Disorders of Cell Growth & Neoplasia

Lecture 1
Normal tissue growth & non-neoplastic growth disorders

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Recommended Textbook:
Complementary textbooks:

NORMAL TISSUE GROWTH AND CELL PROLIFERATION

Body / Organ Size

• total cell mass = number of cells (cell division - cell death) + size of cells

• controlled by intracellular programs (genes) which are regulated by extracellular signal molecules.
  ➤ stimulatory factors
  ➤ inhibitory factors

• net growth when excess of stimulators or deficiency of inhibitors.

NORMAL TISSUE GROWTH AND CELL PROLIFERATION

**CELL CYCLE**

- **G₀** (Quiescent, stable cells, e.g., hepatocytes)
- **G₁** (Centrosome duplication, Growth in mass)
- **S** (Chromosome duplication)
- **G₂** (Check for DNA damage (G₁/S checkpoint))
- **M** (Mitosis, Check for damaged or unduplicated DNA (G₂/M checkpoint))

**Continuous cycling labile cells** (e.g., epidermis, GI tract epithelium)

**Permanent cells** (e.g., neurons, cardiac myocytes)
Stem cells

- undifferentiated precursor cells that give rise to a variety of cell types.
- must exhibit asymmetric replication.

a) Embryonic Stem Cells

- from the inner cell mass of the blastocyst.
- can produce most cells / tissues of the body, except for extraembryonic tissue (= pluripotent). Only totipotent cells (zygotes) can produce any fetal or adult cell type.

b) Primordial Germ Cells

- progenitor cells which will form the gametes.

c) Adult (somatic) Stem Cells

- many adult tissues (eg marrow, skin, gut) contain stem cells.
- most adult stem cells are lineage specific (multipotent stem cells).
Stem Cells and Germ Cell Layers

Totipotent stem cell
Embryonic stem cells
Pluripotent stem cells

Multipotent stem cells
EMBRYONIC GERM LAYERS AND SOME OF THE TISSUES IN THEIR LINEAGES

ENDODERM (internal layer)
Pancreas
Liver
Thyroid
Lung
Bladder
Urethra

MESODERM (middle layer)
Bone marrow
Skeletal, smooth and cardiac muscle
Heart and blood vessels
Kidney tubules

ECTODERM (external layer)
Skin
Neurons
Pituitary gland
Eyes
Ears
Adult Stem Cells

STEM CELL STOREHOUSE

Bone marrow

Hematopoietic stem cell

Erythrocytes

Monocyte

Eosinophil

Basophil

Megakaryocyte

Platelets

Neutrophil

Dendritic cell

Adipocyte

Osteoblast

MAPC

T lymphocyte

B lymphocyte

Natural killer cell

Stromal stem cell

Multipotential stem cell

Mesenchymal stem cell

Myeloid progenitor cell

Lymphoid progenitor cell
**Stem cell niches in various tissues.**

**A.** Skin stem cells are located in the bulge area of the hair follicle, in sebaceous glands, and in the lower layer of the epidermis.

**B.** Small intestine stem cells located near the base of a crypt, above Paneth cells (stem cells in the small intestine may also be located at the bottom of the crypt).

**C.** Liver stem (progenitor) cells, known as oval cells, are located in the canals of Hering (thick arrow), structures that connect bile ductules (thin arrow) with parenchymal hepatocytes (bile duct and Hering canals are stained for cytokeratin 7).

DISTURBANCES OF GROWTH

• abnormal cell growth ranges from complete absence of tissue development (agenesis) to totally unregulated growth (neoplasia).

Agenesis

• complete failure of an organ / tissue to develop with no associated primordium.

Aplasia

• failure of an organ / tissue to grow due to failure of development of the primordium.

Hypoplasia

• failure of an organ / tissue to reach its normal size (less severe than aplasia).
Renal agenesis, unilateral

Unilateral renal agenesis if no primordial tissue found on histology. Unilateral renal aplasia if some primordial tissue found on histology.
Hypoplasia

Cerebellar hypoplasia (top), normal cerebellum (bottom), brain, cats

Unilateral hypoplasia (right side), testes, dog.

_Histo:_ **A:** Normal testis showing normal spermatogenesis (arrows). **B:** Hypoplastic testis. The seminiferous tubules are lined only by Sertoli cells (s) and there is no spermatogenesis. There is hyperplasia of Leydig cells (L).

Dysplasia

• in context of organ development, refers to abnormal organization of cells (‘abnormal growth’) eg retinal dysplasia, hip dysplasia, renal dysplasia, etc.

Hip dysplasia, bilateral, dog. Both femoral heads and acetabula are flattened and distorted by periosteal new bone proliferation (arrows)

Tricuspid valve dysplasia, kitten. The free edges of the tricuspid leaflets are directly attached to the papillary muscles (no chordae tendinae in between)
Causes of Developmental Anomalies

• failure of the progenitor cells to proliferate and differentiate appropriately.

1 Genetic causes:
   i) those associated with chromosomal (karyotypic) aberrations.
      - XX/XO mosaicism, etc.

   ii) those arising from gene mutation.
      - chondrodysplasia, collagen dysplasia, etc.

2 Environmental causes:
   i) in utero infections
      - BVD, FPV, etc

   ii) in utero exposure to radiation and drugs / chemicals / toxins
      - thalidomide, Veratrum plants, etc

3 Mutifactorial causes:
   • combination of hereditary and environmental factors.
Hyperplasia

- increased organ/tissue mass due to increased number of constituent cells.
- recall, hypertrophy and hyperplasia are not mutually exclusive.

a) Etiology
   i) Physiologic Hyperplasia
      • physiologic hormonal stimulation
      • compensatory hyperplasia
   
   ii) Pathologic Hyperplasia
      • excessive hormonal stimulation
      • chronic irritation (via growth factors)
Hyperplasia

b) Mechanisms / Biochemistry

• cell proliferation is generally due to:
  ➤ increased production of growth factors / hormones.
  ➤ increased expression of growth factor receptors.
  ➤ activation of specific intracellular signaling pathways.

• once the causative stimulus has been removed it will regress (cf neoplasia).

• pathologic hyperplasia is a “fertile soil” for the development of neoplasia.
**Histo: Regenerative nodules:** Nodules (N) are surrounded by thick bands of fibrous tissue (F)

**Hyperplasia**

**Cirrhotic liver** with multiple regenerative (hyperplastic) nodules, dog
Goitre, thyroid gland, goat fetus. Marked enlargement of the gland (T) due to diffuse.

Cortical hyperplasia (c) of adrenal glands stimulated by an ACTH secreting tumor (T) of the pituitary gland.
Proliferative enteropathy, ileum, pig. Note the prominent mucosal folds (left) in comparison with a normal ileum (right).

Histo: There is notable hyperplasia of enterocytes and intestinal crypts (top). Curved *Lawsonia* bacteria (arrow) are present in the apical cytoplasm of enterocytes (bottom).
Lichenification (epidermal hyperplasia), skin dog. Rough thickened epidermis secondary to persistent rubbing, scratching or irritation.

Histo: Epidermal hyperplasia, skin dog. Marked thickening of the epidermis (A, right micrograph) in comparison with a normal epidermis (arrow, left micrograph)
Nodular Hyperplasia

• causes of nodular hyperplasia are not fully known (preneoplastic):
  - hepatic nodular hyperplasia.
  - pancreatic nodular hyperplasia.
  - adrenal cortical nodular hyperplasia.
  - thyroid nodular hyperplasia.

• can be difficult to distinguish from benign tumors:

  grossly:  - hyperplastic nodules tend to be smaller size and often multiple.
            - benign tumors tend to be larger & usually single.

  microscopically: architecture more similar to that of the normal organ, has no capsule and no compression of adjacent tissue.
**Nodular hyperplasia**, liver, dog. Single pale, raised nodular mass (top left). **Histo (top right)**: The mass is well-defined, non-encapsulated and composed of pale (vacuolated) hepatocytes, pushing the adjacent normal parenchyma (arrows).

**Nodular hyperplasia**, liver, cut surface, dog. Two well-defined, unencapsulated, pale masses are embedded within the normal parenchyma.
Pancreatic nodular exocrine hyperplasia, pancreas, dog. Hyperplastic nodules are white and project above the surface (left, top). Microscopically hyperplastic nodules (N) are composed of numerous small, well differentiated acini (a).

Nodular adrenal cortical hyperplasia, adrenal gland, dog. Multiple white, confluent nodules (arrows) of cortical hyperplasia extend into the medulla.
Metaplasia

- a reversible change in which one adult cell type is replaced by another adult cell type.

- reflects the reprogramming of stem cells to differentiate along a new pathway.

- brought about by changes of soluble factors (cytokines, growth factors, ECM components) that affect tissue specific, differentiation genes.

- represents an adaptive substitution; where cells sensitive to stress are replaced by other cell types better able to withstand a new adverse environment.

- usually an orderly process & reversible (if persists can lead to cancer development).
Metaplasia of columnar to squamous epithelium. A, Schematic diagram. B, Metaplasia of columnar epithelium (left) to squamous epithelium (right) in a bronchus.

Dysplasia

- in the context of mature tissue, it refers to disordered growth of cells.
- see loss of uniformity of the individual cells & architectural disorganization.
- occurs primarily in epithelium; when severe can indicate neoplastic transformation.
- microscopically see cellular atypia:
  1. pleomorphism.
  2. nuclei often hyperchromatic, enlarged (↑ N/C ratio) & large nucleoli.
  3. mitotic figures are more numerous and often in abnormal locations.
  4. tissue architecture is often disorganized.
Normal squamous epithelium. Stratum basale (B), stratum spinosum /lucidum (S), stratum corneum (C).

Dysplastic squamous epithelium. There is no differentiation (maturation), so most cells look like basal cells.

Dysplastic squamous epithelium. Dysplastic cell show large (karyomegaly) hyperchromatic nuclei (arrows).
Hamartoma

- a benign tumor-like mass composed of an overgrowth of mature cells and tissues normally present in the affected part.

- present at birth & probably results from an overgrowth of progenitor cells in the fetus.

Vascular hamartoma (i.e. consisting of well differentiated blood vessels) on the dorsal surface of the tongue, 2-day-old bovine.
Proteus syndrome, a complex hamartomatous disorder characterized by asymmetrical gigantism, epidermal nevi, vascular malformations, hamartomas, lipomas and hyperostosis.
Choristoma

• a mass of histologically normal tissue in an abnormal location (ectopic rest).

Dermoid, cornea. A mass consisting of mature skin and its appendages.

Ectopic pancreatic tissue (choristoma), small intestine (arrow).

http://w3.vet.cornell.edu/nst/nst.asp
Cellular Aging

• aged cells have reduced proliferative & physiologic capacity and ↓ response to injury.

• cell aging is the result of existing cellular programs and the accumulation of metabolic and genetic damage.

Decrease in human physiologic capacities as a function of age.
(from Rubin’s Pathology, 5th edition)

a) Structural and Biochemical changes

• morphologically see organelle abnormalities (nuclei / mitoch. / golgi / ER / lipofuscin).

• functional reduced capacity of biochemical pathways.

• molecular level see increased protein cross-linking, accumulation of oxidative damage to DNA / proteins / membranes and increased misfolded proteins.
b) Accumulated metabolic / genetic damage

• with cell aging see shift in balance of progressive metabolic damage vs repair ability.

Robbin’s fig 1-43. Mechanisms of cellular aging. Genetic factors and environmental insults combine to produce the cellular abnormalities characteristic of aging.
c) Replicative Senescence
• cells have a limited capacity for replication, eg fibroblasts 20-60X in culture 1/α age.
• controlled by:
  ① clock genes
  ② telomere length / telomerase activity
c) Replicative Senescence

- telomerase is an enzyme that maintains telomere length.

Robbin's fig 1-45B. Telomere-telomerase hypothesis and proliferative capacity. Telomere length is plotted against the number of cell divisions. In normal somatic cells, there is no telomerase activity, and telomeres progressively shorten with increasing cell divisions until growth arrest, or senescence, occurs. Germ cells and stem cells both contain active telomerase, but only the germ cells have sufficient levels of the enzyme to stabilize telomere length completely. Telomerase activation in cancer cells inactivates the teleomeric clock that limits the proliferative capacity of normal somatic cells.