

## CELL ADAPTATION/INJURY/DEATH

Reading: Basic Pathology, Chapter 1

**Introduction:** Injuries to cells may result in adaptive or retrogressive changes. Cell death involves two general processes: necrosis and apoptosis, that are not entirely distinct in their mechanisms. As part of adaptation to injury or during retrogression, cells may develop abnormal or increased levels of normal or abnormal constituents, termed inclusions.

### I. TYPES OF CHANGES TO BE STUDIED IN GENERAL PATHOLOGY

- A. Adaptive: cell growth changes - hyperplasia, atrophy, & hypertrophy
- B. Inflammation
- C. Repair/ Regeneration
- D. Retrogressive - degeneration, necrosis
- E. Neoplastic
- F. Hereditary and developmental

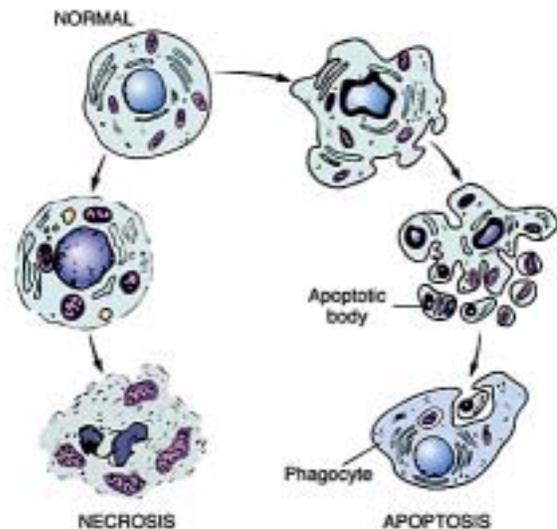
### II. GENERAL CAUSES OF DISEASE

- A. Environmental - chemical, physical, various parasites.
- B. Internal - genetic, developmental, degenerative, immunological.

III. **LESIONS** - gross, microscopic, biochemical, immunological.

### IV. RETROGRESSIVE CHANGES -CELL INJURY AND DEATH- NECROSIS, APOPTOSIS (Figure 1)

- A. Necrosis - Non-programmed cell death as a result of the degradative action of enzymes. Does not require energy. Effects on subcellular organelles: biochemical, physiological, and morphological changes;  $\uparrow$  intracellular Ca. Repair is possible to a point; then changes are irreversible, and cells form inclusions or activate and release intracellular lysosomal hydrolases, causing lysis & subsequent inflammatory response (as opposed to apoptosis).



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#### 1. Vulnerable sites in cells.

- a. Energy generating systems - mitochondrial damage results in lack of ATP and other critical metabolites. Resultant mitochondrial dysfunction causes free radical formation & membrane damage. Mitochondria also important in apoptosis.
- b. Membrane damage - failure of pump function due to mitochondrial damage and the lysosomal enzyme release result in characteristic cell swelling due to intracellular water and ion alterations - water, calcium and sodium enter cell, potassium exits.

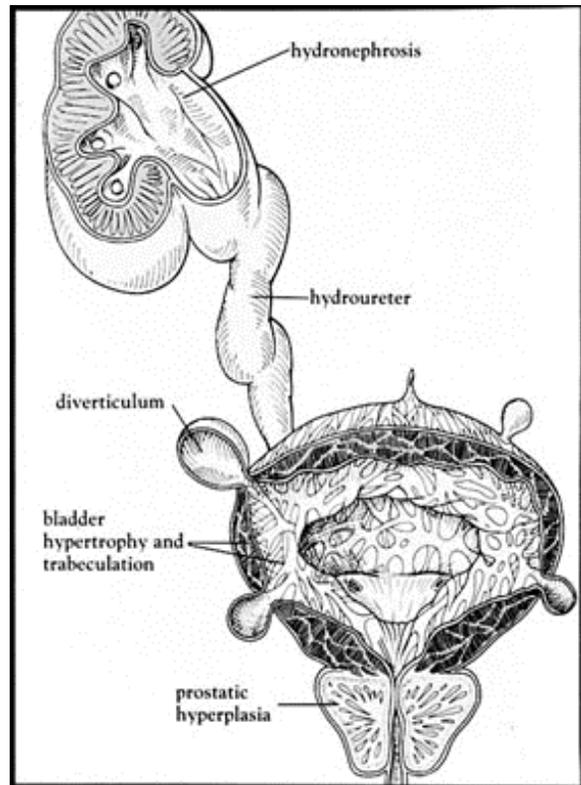
- c. Protein synthesis interrupted by disruption of polysomes. Glycosylation of proteins in diabetes - advanced glycosylation end products (AGEs).
  - d. Lipid metabolism decreased and membrane lipids damaged by free radicals.
- 2. More on membranes and free radicals.
  - a. free radicals - unpaired electron; their role in tissue damage, especially cytoskeletal & membrane damage; chromosome breaks due to damage to nucleic acids; cross-linking proteins. Critical enzymes are superoxide dismutases (SODs), catalase, and anti-oxidant systems - possible role of SOD mutations in amyotrophic lateral sclerosis (Lou Gehrig's disease)
  - b. Lysosomal membrane damage results in release into surrounding tissues of destructive enzymes
- 3. Examples of classical descriptions of morphological changes
  - a. cellular swelling - cloudy swelling & hydropic degeneration
  - b. hyalin change - glassy appearance - various causes such as denatured proteins
- 4. Types of cell necrosis: death at the tissue level. Calcification is often associated with necrosis. Infarct - a localized area of tissue death due to ischemia
  - a. coagulation necrosis. Cellular outlines and nuclei preserved until very late, inflammation, increased tissue eosinophilia. Ultimately, there is cell lysis and healing by fibrosis (a special form of coagulation necrosis is termed caseous necrosis - seen in TB, histoplasmosis, etc).
  - b. liquefaction necrosis - tissue liquefied by autolysis. Liquid often adsorbed resulting in a hole.
  - c. fat necrosis - seen in pancreas - relationship to lipases and calcium.
  - d. fibrinoid necrosis - see lectures on autoimmune diseases
- B. Apoptosis. This form of cell death is seen in atrophy, tumor regression, immunocytotoxic injury, during morphogenesis, and in response to hypoxia and radiation. It is characterized by nuclear segmentation with DNA fragmentation, by membrane blebs, and by cytoplasmic protein cleavage; so, cells program their own demise (Fig 1-1). Some gene products potentiate apoptosis (ex. p53, BAX); others inhibit it (ex. BCL-2, BCL-x). Proapoptotic proteins move from the cytoplasm to the mitochondrial membrane causing the release of cytochrome c into the cytoplasm; cytochrome c then associates with apoptotic protease activating factor (Apf-1) and procaspase-9, resulting in its activation and the activation of other caspases (esp. caspase-3) - see Fig 1-26 in text. Caspases inactivate proteins, disassemble cell structures, and contribute to fragmentation of DNA. Additional aspects of apoptosis are:
  - 1. nuclear fragmentation - pyknosis, karyorrhexis, and karyolysis as a result of DNA breaks. An endonuclease enters nucleus and chops DNA .
  - 2. phagocytosis of cell with no enzyme release or inflammation - absence of inflammatory response, as opposed to necrosis that is associated with inflammation.
  - 3. in some forms of apoptosis such as those involving TNF, caspase activation does not require cytochrome c or Apaf. There may be a form of apoptosis that does not involve caspases - release of an apoptosis-inducing factor (AIF) from stressed mitochondria, followed by generation of a potent nuclease.
  - 4. General mechanisms for induction of apoptosis:
    - a. positive: induction by injurious agents such as radiation or tumor necrosis factor (TNF) or TNF- like ligand; latter result in direct release of both caspases and nuclear transcription factor NF- $\kappa$ B (see inflammation lectures for more on NF $\kappa$ B).
    - b. negative: induction by absence of growth factor causing release of a caspase.
  - 5. Therefore, death at the cellular level can be explosive (necrosis after membrane

injury) or implosive (apoptosis); however, distinction is not absolute: necrosis may involve apoptotic mechanisms - a free radical product, radiation, chemicals, or oxygen deprivation may induce either. Cytochrome c release,  $\uparrow$  Ca, and caspase activation may be common to both processes. Mitochondrial loss of cytochrome c may release caspase activity (apoptosis) or disrupt oxidative phosphorylation (necrosis). In the ischemic region present immediately after a coronary occlusion, about 85% of myocytes show apoptotic changes, and 15% necrotic. Later, the cells that were initially apoptotic become necrotic.

- B. Lysosomal catabolism.
  - 1. Heterophagy - materials from environment taken up by cells by endocytosis. Phagocytosis involves uptake of particles; pinocytosis, of soluble macromolecules. End result is destruction by lysosomal enzymes.
  - 2. Autophagy - basically, self-phagocytosis by lysosomal enzymes.
  - 3. Autolysis - self-digestion; seen only in dead tissues. Drop in pH gives rise to activation of lysosomal enzymes. No inflammatory response.
    - a. Putrefaction. bacterial induced decomposition
    - b. Gangrene. putrefaction + necrosis.
- C. Response of Cells to Injury. Cells were thought to be passive in the face of the various insults to which they are subject. In actuality, almost all cells respond to stress by synthesizing heat-shock proteins (HSPs), often chaperones, that protect against aggregation or promote proper folding of proteins. At least one HSP is also an antioxidant. Ubiquitin is a protein HSP, that is added to proteins destined for destruction, which then takes place in proteasomes. An important degenerative disease of the CNS, Parkinson's Disease, is now thought to be due to dysfunction of ubiquitination, resulting in accumulation of toxic proteins.

- V. **CELLULAR INCLUSIONS/** extracellular infiltrations: accumulations of abnormal or excess of normal substances that don't belong where you see them. Loss of intracellular balance.
  - A. fatty change - fat in parenchymal cells; usually liver but may be present in heart, muscle, or kidney
  - B. carbohydrates - glycogen storage diseases are rare congenital diseases; advanced glycation end products (AGEs), caused by non-catalytic glucose addition to proteins, are seen in poorly controlled diabetics.
  - C. complex lipids or carbohydrates - various storage diseases
  - D. pigments - exogenous - carbon (anthracosis); endogenous-lipofuscin, melanin, bilirubin. Numerous other exist.
  - E. calcification
    - 1. dystrophic calcification - deposition of calcium in damaged or dead tissues; blood calcium level normal.
    - 2. metastatic calcification - occurs when the solubility product ( $\text{Ca}^{++} \times \text{PO}_4^{-3}$ ) is exceeded. This may happen when  $\text{Ca}^{++}$  is high, or normal. In the latter instances, phosphate is high.
  - F. iron - iron is adsorbed from the gastrointestinal tract, transported by transferrin in the blood, and deposited in tissues as ferritin; denatured iron in tissues is termed hemosiderin, and an excess is hemosiderosis; hemochromatosis is a disorder in iron adsorption leading to large excess of iron in tissues; mutation present in 10% of Americans of European origin.
  - G. uric acid - overproduction or decreased excretion seen in gout
  - H. amyloid -  $\beta$  pleated protein sheets deposited in tissues in several disease states result in pressure atrophy and organ dysfunction.

- VI. **ADAPTIVE CHANGES.** (Fig. 2) These can be physiological or pathological.
- Atrophy - an acquired decrease in cell number and/or size resulting in a decrease in organ size. Apoptosis is often important in atrophy. Can be due to decreased workload (disuse), denervation, decreased blood supply, poor nutrition, loss of endocrine stimulation, abnormal pressure, aging, etc.
  - Hypertrophy - an increase in cell (and thus organ) size; usually occurs in non-dividing cells that perform work.
  - Hyperplasia - a regulated increase in cell number; occurs in cells with capacity to divide. Both hypertrophy and hyperplasia may be regulated by cell growth genes.
  - Metaplasia - reversible change from one adult cell type to another. Usually as a result of chronic irritation.
  - Dysplasia - alteration in size, shape, or organization of adult cells. Pre-cancerous. See neoplasia lectures later.



- VII. **AGING.** Damaged or senescent cells are usually removed by apoptosis, but inappropriate apoptosis may also remove irreplaceable cells such as neurons, thereby resulting in dysfunction.
- Among other possible causes, the following have been considered responsible for aging: programmed cell life span, cumulative DNA damage (mutations), neuroendocrine programming, decreased activity of the immune system, cumulative free radical damage, defects in the insulin/insulin-like growth factor signaling pathway, defects in DNA repair, poor calorie restriction, activity of SIR2, a histone deacetylase, and recurrent injuries to vital organs.
  - It is currently thought that senescence may be due at least in part to telomere shortening in combination with the accumulated effects of mutations and free radical damage (see Fig. 1-27 in text). For instance, short-lived birds lose more telomeric sequences with aging than do long-lived species. Telomeres protect chromosomal DNA from degradation. They are there because a polymerase replicating DNA can't make it to the end of the DNA strand it's copying. In the absence of telomerase, the length of DNAs shorten with each cell division, which is exactly what happens in normal human cell, leading to an end to cell division (senescence). The telomerase complex consists of 20-70 terminal DNA -TTAGGG-repeat telomeres, an RNA template, and the telomerase enzyme, a reverse transcriptase that makes telomeres. Telomerase is absent in most normal human tissues, but is expressed in cancers.
  - Tying things together: In heart failure it is thought that stretching of heart muscle fibers leads to shortening of telomeres, that in turn causes caspase activation and apoptosis.

Summary: It's important for you to learn about cell death mechanisms. Most pathological conditions you will treat (coronary occlusions, infections, etc) end in necrosis, unless you intervene. Regulation of apoptotic death is under intense study; a mechanism for activating apoptosis in unwanted tissues (malignant tumors, for instance) may be developed in the

foreseeable future. The nature of inclusions may provide clues to the diagnosis of some diseases.