 Fall 2019
Introduction
Cancer Biology PATHG4500-001

Meets on select Mondays and Wednesdays

• Course Directors: Anna Lasorella, MD
  Richard Baer, PhD

• Mid-term and Final Exams: both “take-home, open book” format; about one week’s time to complete each exam

• Course Website: icg.cpmc.columbia.edu
Cancer: Importance

Affects 20% of the U.S. population

• Older adults: epithelial cancers (carcinomas) of the lung, breast, colon/rectum, prostate, pancreas, other sites; cancers of the lymphoid system (lymphomas)

• Children and young adults: bone marrow (leukemias), brain, soft tissues (sarcomas), kidney (Wilms), testis

Genetic aberrations in cancer cells point to fundamental biological processes: cancer research subsumes research into basic biology
Cancer Cells: Acquired Characteristics

- Relentless cell proliferation
- Failure of cellular differentiation
- Resistance to cell death
- Angiogenic capacity
- Metastatic potential

Molecular Safeguards
= Tumor Suppressor Genes
Normal cell

DNA damage

Mutations

Proto-oncogenes
Apoptosis genes
Tumor suppressor genes

Carcinogens; Radiation; Viruses
Deficiencies in DNA repair

Epigenetic changes

Malignant neoplasm

Too many “insults”
• Course overview
  Lasorella
• Tumor pathology
  Hibshoosh
• Cancer Cytogenetics
  Murty
• Oncogenes 1, 2
  Baer
• Carcinogens/DNA repair
  Zha
• Cell cycle/Rb/Tumor suppressor
  Iavarone
• P53 tumor suppressor
  Gu
• T cell lymphoma
  Palomero
• Leukemia
  Ferrando
• Stem cells
  Dalerba
• Tumor Stroma
  Gonda
• Cancer Metabolism
  Chio
• Mouse models of cancer
  Olive
• Pancreatic cancer
  Su
• Apoptosis
  Troy
• Invasion/Metastasis
  Acharyya
• Systems Biology
  Sims
• MicroRNAs
  Basso
• Lymphoma, leukemia genetics
  Pasqualucci
• Skin cancer
  Kim
Tumor Pathology

• Cancers classified by histological criteria; histology often predicts biological behavior.

→ *importance of using a precise nomenclature*

• Cancer is a multi-stage disease. Changes in histology reflect molecular progression: benign → malignant.

• Histology is the current “gold standard” for treatment and prognosis; but *molecular analysis* is an increasingly important adjunct...

→ *cancer research is driven by the interplay between tumor pathology and molecular biology*
Mol. Pathology: chromosome painting

Normal cell

Breast cancer cell

Figure 1.11b The Biology of Cancer (© Garland Science 2007)
Dominant Oncogenes

Acutely transforming retroviruses
  • animal models; discovery of viral oncogenes in the 1970’s (prototype: v-src)

Discovery of endogenous “proto-oncogenes”
  • transformation assays by transfection of cultured cells; mutated HRAS gene discovered in the early 1980’s

Multiple mechanisms of oncogene activation
  • Point mutation, chromosomal translocation, gene amplification

Role of proto-oncogene activation in human cancers
  • N-myc gene amplification: neuroblastoma
  • K-ras/B-raf mutations: colon and pancreatic CA; melanoma
  • Beta-catenin activating mutations: diverse cancers
  • Oncogenes activated by chromosomal translocations: leukemias, sarcomas; some carcinomas
Functions of Proto-Oncogenes

• Growth factors (tyrosine kinases) and their receptors
  • PDGFb, FGFs, IGF1 and IGF2
  • EGF receptors (erb-B family: HER2/Neu)
  • Ret proto-oncogene

• Cytoplasmic signal transduction proteins
  • Ras, Abl

• Transcription factors
  • C-Myc, N-Myc (amplification and translocations)
  • Chimeric transcription factors from fusion genes (translocations)

• Cell cycle regulators
  • Cyclin D, CDK4

• Anti-apoptotic proteins
  • Bcl-2
Carcinogens and DNA Damage

Preventable causes of the common adult cancers

• Tobacco smoking (lung, oral cavity)
• Dietary fat (colon, breast)
• Sunlight/UV (skin)
• Occupational carcinogens (asbestos: mesothelioma)

Mechanisms of DNA damage

• Carcinogen activation
• Carcinogen targets (DNA adducts; mutations)
• Spontaneous DNA strand breakage
DNA Damage Sensors are Tumor Suppressors

DNA damage

- p53
- p21
- ATM/ATR
- MRN
- Chk1,2
- cdc25
- cyclinB/cdk1

- Cyclin/cdk
- Rb
- E2F1

- G1 → S → G2 → M
Tumor Supressors/Oncogenes at the G1-S Phase of the Cell Cycle

Rb (active suppressor) → CyclinD-Cdk → G1-S transition → Rb~P (inactive)

Cell proliferation

G0 → G1 → S → G2 → M → G0
Central TS Proteins: Rb and p53

- **Rb**
  - Restrains cell proliferation in normal tissues
    - Rb protein suppresses transcription of S-phase genes
    - Promotes cell differentiation
- **p53**
  - Activates a “checkpoint” in cells that have undergone DNA damage, pathological proliferation, or hypoxic stress
    - p53 activates transcription of specific target genes after binding directly to DNA
    - Leads to growth-arrest or apoptosis
Central Interactions: p53 and Rb

- **p14Arf**
- **MDM2**
- **E2F-1**
- **p53**
- **CyclinD/Cdk4, 6**
- **p16**

**Transcriptional activation**

**Phosphorylation**

**Ubiquitin-mediated proteolysis**
Developmental Regulators can be Tumor Suppressors

\[ \text{TGFb} \quad \text{HH} \quad \text{WNT} \]
Pancreatic Cancer

Pathogenesis
- K-ras gain-of-function mutations
- p53 loss-of-function mutations
- Additional tumor suppressor losses (p16, DPC4/SMAD4)

Special issues in therapy
- Highly drug-resistant
- Stroma-rich: important roles of cancer-associated fibroblasts (CAFs); tumor-associated macrophages (TAMs)
- Imaging for dx and screening?
Cancer Metabolism

Understanding cancer and providing effective therapy requires a study of the metabolic processes involved.

Pancreatic ductal adenocarcinoma studies indicate that cancer cells harness reactive oxygen species for cell viability and tumor-stroma co-evolution.

• Redox and metabolic adaptations can create cancer-specific vulnerabilities that could lead to better therapy.
Using model systems to study cancer

Studying cancer is greatly enhanced by using various model systems: cells, human cell lines, mouse, primates etc.

• Evaluating novel drugs in model systems

• Pharmacokinetic analyses; imaging, microscopy, biochemical and molecular analyses

• Translational efforts to understand biology of tumor response and/or resistance to therapy
Cancer Stem Cell

- Understanding cancer stem cells to better understand cancer and mechanisms of cellular responses to therapy
- Application of single-cell technologies to analyze tissue cell composition
- Identification and development of biomarkers to guide therapeutics in specific human cancers
Tumor microenvironment

- Stromal composition with a focus on cancer associated fibroblasts (CAFs)
- Understanding the role of epigenetics in stromal cells
- Role of tumor microenvironment in cancer development and progression
- Tumor cell-derived signaling in cancer
Systems Biology

**Single Cell Genomics and Transcriptomics:** Single cell approaches to analyze biological samples and study-
- Phenotypic transitions occurring during tumor progression
- Evolution of drug resistance in cancer

**Translatomics - Systems Biology of Protein Synthesis:** Cell type-specific measurements of protein synthesis
- Broad questions about translational regulation
- Role of translational regulation in development and disease
- New tools for genome-wide measurements of protein synthesis

Control of Apoptosis

- **Bcl-2 family proteins**
  - modulators of the apoptosis set-point
  - control mitochondrial integrity; cytochrome C release

- **Caspases**
  - effectors of cell death; activated in a protease cascade

- **IAP-related proteins**
  - endogenous caspase inhibitors

- **Input from signaling pathways**
  - TNF receptor family
  - p53 tumor suppressor
TP53: apoptotic sentinel system

DNA damage

Cytochrome C

CASPASES

Apoptosis

Trophic growth factors (IGF’s; PDGF)

Myc

Ras*

ARF

Bax

AKT

Bcl2/Bcl-X

p53

TP53: apoptotic sentinel system
Cancer Metastasis

Figure 14.10c *The Biology of Cancer* (© Garland Science 2007)
Cancer Invasion and Metastasis

- Ability of tumor cells to breach basement membranes, to travel in the bloodstream or lymphatics to distant sites, and to colonize these sites to form metastatic tumors.

- Multiple genetic events required for the metastatic phenotype
  - Loss of cell-cell adhesion (loss of cadherins, integrins)
  - Secretion of proteases (MMP-2/collagenase)
  - Increased cell motility (hepatocyte growth factor); epithelial→mesenchymal transition (EMT)
  - Other as yet unknown genetic events
B-cell Lymphoma: Comprehensive Analysis of a Human Cancer

Lymphoma pathogenesis: integrating histopathology and molecular biology

- Burkitt lymphoma: t(8;14) C-Myc dysregulation
- Follicular lymphoma: t(14;18) Bcl-2 dysregulation
- Large cell lymphoma: t(3;various) Bcl-6 dysregulation

Basic principals of cancer biology can be formulated, but each type of cancer has a specific molecular profile, related to the stage of development of its precursor cells.
BRAIN Tumors as a model for differentiation defects in cancer
T-cell Lymphoma

Overview of concepts, literature and current knowledge about the disease

Molecular players, pathways and mechanistic information about T-cell lymphoma

Current research in T-cell lymphoma
Understanding the molecular mechanisms involved in T-cell leukemia and lymphoma

• Analysis of the role of specific oncogenes in pathogenesis of leukemia

• Understanding glucocorticoid resistance and its effect in T-cell Acute Lymphoblastic Leukemia (T-ALL)

• Characterizing oncogenes in T-ALL

• Identifying new oncogenes and tumor suppressors in T-cell leukemias and lymphomas

• Understanding the resistance to chemotherapy in acute lymphoblastic leukemia
Skin Cancer

Three major types:

Basal Cell Carcinoma (BCC)
Squamous Cell Carcinoma (SCC)
melanoma