Acute irreversible cellular injury

Cell death

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Necrosis in rapidly growing tissue – SCC in lung
Two major forms of cell death

APOTOPSIS
- Morphologically distinct
- Energy dependent
- Requires protein synthesis
- Does not trigger inflammation
- “Programmed cell death”
- Extrinsic and intrinsic pathways
  - Important for:
    1. Homeostasis
    2. Development
    3. Unnecessary cellular stress
    4. Neoplasia
    5. Control of viral (and other) infections

ONCOSIS
- Morphologically distinct
- Energy independent
- No protein synthesis
- Triggers inflammation
- Also:
  - Cellular swelling
  - Breakdown in mechanisms supplying energy
  - Ruptured cell membranes

Important for:
1. Homeostasis
2. Development
3. Unnecessary cellular stress
4. Neoplasia
5. Control of viral (and other) infections

Breakdown in mechanisms supplying energy
Ruptured cell membranes
After cells die - NECROSIS

Most commonly:
- Oncotic necrosis
- Also: apoptotic necrosis

Typically: inflammatory reaction and fever
Events:
- Calcium salts
- Cholesterol deposits
- Membrane phospholipids form myelin figures

Types:
- Coagulative necrosis
- Liquefactive necrosis
- Caseous
- Fat necrosis
- Gangrene:
  - Wet – modified by bacteria; includes gas gangrene
  - Dry – modified by air

Coagulative necrosis – example: renal infarct

Liquefactive necrosis – example: Russian knapweed intoxication
Hemorrhagic necrosis in ovine brain - dehorning injury

Caseous necrosis – example: TB in lung

Fat necrosis – example: mesenteric tissue
Cell death and necrosis in special tissues

- Central nervous tissue
  - Excitotoxicity (esp. L-glutamate)
  - Esp. prone to free radical damage (iron)
  - Liquefaction
    - High fat content and scant connective tissue
- Adipose tissue:
  - Steatonecrosis
  - Local irritant
  - Calcification (“taches de bougie” – candle wax)
- Bone tissue:
  - “Sequestrum” when infected
- Luminal organs like gut:
  - Bacterial complications
Mitochondrial events in cellular injury leading to necrosis or apoptosis.
Intracellular sources of free radicals

- Normal redox reactions generate free radicals
- Nitric oxide (NO) acts free radical
- Ionizing radiation (UV, X-rays) hydrolyzes water to hydroxyl (OH·) and hydrogen (H·) free radicals
- Metabolism of some exogenous chemicals (e.g., CCl₄) generates free radicals
- Free radical generation during physiological antimicrobial reaction
### Dealing with free radicals

- Spontaneous decay
- Superoxide dismutase (SOD):
  - \( 2\text{O}_2^- + 2\text{H} \rightarrow \text{O}_2 + \text{H}_2\text{O}_2 \)
- Glutathione (GSH):
  - \( \text{OH}^+ + 2\text{GSH} \rightarrow 2\text{H}_2\text{O} + \text{GSSG} \)
- Catalase:
  - \( 2\text{H}_2\text{O}_2 \rightarrow \text{O}_2 + \text{H}_2\text{O} \)
- Endogenous and exogenous antioxidants (vitamins E, A, C and \( \beta \)-carotene)

### Free radicals that are not neutralized

**Cellular damage due to**
- Lipid peroxidation of membranes:
  - Double bonds in polyunsaturated membrane lipids vulnerable to attack by oxygen free radicals
- DNA fragmentation:
  - Free radicals react with thymine in nuclear and mitochondrial DNA and produce single strand breaks
- Protein cross-linking:
  - Free radicals promote sulphydryl-mediated protein cross-linking, resulting in increased degradation or loss of activity

### Reperfusion injury

- If cells are reversibly injured due to ischemia, restoration of blood flow paradoxically results in accelerated injury
- Clinically important
  - Esp. myocardial and cerebral infarctions (human)
  - Esp. intestinal injury (horses)
- Exact mechanisms are unclear, but
  - Restoration of flow exposes compromised cells to high concentrations of calcium,
  - Reperfusion results in increased free radicals production from compromised mitochondria and circulating inflammatory cells
Apoptosis
Viable cell
Apoptosis
Viable cell
Necrosis
Membrane damage
- Reactive oxygen species
- Lipid peroxidation
- Phospholipid synthesis
- Phospholipid degradation
- Cytoskeletal damage
- Cytochrome C activation
- Protease activation
- Lipid breakdown products
Autolysis

- Self-digestion of tissues after death
- Necrosis and post-mortem autolysis are different processes
- Two major components for degradation of carcass:
  - Autolytic enzymes
  - Clostridial overgrowth
- Retarded by cooling of carcass (or tissue(s))
- Hierarchy of rate of autolysis:
  - Fast: kidney/gallbladder/pancreas/mucosa/retina/liver
  - Moderate: brain and muscle
  - Slow: skin and testes