Cell Injury II – Cellular Adaptations

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Lecture Objectives

1. To illustrate the ways in which cell injury differs from apoptosis and necrosis

2. To list the various etiologies underlying hyperplasia, hypertrophy, and atrophy

3. To describe the role of metaplasia in tissue response to injury

4. To recognize the different types of intra- and extracellular accumulations of endogenous and exogenous substances
Figure 1-1 Stages of the cellular response to stress and injurious stimuli.
Hyperplasia

- Increase in the *number* of cells in an organ or tissue
- May or may not be seen together with *hypertrophy*
- Can be either *physiologic* or *pathologic*
Physiologic Hyperplasia

- Hormonal
  - Hyperplasia of uterine muscle during pregnancy; breast during puberty
- Compensatory
  - Hyperplasia in an organ after partial resection
- Mechanisms include increased DNA synthesis
- Growth inhibitors will halt hyperplasia after sufficient growth has occurred
Pathologic Hyperplasia

- Due to excessive hormonal stimulation
  - Endometrial proliferation due to increased absolute or relative amount of estrogen
- Due to excessive growth factor stimulation
  - Warts arising from papillomaviruses
- Not in itself neoplastic or preneoplastic – but the underlying trigger may put the patient at increased risk for developing sequelae (e.g., dysplasia or carcinoma)
Hypertrophy

- Increase in the size of cells leading to an increase in the size of the organ (often seen in tissues made up of terminally differentiated cells – they can no longer divide, \( \therefore \) their only response to the stress is to enlarge)
- End result is that the amount of increased work that each individual cell must perform is limited
- Can be either \textit{physiologic} or \textit{pathologic}
Hypertrophy (cont’d)

- Physiologic
  - Due to hormonal stimulation (e.g., hypertrophy of uterine smooth muscle during pregnancy)

- Pathologic
  - Due to chronic stressors on the cells (e.g., left ventricular hypertrophy due to long-standing increased afterload such as HTN, stenotic valves)
Figure 1-3 Physiologic hypertrophy of the uterus during pregnancy. A, Gross appearance of a normal uterus (right) and a gravid uterus (removed for postpartum bleeding) (left). B, Small spindle-shaped uterine smooth muscle cells from a normal uterus, compared with C, large plump cells from the gravid uterus, at the same magnification.
If the stress that triggered the hypertrophy does not abate, the organ will most likely proceed to failure – e.g., heart failure due to persistently elevated HTN.

Hypertrophied tissue is also at increased risk for development of ischemia, as its metabolic demands may outstrip its blood supply.
Atrophy

- Shrinkage in the *size* of the cell (with or without accompanying shrinkage of the organ or tissue)
- Atrophied cells are smaller than normal but they are still viable – they do not necessarily undergo apoptosis or necrosis
- 🔄 specialized organelles; less functionally capability than nonatrophic cells
- Can be either physiologic or pathologic
Atrophy (cont’d)

- **Physiologic**
  - Tissues / structures present in embryo or in childhood (e.g., thymus) may undergo atrophy as growth and development progress
  - Decreased hormonal stimulation (e.g., endometrial and ovarian atrophy after menopause)

- **Pathologic**
  - Decreased workload
  - Loss of innervation (e.g., spinal cord injury)
  - Decreased blood supply
  - Inadequate nutrition
  - Physical stresses (e.g., pressure)
Figure 1-5 Atrophy. A, Normal brain of a young adult. B, Atrophy of the brain in an 82-year-old male with atherosclerotic cerebrovascular disease, resulting in reduced blood supply. Note that loss of brain substance narrows the gyri and widens the sulci. The meninges have been stripped from the right half of each specimen to reveal the surface of the brain.
Metaplasia

- A *reversible* change in which one mature/adult cell type (epithelial or mesenchymal) is replaced by another mature cell type
  - If injury or stress abates, the metaplastic tissue *may* revert to its original type
- A *protective* mechanism rather than a premalignant change
Metaplasia (cont’d)

- Bronchial (pseudostratified, ciliated columnar) to squamous epithelium
  - E.g., respiratory tract of smokers
- Endocervical (columnar) to squamous epithelium
  - E.g., chronic cervicitis
- Esophageal (squamous) to gastric or intestinal epithelium
  - E.g., Barrett esophagus
Figure 1-6 Metaplasia of columnar to squamous epithelium. A, Schematic diagram. B, Metaplasia of columnar epithelium (left) to squamous epithelium (right) in a bronchus.
Reprogramming of epithelial stem cells (a/k/a reserve cells) from one type of epithelium to another

Reprogramming of mesenchymal (pluripotent) stem cells to differentiate along a different mesenchymal pathway
Intracellular Accumulations

- Cells may acquire (either transiently or permanently) various substances that arise either from the cell itself or from nearby cells
  - Normal cellular constituents accumulated in excess (e.g., from increased production or decreased/inadequate metabolism) – e.g., lipid accumulation in hepatocytes
  - Abnormal substances due to defective metabolism or excretion (e.g., storage diseases, alpha-1-AT deficiency)
  - Pigments due to inability of cell to metabolize or transport them (e.g., carbon, silica/talc)
Figure 1-29 Mechanisms of intracellular accumulations discussed in the text.
Lipids

- **Steatosis** (a/k/a fatty change)
  - Accumulation of lipids within hepatocytes
  - Causes include EtOH, drugs, toxins
  - Accumulation can occur at any step in the pathway – from entrance of fatty acids into cell to packaging and transport of triglycerides out of cell
- **Cholesterol** (usu. seen as needle-like clefts in tissue; washes out with processing so looks cleared out) – E.g.,
  - Atherosclerotic plaque in arteries
  - Accumulation within macrophages (called “foamy” macrophages) – seen in xanthomas, areas of fat necrosis, cholesterolosis in gall bladder
Figure 1-30 Fatty liver. A, Schematic diagram of the possible mechanisms leading to accumulation of triglycerides in fatty liver. Defects in any of the steps of uptake, catabolism, or secretion can result in lipid accumulation. B, High-power detail of fatty change of the liver. In most cells the well-preserved nucleus is squeezed into the displaced rim of cytoplasm about the fat vacuole. (B, Courtesy of Dr. James Crawford, Department of Pathology, University of Florida School of Medicine, Gainesville, FL.)
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Rubin Fig 1-12
Figure 1-31 Cholesterolosis. Cholesterol-laden macrophages (foam cells, arrow) in a focus of gallbladder cholesterolosis. (Courtesy of Dr. Matthew Yeh, Department of Pathology, University of Washington, Seattle, WA.)
Accumulation may be due to inability of cells to maintain proper rate of metabolism

- Increased reabsorption of protein in renal tubules → eosinophilic, glassy droplets in cytoplasm

Defective protein folding

- E.g., alpha-1-AT deficiency → intracellular accumulation of partially folded intermediates
- May cause toxicity – e.g., some neurodegenerative diseases
Figure 5-14 Gaucher disease involving the bone marrow. Gaucher cells (A, H&E; B, Wright stain) are plump macrophages that characteristically have the appearance in the cytoplasm of crumpled tissue paper (B), due to accumulation of glucocerebroside. (Courtesy of Dr. John Anastasi, Department of Pathology, University of Chicago, Chicago, IL.)
Glycogen

- Intracellular accumulation of glycogen can be normal (e.g., hepatocytes) or pathologic (e.g., glycogen storage diseases)
- Best seen with PAS stain – deep pink to magenta color
Pigments

- Exogenous pigments
  - Anthracotic (carbon) pigment in the lungs
  - Tattoos
Pigments

- Endogenous pigments
  - Lipofuscin ("wear-and-tear" pigment)
  - Melanin
  - Hemosiderin
Lipofuscin

- Results from free radical peroxidation of membrane lipids and proteins
- Not readily degraded → accumulate in long-lived cells (e.g., hepatocytes, myocardial cells)
- Finely granular yellow-brown pigment
Figure 1-33 Lipofuscin granules in a cardiac myocyte shown by (A) light microscopy (deposits indicated by arrows), and (B) electron microscopy (note the perinuclear, intralysosomal location).
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Melanin

- The only endogenous brown-black pigment
- Often (but not always) seen in melanomas
Hemosiderin

- Derived from hemoglobin – represents aggregates of ferritin micelles
- Granular or crystalline yellow-brown pigment
- Often seen in macrophages in bone marrow, spleen and liver (lots of red cells and RBC breakdown); also in macrophages in areas of recent hemorrhage
- Best seen with iron stains (e.g., Prussian blue), which makes the granular pigment more visible
Figure 1-34 Hemosiderin granules in liver cells. A, H+E stain showing golden-brown, finely granular pigment. B, Prussian blue stain, specific for iron (seen as blue granules).
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Dystrophic Calcification

- Occurs in areas of necrotic or dying tissue in the setting of normal serum calcium; also occurs in aging or damaged heart valves and in atherosclerotic plaques

- Gross: Hard, gritty, tan-white, lumpy
  - May cause organ dysfunction (e.g., valvular dz)

- Micro: Deeply basophilic on H&E stain; glassy, amorphous appearance; may be either crystalline or noncrystalline
Figure 1-35 Dystrophic calcification of the aortic valve. View looking down onto the unopened aortic valve in a heart with calcific aortic stenosis. It is markedly narrowed (stenosis). The semilunar cusps are thickened and fibrotic, and behind each cusp are irregular masses of piled-up dystrophic calcification.
Metastatic Calcification

- May occur in normal, viable tissues in the setting of hypercalcemia due to any of a number of causes (e.g., chronic renal failure)
  - Calcification most often seen in kidney, kidneys, lungs, arteries
  - Acid-excreting tissues (internal alkaline compartment) predisposes to metastatic calcification