Disorders of Cell Growth & Neoplasia

Lecture 1
Normal tissue growth & non-neoplastic growth disorders
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 genes and regulated by extracellular signal molecules.
  ➤ stimulatory factors
  ➤ inhibitory factors

• Excess of stimulators or deficiency of inhibitors  ➔ net growth

NORMAL TISSUE GROWTH AND CELL PROLIFERATION

- most adult organs contain a mixture of cells with different capacities for cell division

1. **Continuously dividing (labile) cells**
   - proliferate throughout life; replace cells that are continuously lost
     eg. blood, skin, surface epithelia.

2. **Quiescent (stable) cells**
   - low level of division; respond rapidly to stimuli
     eg. parenchymal cells, fibroblasts, osteoblasts, chondroblasts, endothelia

3. **Nondividing (permanent) cells**
   - cannot undergo mitosis
     eg. Neurons, skeletal* and cardiac muscle
     * can regenerate if sarcolemmal sheaths intact
Stem cells

- undifferentiated precursor cells that give rise to a variety of cell types.
- asymmetric replication (maintain self renewing capacity & supply cells for replacement)

a) Embryonic Stem Cells

- from the inner cell mass of the blastocyst.
- produce most cells / tissues, 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)
• Restricted differentiation capacity (multipotent stem cells); lineage specific
Adult Stem Cells

STEM CELL STOREHOUSE

Bone marrow

Hematopoietic stem cell

Stromal stem cell

Adipocyte

Osteoblast

Multipotential stem cell

Mesenchymal stem cell

T lymphocyte

B lymphocyte

Natural killer cell

Erythrocytes

Monocyte

Myeloid progenitor cell

Lymphoid progenitor cell

Eosinophil

Basophil

Megakaryocyte

Platelets

Dendritic cell

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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

- Range 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.

Renal agenesis, unilateral.
K = left kidney, A = adrenal glands
Uterine aplasia, unilateral and segmental, pigs. Note the remnants of connective tissue (primordium; p)

**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)

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

Unilateral renal hypoplasia, calf.
Unilateral hypoplasia (right sided), 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. Leydig cells (L) are not affected.

Dysplasia

• **in organ development:** abnormal organization/maturation of cells (‘eg retinal dysplasia, hip dysplasia, renal dysplasia, etc.)

*Renal dysplasia,* dog. The external surface is lobulated. Cut surface reveals irregular thickness of the cortex and heterogeneous tissue.

*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) chromosomal (karyotypic) aberrations.
      - XX/XO mosaicism, etc.
   ii) 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 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)
b) Mechanisms / Biochemistry

- increased production of growth factors / hormones.
- increased expression of growth factor receptors.
- activation of specific intracellular signaling pathways.

• It is reversible, it regresses when stimulus is removed (unlike neoplasia).

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

**Hyperplasia**

**Cirrhotic liver** with multiple hyperplastic (regenerative) nodules, dog. From Noah’s arkive
Goiter, thyroid gland, goat fetus. Marked enlargement of the gland (T) due to diffuse proliferation of follicular cells.

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.
  - splenic nodular hyperplasia

- can be difficult to distinguish from benign tumors:

  grossly:  - small 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.
Nodular hyperplasia, spleen, dogs. Multiple, red to pale, firm, well-delineated and nonencapsulated nodules are present within the spleen. These are a common age-related change in dogs. Need to differentiate these masses from benign and malignant tumors.
Metaplasia

• one adult cell type is replaced by another adult cell type (e.g., squamous, intestinal, or bone metaplasia)

• reprogramming of stem cells to differentiate along a new pathway

• changes of soluble factors → tissue specific (differentiation) genes

• an adaptive substitution; cells sensitive to stress are replaced by a more resistant cell type

• causes:
  • chronic inflammation
  • vitamin A deficiency

• usually 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 mature tissues**, it refers to disordered growth of cells.

- loss of cell uniformity & architectural disorganization.

- primarily in epithelium; early indicator of neoplastic transformation.

- characterized by cellular atypia:
  1. **pleomorphism**.
  2. nuclei often hyperchromatic, enlarged (↑ N/C ratio) & large nucleoli.
  3. more mitotic figures; 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 organ

- present at birth (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.

Joseph Merrick photographed in 1889 “The Elephant Man”
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).