Neoplasia –
Tumor genes, metastasis and paraneoplastic syndromes

Dr. Stephanie Montgomery

I. TUMOR GENES

Oncogenes
- Cause transformation of normal cells into tumor cells
- Encode oncogenes, or proteins responsible for cellular transformation
- Proto-oncogenes are genes that if mutated or expressed at a high level can become oncogenes
- Categories of oncogenes: growth factors, growth factor receptors, cell cycle regulators, signal transducers, regulatory proteins
  - Think of oncogenes as a “green light” for cell growth
  - Lead to gain of function
- “oncogenic” meaning that they activate gene expression or gene function
  - Gene amplification – could have 100 repeat copies of same gene
  - Gene translocation – strong promoter next to foreign gene
  - Promoter insertion – associated with retroviruses inserting into genome
- Example: cyclin B
  - Cell cycle regulator: regulates M phase (mitosis) of cell cycle
  - Cell cycle review:
    - G0 (Gap 0): cell resting (not dividing)
    - Interphase
      - G1: cell growth
      - S (synthesis): DNA replication
      - G2: cell growth
    - Mitosis: cell division
  - Deregulation leads to cellular transformation (unregulated proliferation)
- Example: myc
  - Transcription factor that regulates transcription of genes that lead to cell proliferation

Tumor suppressors
- These proteins play critical roles in controlling normal cell growth
  - Think of these as removing a red light at stages in cell growth
  - Many tumor supressors regulate proliferation by governing movement of cell through cell cycle
- Usually must loose/mutate both copies of gene (allele): loss of function
- Categories of tumor suppressors: DNA repair regulators, regulators of apoptosis (cellular suicide), intracellular signal transduction regulators
- Example: p53
  - Functions as a “cellular policeman”
    - Not involved in normal cell cycle regulation
    - Increased amount and lifespan of p53 during times of DNA damage
    - Regulates entry into the cell cycle AND stimulates DNA repair genes AND induces apoptosis (cellular suicide) if DNA damage too severe
  - Mutations, viral proteins (papilloma viruses), cellular proteins can inactivate p53
    - Inactivated p53 = loss of function
  - Because of its key role as a cell cycle regulator, if loose even one copy of p53, have unregulated cell cycle and thus have risk of cellular transformation
- Individuals that inherit one copy of a mutant copy have 25-fold greater risk of cancer by age 50
  - >50% of human neoplasms contain a mutation in p53

II. METASTASIS
- The spread of a tumor to a site different, and often distant, from its origin
  - Means that the tumor has successfully evaded host defenses
- Estimated ~30% of solid tumors in humans have metastasized by time of diagnosis
- A lot of cells may be shed from a tumor but only a very small amount of cells in circulation (<0.01%) give rise to a metastasis
- Not all malignant tumors metastasize
  - For unknown reasons, certain tumors rarely metastasize (intraocular, CNS)
- No benign tumors metastasize
- Pathways for metastasis to occur
  - Blood (hematogenous)
    - “1st capillary bed” theory
      - easy for tumor cells to become “caught” in the first vascular bed that they hit in the natural path of blood circulation
        - liver, lungs are common sites for metastatic tumors
          - Must examine these sites in cancer patients
            - i.e., tumor originating from GI tract hits the liver first
            - i.e., breast cancer tumor hits the lungs first
      - not a perfect theory, in reality slightly more complicated
        - Receptor interactions at cellular level mean there is a predilection of some sites of metastasis for certain tumors
  - Common in sarcomas
  - Lymphatics
    - Same idea as hematogenous: tumor cells can enter the lymph and gain access to distant sites in the body via lymph circulation
    - Spread to regional lymph nodes
    - Because lymphatics are connected to blood circulation, this method is not completely separate from hematogenous
    - Common in carcinomas
  - Implantation (transcoelomic)
    - A tumor breaks through the lining of an organ, tumor cells are shed and can coat adjacent organs
    - carcinomatosis: the seeding of the body cavities with tumor metastases
- Mechanism for metastasis
  - 1. Cells detach from main tumor mass
    - For cells to individualize, must down-regulate tight junctions
  - 2. Cells invade and pass through the basement membrane (BM) on which they normally rest atop
    - Tumor cells actively degrade BM by increased cellular protease activity
  - 3. Tumor cells enter and pass through the extracellular matrix (ECM)
    - Tumor cells contact components of the ECM (collagen, fibronectin, etc.) and up-regulate receptors for these components
    - At multiple points in metastasis, tumor cells actively migrate by interacting with the cytoskeleton and cellular adhesion structures
  - 4. Tumor cells invade blood vessels or lymphatics
  - 5. Cells travel through the bloodstream
    - Once inside, tumor cells tend to associate, forming a small clusters (embolus)
    - Tumor cell emboli may be recognized by the host’s immune system
6. Cells extravasate from vessel and invade ECM at metastatic site
7. Angiogenesis: blood vessel growth to support metastatic tumor cells
   - Tumors cannot grow beyond 1-2mm diameter without blood supply
     - Center of tumor mass would be starved of blood
   - Tumors able to induce new blood vessel growth for its own supply
   - Several angiogenesis inhibitors are FDA approved for use in humans as components of anti-cancer treatments
     - Theoretically fascinating, but efficacy has been disappointing
8. Growth of metastasis

III. PARANEOPlastic Effects
- Many cell types produce and secrete products (usually peptides) that normally function locally. However, when such cells become transformed and form masses, excessive amounts of this product may be produced and subsequently disrupt systemic homeostasis.
- Examples of paraneoplastic effects:
  - **Cachexia**
    - Term means loss of condition (loss of body fat and muscle mass), diminished immune system, and generalized weakness seen in many cancer patients
    - Effects are not proportional to size of tumor
    - It is not simple anorexia or starvation
    - Disturbances of metabolism of carbohydrates, proteins, & lipids
    - Not well understood, Tumor necrosis factor alpha (TNF-alpha), interleukin-1 (IL-1), and gamma interferon (IFN-gamma) may be involved
  - **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 the islets of the pancreas produce insulin, which in turn decreases blood glucose
      - Beta cell carcinoma (“insulinoma”) can lead to excess uncontrolled insulin release and thus hypoglycemia
    - Other tumors also have the ability to cause hypoglycemia
      - Not all mechanisms of lowered glucose by tumors are understood
  - **Hypercalcemia**
    - Increased calcium in the serum
    - Tumors can cause excess parathyroid hormone, the major regulator of calcium levels in the body
      - Neoplastic tissue may produce ectopic parathyroid hormone
    - High calcium can also occur via direct tumor invasion & destruction of bone; however, this method is not truly paraneoplastic but rather direct
    - Commonly seen in lymphoma patients
  - **Sertoli Cell Tumors: Feminization**
    - Sertoli cells are cells of the seminiferous tubules in the testes that secrete estrogen or estrogen-like substances
    - Believed that estrogen released usually only has local effects but when a tumor develops a large enough mass, enough estrogen is released that males become feminized
      - Feminization signs in dogs: symmetric hair loss, enlarged mammary glands, attractiveness to other male dogs
IV. INFECTIOUS CANCERS

Certain viral and bacterial infections can lead to cancer

- Example: Human papillomavirus (HPV)
  - Family of DNA viruses that infects stratified epithelium and mucous membranes
  - Some serotypes cause noncancerous warts by inducing skin proliferation
  - Other serotypes can cause cervical cancer
    - HPV-16 and HPV-18 responsible for 70% of cervical cancers
    - Infection causes a series of cytologic changes that ultimately convert squamous epithelium to glandular epithelium
      - Most infections naturally cleared by the host
      - Persistent infections w/ high risk serotypes lead to cervical cancer
    - Pap smear is a screen to look for abnormal cells (precancerous changes)
      - Most successful cancer screening test in history
      - Since the introduction of the pap smear there has been an 80% reduction in cervical cancer cases
      - Worldwide, cervical cancer is the most common cause of cancer death, but in the US it is #13 due to widespread usage of the pap smear
  - In 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, just most common, including HPV-16 and -18
    - No data currently that it prevents cancer (study would be long); rather, current data shows that it prevents the precursor changes that are seen before cervical cancer develops

Non viral/bacterial transmissible cancers (sometimes called “parasitic cancers” though they are not caused a parasite)

- Example: Devil Facial Tumor Disease (DFTD)
  - Tasmanian devils are carnivorous marsupials only found in Tasmania
  - Mysterious aggressive facial tumors arose in last 20 years
    - 1st case described in 1996, not appreciated until 2000
  - Pattern of cancer spread was that of an infectious disease
  - Fatal within 6-9 months of appearance of tumors
  - 50% decrease in natural population of devils, threatens extinction by 2035
  - Tumors are caused by a clonal line of malignant cells as an allograft
    - Tumor cells from all infected individuals are genetically similar
    - Different chromosome # between devil host (14) and cancer cells (13)
    - Likely a schwann cell (myelin sheath around neurons) that gave rise to this transmissible tumor
  - Pathogenesis not completely understood
    - Tumor cell spread via biting from affected host to unaffected host
    - Tumor cell evades host immune response (aided by inbred population)
    - Cells take up residence in new host and grow into large tumor
    - Ultimately grow so large that tumor can block vision, breathing, eating and resulting in death