NEOPLASIA 1: OVERVIEW

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WHO AM I, AND WHAT AM I DOING HERE?

MICROSCOPIC ANATOMIST & HISTOLOGIST

VMRCM FACULTY SINCE 1987

• Histology
• Electron Microscopy
• Intro Path

ADJUNCT VCOM FACULTY

• Working with Dr Santo 2 years
• Path Web Site Cases
NEOPLASIA

• Literally, “new growth” of cells
• Growths are “neoplasms” defined as:
  “An abnormal mass of tissue whose growth exceeds normal, is uncoordinated, and independent of external control”
• Neoplasia is often the “end point” of a progression of changes in tissues:
  – Metaplasia > Dysplasia > Neoplasia
METAPLASIA

• A *reversible* cellular change from one adult cell type to a second adult cell type *not normal to a given tissue or organ*
  – *e.g.*, change from stratified squamous to columnar epithelium
    • Barrett’s esophagus an example of squamous to columnar metaplasia
    • Only found in tissues capable of replication

Squamous to columnar metaplasia in Barrett’s esophagus
FEATURES OF METAPLASIA

• An *adaptive response* to external influence
  – GERD, smoking, etc.

• Occurs “within” but not across primary germ layers
  – No replacement of ectodermal structures with mesodermal, *e.g.*
  – *Most* common in epithelia

• Signalled by soluble factors, *e.g.*, cytokines, growth factors, etc.

• Undifferentiated stem cells “go wrong”
DYPLASIA

• Abnormality of development, principally in epithelia

• In the cellular context:
  – Alterations in size of cells
  – Alterations in shape of cells
  – Alterations in number of cells
    • Loss of uniform appearance
    • Loss of normal orientation
    • Increased & aberrant mitosis
FEATURES OF NEOPLASMS

• CLONAL NATURE
  – All cells of a neoplasm arise from a single ancestor
    • Multiple mutation events may occur in successive generations

• GENETICALLY ALTERED CELLS
  – Mutations from the normal genotype
  – Somatic cell alterations

• AUTONOMOUS GROWTH
  – Outside the normal control mechanisms
  – May often be initiated by external factors

• PROLIFERATIVE
  – Degree varies considerably
    • Related to progression & prognosis
“BENIGN” vs MALIGNANT

• “BENIGN” isn’t “HARMLESS”
  – “Benign” tumors can be fatal!

• Benign neoplasms = “not invasive”
  – Localized
  – Circumscribed
  – Well differentiated cells
“BENIGN” **vs** MALIGNANT

- **“MALIGNANT” = “INVASIVE”**
  - Cells are unrestrained in proliferation
    - Lose control of growth cycle
      - Rate of growth variable
    - Escape locale of origin
      - Locally invasive or may go farther
    - Gain access to interstitium and/or circulation
    - Can seed new growth, i.e., metastasize
• **BENIGN NEOPLASMS**
  
  – **“-OMA”**
  
  • *Fibroma*, of fibroblast (CT) origin
  • *Osteoma*, of bone origin
  • *Chondroma*, of cartilage origin
  • *Adenoma*, of epithelial origin, and/or with a “glandular” architectural pattern
    
    – *Papilloma*, wart-like pattern, from “papilla”
DUCTAL HYPERPLASIA

- **Benign lesion**
  - No spread outside duct wall
  - Cells are essentially normal in appearance, well differentiated
BENIGN PROSTATIC HYPERPLASIA
PAPILLOMAS

• Warty, benign epithelial growths
  – “Cauliflower” appearance
POLYPS

• Benign adenomas projecting visibly above an epithelial sheet
• Have a CT stalk
• May be pre-cancerous lesions
TERMNOLOGY

• MALIGNANT NEOPLASMS
  – “Sarcoma” from mesenchymal tissues (mesodermal origin)
    • Liposarcoma, osteosarcoma, rhabdomyosarcoma
  – “Carcinoma” from epithelial tissue (ectodermal or endodermal origin)
    • Adenocarcinoma, squamous cell carcinoma, etc.
    • May be named for organ/tissue of origin
CHARACTERISTICS OF NEOPLASIA

- **Variably differentiated cells**
  - More differentiated, usually less invasive
- **Cells are pleiomorphic**
  - Vary in size, shape, nucleus:cytoplasm ratio
- **Nuclear morphology is aberrant**
  - Hyperchromicity
    - $\uparrow$ DNA $\uparrow$ binding of dye
- $\uparrow$ **mitoses** (high mitotic index)
  - Mitotic figures often atypical
    - May have unequal separation, multiple spindles
- **Loss of polarity**
  - Normal cells have a “top” & “bottom” related to function

Abnormal mitotic figure in a lung cancer cell →
• Benign tumors usually well differentiated
  – Often are “functional” tissue
  – Maybe HYPER-functional!

• Degree of differentiation related to behavior
  – More differentiated neoplasms *usually* less invasive

• Malignant tumors vary
  – “Well-”, “moderately-”, or “poorly-”
  – “Anaplasia” = lack of differentiation
    • *Malignancies tend to be anaplastic*

• Undifferentiated cells lose normal function
  – ↑ anaplasia means ↓ functionality

**DIFFERENTIATION**

**ANAPLASIA & PLEOMORPHISM IN BREAST CANCER**
THE SPECTRUM OF DIFFERENTIATION

NORMAL URINARY EPITHELIUM

Not Invasive

HIGHLY INVASIVE

URINARY CELL CARCINOMA

NORMOPLASIA > METAPLASIA > DYSPLASIA > NEOPLASIA

CELLS SHOW COMPLETE, NORMAL DIFFERENTIATION

CELLS ARE ANAPLASTIC, SHOW COMPLETE LACK OF DIFFERENTIATION
GROWTH AND DEVELOPMENT OF NEOPLASTIC LESIONS

- Neoplasms begin with a single cell
- Clonal development
  - Subclones may develop
  - A Darwinian process
  - Numerous barriers to clonal expansion
    - MOST neoplastic cells don’t survive
    - Continual “weeding out” means the “fittest” do
      - “Fittest” = “Most aggressive and adapted” i.e., able to
        avoid removal by body’s self-corrective mechanisms
CAUSES OF NEOPLASIA

• Neoplasia is a GENETIC change
• *Anything* capable of injuring DNA can elicit it
  – Environmental contaminants
  – Ionizing radiation
    • X-rays, gamma rays, other WL of EM spectrum
    • UV rays
• Chemical carcinogens & Mutagens
  • Natural & Artificial
    – Pharmaceuticals
    – Industrial products
    – Particulates & gases (formaldehyde, soot, radon)
    – Fungal toxins (aflatoxin)
• Disease agents
  • Viruses
• These materials often produce free radical injury to DNA
• RTECS: Registry of Toxic Effects of Chemical Substances
  ([www.cdc.gov/niosh/rtecs/default.html](http://www.cdc.gov/niosh/rtecs/default.html))
SOURCES OF RADIATION

...AND...DON’T FORGET MEDICAL X-RAYS!
THE E-M SPECTRUM

Does TV Cause Cancer?
ULTRAVIOLET LIGHT

• Major cause of skin cancer
  – Highest rate in Australia, lowest in Japan
  – Skin tone affects susceptibility
  – Induces mutations in basal cells & melanocytes
TOBACCO SMOKE

• Most important single environmental cause of cancer in the world
  – Associated with many forms of cancer, not just lung cancer
CHEMICAL CARCINOGENS

- **Initiators & Promoters**
  - “Collaborate” in neoplastic transformation
  - Neither is sufficient alone

- **Initiators**
  - Cause *permanent* DNA damage
  - “Sets the stage” for neoplasia

- **Promoters**
  - NOT tumorigenic
    - No permanent DNA damage
  - Effects are reversible
  - Enhance proliferation of transformed cells

SHIPS OF THE JAMES RIVER “GHOST FLEET” CONTAIN PCBs & OTHER CARCINOGENS
INITIATORS

- May be chemically inert
- Metabolic conversion to active form
  - Liver cytochrome system creates a mutagen
  - Greatly complicates drug discovery!
- List of known initiators long and growing
THE AMES TEST

- Mutagenesis predicts carcinogenesis
  - *S. typhimurium* mutant lacking ability to make histidine
  - Mutagenesis can revert the defect
  - The more colonies the more powerful the mutagen
  - Standard lab assay, widely used, cheap, reliable
PROMOTERS

- May increase cellular proliferation in initiated clones
  - Activation of internal signal pathways (PI 3-Kinase)
- May suppress inhibitory exogenous signals
  - Could block a receptor or suppress its expression

TETRADECANOYLPHORBOL ACETATE (TPA)
A KNOWN PROMOTER
INTERPLAY OF INITIATOR & PROMOTER

- Promoter must follow initiator
- Threshold level of promotion must be met
- Initiator *may* cause neoplasia if exposure is repetitive
FACTORS IN MALIGNANCY

• **Mutation Rate**
  – Probability per gene/time-unit of change
    • Can be greatly affected by external factors
    • The more time available the greater the chances for “favorable” mutations

• **Size of Initial/Subsequent Populations**
  – The more, the better the chances

• **Reproduction Rate**
  – Number of generations per time unit
    • Fast-dividing clones make more opportunities

• **Selective Advantages Conferred**
  – If any!
  – Must deal with protective/corrective measures
  – Must ↑ suitability for environment
IF YOU WANT TO BE A MALIGNANT NEOPLASM…

• **Be a non-conformist!**
  – Mutate, and better yet, become genetically unstable

• **Stay forever young!**
  – Avoid “replicative senescence”

• **Escape!**
  – Get away from “home” by migrating (i.e., become invasive)

• **Do your own thing, be a Free Spirit!**
  – Don’t differentiate or stop dividing in response to exogenous signals

• **Don’t be noble and self-sacrificing!**
  – Avoid apoptosis

• **Adapt!**
  – Figure out how to survive in distant sites (i.e., metastasize)
IT ALL STARTS WITH A SINGLE CELL

• Initial event is a *random* mutation in a *susceptible* cell
  – Cell acquires a selective advantage
  – ▲ population = ▲ chance of more mutations

• Subsequent mutations may increase advantage
  – Subclones are selected
  – Successive subclones are more successful, less controllable

• Chance plays a large role!
  – Many barriers to overcome to become malignant
HOW FAST DOES IT HAPPEN?

• Minimum palpable mass ≥ 1.0cm
  – $10^9$ cells
  – X-ray detection limit about $10^8$ cells

• Division rate approximately the same as normal cells!

• A 10μm cell has to double 30 times to reach detectable # and size
  – Assumes NO losses
  – With 3-day replication time, about 90 days, BUT…

• Rate-limiting factors:
  – Doubling time
  – Available pool of replicating cells (growth fraction)
  – Balance between production and loss (turnover)
    • Apoptosis
    • Arrest of cell cycle by control mechanisms

• A 2.0-cm mass takes 2-3 years growing to that size
  – Most of its life cycle is completed before detection

MORAL: GET A MAMMOGRAM!
THE “TWO-HIT” MODEL

- One mutation is not enough
  - Both alleles have to be defective
- Explains the behavior of tumor initiation for hereditary and sporadic tumors
THE OLDER THE BETTER

• Malignancies increase with increasing age
  – More time to accumulate mutations!
    • Mutation/change is a STATISTICAL PROCESS
  – More time to enlarge susceptible populations
  – Better chance of selecting aggressive subclones

“…most of us die before cancer has had time to develop.”
- Cells leave the “proliferative pool” by entering G₀ or by differentiating; or removal/death by apoptosis
• Tumor cells are inherently unstable
  – Lack ability to repair DNA damage
  – Lack ability to correct transcription errors
  – Lack ability to maintain normal chromosomes
    • Translocations, deletions, fusions, transpositions, etc.
• Most mutations are harmful to survival
  – Cells lost to replicative pool
    • Metabolic death & removal, or apoptosis
• Instability ↑ chances of a “favorable” mutation in at least one cell
  – Probably essential for tumor progression
  – More varieties of sub-clones are potentiated
  – Some will have ability to overcome barriers
• Congenital heterozygosity favors instability
  – Only one more “hit” needed
REPLICATIVE SENESCEENCE

• Most normal cells have a built-in limit on division
  – Typically 60 cycles in culture
  – Obvious exceptions: skin, gut lining, etc., mostly epithelial

• Mechanism of arrest is telomere shortening
  – Telomeres are specialized DNA sequences at ends of chromosomes
    • Highly conserved in evolution
  – Repeated nucleotides in tandem
  – Important to efficient replication
  – Form “fold-overs” to protect ends of DNA
    • Lagging end might otherwise be mistaken for breaks

• Telomere sequence extended by telomerase enzyme
  – Replication of telomere DNA is incomplete
  – Telomere shortens and is considered “damage”
  – p53 arrests cell cycle
  – Division stops
  – MOST NORMAL CELLS DO NOT EXPRESS TELOMERASE

• Mutant cells regain capacity to produce telomerase
  – Become “immortal”
THE GREAT ESCAPE
benign tumor of epithelium → basal lamina → break through basal lamina → invade capillary

connective tissue

capillary

travel through bloodstream (less than 1 in 1000 cells will survive to form metastases)

adhere to blood vessel wall in liver → escape from blood vessel (extravasation) → proliferate to form metastasis in liver
STAGES OF PROGRESSION, CERVICAL CANCER

Note progressively larger area of proliferation with higher grades
**BARRIERS TO SPREADING**

<table>
<thead>
<tr>
<th>escape from parent tissue</th>
<th>travel through circulation</th>
<th>colonization of remote site</th>
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<tr>
<td>entry into bloodstream or lymphatic vessel</td>
<td>survival in the circulation</td>
<td>arrest in capillary or other small vessel</td>
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- **DIFFICULT**
- **EASY**
- **DIFFICULT**

**Inherently inefficient**
- Many tumor cells lost at various points
- Only those with “right” mutations can survive
- Emphasizes importance of genetic instability & clonal selection
- Exact nature of mutations needed largely unknown
TO BE CONTINUED...