Chapter 1

CAUSES, PATHOGENESIS AND MORPHOLOGY OF CELL INJURY

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Cell Injury

- Stressed so severely, can’t adapt further
- Exposed to inherently damaging agents
- Reversible or irreversible
- Outcome depends on
  - Type, duration and severity of injury
  - Type, state, and adaptability of cell
Agents of cell injury

1. Oxygen (too much or too little)
2. Physical agents (trauma, temp, pressure, electric shock)
3. Chemical agents (CN⁻, Hg, O₃, CO, EtOH, drugs, ROS)
4. Infectious agents (viruses, bacteria, fungi)
5. Immunologic reactions (anaphylaxis, autoimmune diseases)
6. Genetic defects (Sickle cell disease, Down synd, Tay-Sachs)
7. Dietary (vitamins def/x’s, malnutrition, x’s calories)
Mechanisms of cellular injury

- ATP depletion
- Mitochondrial damage
- Membrane damage
- Altered ion concentrations (Na, K, Ca)
- Activation of proteases, phospholipases
- Inactivation of enzymes
- Proteolysis of cytoskeleton
- Detachment of ribosomes
- Increased ROS production
- DNA damage
Important targets of injury

- Mitochondria (aerobic respiration; apoptotic signals)
- Membranes (cell and subcellular organelles)
- Protein synthesis machinery
- Cytoskeleton
- Genetic apparatus (DNA)
Agents of cell injury

Oxygen

1. Too much via ROS production

2. Too little via
   hypoxia.....decreased $O_2$ content of blood
   ischemia.....inadequate blood flow (compromises delivery of nutrients and removal of wastes)

NB: ischemia worse than hypoxia
Ischemia → Mitochondrion → ↓ Oxidative phosphorylation → ↓ ATP → ↓ Na pump, ↑ Influx of Ca++, H₂O, and Na⁺, ↑ Efflux of K⁺ → ER swelling, Cellular swelling, Loss of microvilli, Blebs, ↑ Anaerobic glycolysis → ↓ Glycogen, ↓ pH → Clumping of nuclear chromatin → ↓ Protein synthesis → Detachment of ribosomes, etc. → Lipid deposition
Mitochondrial injury or dysfunction
(Increased cytosolic Ca^{2+}, oxidative stress, lipid peroxidation)

ATP production

Cytochrome c

Mitochondrial permeability transition (MPT)

Cytochrome c, other pro-apoptotic proteins

Mitochondrial membrane

Apoptosis

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Ischemia-reperfusion Injury

ATP → ADP → AMP → Adenosine → Inosine → \( ^{\uparrow} \text{Hypoxanthine} \)

Ischemia

XDH → No Rx (no O_2)
Ischemia-reperfusion injury

XDH (xanthine dehydrogenase)

Ca-activated protease

XO (xanthine oxidase)
(produces uric acid + superoxide)
Ischemia-reperfusion Injury

ATP → ADP → AMP → Adenosine → Inosine → \( \uparrow \) Hypoxanthine → Reperfusion

Reperfusion

\( \text{Ca-activated protease} \)

\( \text{XDH} \)

\( \text{XO} \)

O2 → Uric Acid + Superoxide

PMNs
Reactive Oxygen Species (ROS)

- Have unpaired electron (most)
- Very-to-Extremely reactive
- Non-specific
- Self propagating
- Referred to as ROS, ROM, free radicals
- Usually damaging (2 exceptions)
Major ROS

- Superoxide ($O_2^-$)
- Hydrogen peroxide ($H_2O_2$)
- Hydroxyl radical (HO·)
- Nitric oxide (NO·)
Sources of ROS

- UV light, ionizing radiation
- Mitochondrial ETS
- Enzymes (P450, XO, NADPH oxidase)
- Reduced metals (Fe, Cu, etc)
  - NB: Fenton reaction
Effects/Targets of ROS

- Membranes (lipid peroxidation)
- Proteins (via SH, TRP and TYR ox, etc)
  - Cross linking; fragmentation
- DNA damage
  - Strand breakage, T-T dimers
A. FREE RADICAL GENERATION

- Inflammation
- Radiation
- Oxygen toxicity
- Chemicals
- Reperfusion injury

- P-450 oxidase
- NADPH oxidase

- Reactive oxygen species:
  - $O_2^\bullet-$, $H_2O_2$, $OH^-$

- Membrane lipid peroxidation
- Protein cross-linking and fragmentation
- DNA fragmentation

B. CELL INJURY BY FREE RADICALS

- ER
- Mitochondrion
- Respiratory chain enzymes
- Cytosolic enzymes
- Peroxisome
- Oxidase

- All membranes
  - Vitamins E and A
  - $\beta$-carotene

- Mitochondria
  - SOD
  - Glutathione peroxidase
  - Ferroin
  - Ceruloplasmin

C. NEUTRALIZATION OF FREE RADICALS – NO CELL INJURY
Cellular defenses against ROS
(Antioxidants)

- Enzymatic
  - SOD, catalase, GPX
- Non-enzymatic
  - Vitamins A, C, E
  - Glutathione (GSH)
  - Metal binding proteins (transferrin, ceruloplasmin, etc)
  - NB: lipid and water soluble species