Neoplasia - 2

Lecture Outline

I. TUMOR GENES
   a. oncogenes
   b. tumor suppressors

II. METASTASIS
   a. factors
   b. target processes

III. PARANEOPLASTIC SYNDROMES

IV. INFECTIOUS CANCERS
   a. viral cancers
   b. transmissible tumors

Oncogenes

- Oncogenes
  - Transform normal cells into neoplastic cells
  - Activate gene expression
  - Encode oncoproteins

- Proto-oncogenes
  - Can become oncogenes if mutated or over-expressed

  - Growth factors, growth factor receptors, cell cycle regulators, intracellular signal transducers
  - Give green light for cell growth
  - Can lead to uncontrolled cell growth
  - Only need one copy of gene to be altered; get GAIN of function
Ways proto-oncogenes become unregulated

- Gene amplification
- Gene translocation
- Promoter insertion
  - Retrovirus inserts its genome into host genome

Examples of oncogenes

- Cyclin B
  - Normally regulates M phase
  - If mutation leads to deregulation, cellular transformation results
  - Over-expression: poor prognosis
    - Resistance to therapy
    - Enhanced & unregulated cancer

- Nerve
  - Transcription factor for genes involved in cell proliferation
  - Regulates expression of >1% of all genes
  - Over-expressed in majority of breast, hepatocellular, metastatic tumors

Tumor suppressors

- Play critical role in cell growth
- Mammal regulate proliferation by governing movement through cell cycle
- Normally function as "red lights" for the cell cycle
- Typically must alter both gene copies to lead to neoplasia
- Mutations in tumor suppressors lead to LOSS of function (i.e., LOH/Removal of tumor suppression)
- DNA repair regulators, regulators of apoptosis, intracellular signal transduction regulators
Example of a tumor suppressor: p53

- Not a normal cell cycle regulator
- Increased amount of p53 and lifespan if DNA is damaged and cell must repair itself
- A "cellular policeman"
  - Regulates entry into cell cycle
  - Stimulates DNA repair genes
  - Induces apoptosis if DNA damage too severe
- Critical! Losing 1 copy can lead to cancer
  - >90% of human cancers have a p53 mutation
  - If inherit 1 bad copy of p53, have 10-fold greater cancer risk

Tumor metastasis

- Tumor spread to a different site from its origin
  - Tumor has successfully evaded host defense
  - No benign tumors, act all malignant tumors
  - Not all tumor cells give rise to a metastasis
  - Metastasis is major cause of mortality
- Stages:

Primary or metastatic tumor?
Pathways of Tumor Metastasis

- **Hematogenous – blood**
  - 1st capillary bed theory
    - Cells become caught in first vascular bed that they hit
    - Lungs
    - Liver
    - In reality, more complicated
    - Common with sarcomas

- **Lymphatic**
  - Tumours gain systemic access via lymph
    - Similar idea as hematogenous pathway of spread
    - Spread to regional lymph nodes
    - Not truly separate from hematogenous pathway
    - Common with carcinomas

- **Implantation or Transseptal**
  - Tumour breaks through lining of organs
  - Tumour cells are shed and can coat adjacent organs
  - Carcinomatosis: seeding of a body cavity with tumor metastasis
    - Carcinomas of ovary, GI, lung
Mechanism of Metastasis

1. Cells detach from main tumor mass
2. Cells invade and pass through the basement membrane (BM) on which they normally rest
3. Cells enter and pass through the extracellular matrix (ECM)

Mechanism of Metastasis

4. Invade blood vessel (or lymphatics)
5. Travel through the bloodstream
6. Cells extravasate from vessel and invade ECM at metastatic site

Mechanism of Metastasis

7. Angiogenesis: blood vessel growth to support metastatic tumor cells
   - Several angiogenesis inhibitors FDA approved for use in humans as components of antitumor treatments
   - Theoretically interesting, but efficacy disappointing
8. Growth of metastasis
Paraneoplastic syndrome
- Symptom that is secondary to the presence of cancer in the body
- May be noticed before the cancer itself
- Caused by tumor cell product
  - More cells produce, secrete products that normally function locally
  - When these cells become tumors, excessive amounts of product may be produced and disrupt systemic homeostasis
- More commonly seen with certain cancers

Cachexia
- Loss of condition (body fat and muscle mass)
- Diminished immune system
- Generalized weakness
- Effects not proportional to size of tumor
- Increased chance of death if present
- Poorly understood
  - Tumor necrosis factor alpha (TNF-alpha)
  - Interleukin-1 (IL-1)
  - Gamma interferon (IFN-gamma)

Fever
- Can occur in cancer patients without an obvious reason
- May be caused by release of cytokine (IL-1 or IL-6) by tumor cells
Hypoglycemia

- Low glucose in the serum (low blood sugar)
- Can lead to seizures & death
- Beta cells in islets of the pancreas produce insulin
  - Insulin decreases blood glucose
  - Beta cell carcinoma ("insuloma")
  - Excess uncontrolled insulin release, hypoglycemia

- Other tumors also can cause hypoglycemia
  - Not all mechanisms of lowered glucose by tumors are understood
  - Hemangiosarcoma, hepatocellular carcinoma, leiomyosarcoma

Hypercalcemia

- Increased calcium in the serum
- Tumors cause excess parathyroid hormone (PTH), the major regulator of calcium levels in the body
  - Neoplastic tissue may produce ectopic parathyroid hormone
  - PTH-related protein

- Commonly seen in lymphoma, apocrine gland anal sac adenocarcinoma (dogs)
- High calcium can also occur via direct tumor invasion & destruction of bone
  - Direct, not true paraneoplasia

Sertoli cell tumor: Feminization

- Sertoli cells
  - Narrow, developing sperm cells in seminiferous tubules (testes)
  - Secretes estrogen or estrogen-like substances
  - Estrogen usually only has local effects

- When a tumor develops a large enough mass, enough estrogen is released that male becomes feminized
- Feminization signs in dogs: symmetric hair loss, enlarged mammary glands, attractiveness to other male dogs
Cancers caused by infectious agents

- ~15% of human cancers

Human Papillomavirus (HPV)

- DNA virus
- More than 40 in HPV family
  - Low-risk vs. High risk
    - Both can cause abnormal cell growth
    - Only high-risk HPVs lead to cancer
  - HPV on L & HPV-8: 90% of cervical cancers
- Persistent infection vs. cleared infection
- Majority of infections, even with high-risk HPV, are cleared
- Persistent infections with high-risk HPV serotypes are now recognized as the cause of essentially all cervical cancers

Human Papillomavirus (HPV)

- Infection causes a series of cytologic changes that ultimately convert squamous epithelium to glandular epithelium
  - Benign proliferative reactions
  - Dysplasia (low) → carcinoma in situ (0.1%) → carcinoma (0.6%)
Pap smear
- Pap smear is a screen to look for abnormal cells (precancerous changes)
- Most successful cancer screening test in history
- Since its introduction, 86% reduction in cervical cancer cases
- Worldwide #1 cause of cancer death in women
- In the US, it is #2 due to widespread usage of the pap smear

HPV vaccine
- 2006: FDA approved preventative HPV vaccine
- 100% effective at preventing development of pre-cancerous cytologic changes caused by infection with serotypes contained in the vaccine
- Not all cancer-causing serotypes included in vaccine
- Most common, including HPV-6 and -11
- No data if prevents cancer; rather, current data shows it prevents precursor changes seen before cervical cancer develops

Transmissible Cancers: Devil Facial Tumor Disease (DFTD)
- Transmissible cancers
  - Infectious tumor cells that can be transmitted from one individual to another
- Mysterious aggressive facial tumors recently emerged in Tasmanian devils
- Carnivorous marsupials found only in Tasmania
- 1st case described in 1996, not appreciated until 2000
- Pattern of spread was that of an infectious disease
Devil Facial Tumor Disease (DFTD)

- Fatal within 6–9 months of appearance of tumors
- 90% decrease in natural population of devils, threatens extinction by 2035

Genetics of a Transmissible Tumor

- Allograft Theory:
  1. Caused by a single clonal line of malignant cells propagated in an allograft
  2. Spread via contact (kissing)
  3. Tumor cells from different individuals contained identical, complex chromosomal rearrangements
  4. Genotype abnormalities: aberrant X and appearance

- Diagrams of tumor cells and devils

DFTD: Recent discoveries

- Allograft theory is further supported by genetic analysis of highly variable regions of DNA
  - Tumors are geographically similar at all loci regardless of sex, location, age of the devil from which they were isolated
  - Genetic consistency supports epidemiologic evidence of recent origin
- Likely a schwann cell (myelin sheath) origin

Structure of a Typical Tumor Cell

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Devil Facial Tumor Disease

- Pathogenesis not completely understood
  - Tumor cell spread is alleged via biting from affected host to unaffected host
  - Tumor cell evades host immune response
    - Little genetic diversity in devil, so immune system unable to detect cancer as foreign
    - Cells take up residence in new host and grow into large tumor
  - Ultimately grow so large that tumor can interfere with vision, breathing, and eating, resulting in death