

## GENERAL PATHOLOGY

### LECTURE – 5

## CELL INJURY Contd.

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## CELL INJURY

### 2. MEMBRANE DAMAGE

#### – Direct Damage

- **Bacterial toxins.** Clostridium –phospholipase
- **Viral proteins.**
- **Cytolytic lymphocytes.**
- **Physical agents.**
- **Irradiation**
- **Chemical toxins or drugs**
- **Complement Components**

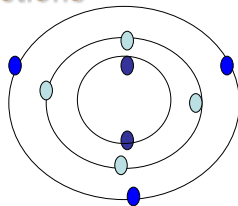
#### – Lipid peroxidation      Free Radicals

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### Membrane Damage

- **Lipid peroxidation**
- **Free Radicals**

- **F.R.** Chemical has unpaired electron in outer orbit -- **oxidation reduction reactions**



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### Membrane Damage

- **Free Radicals**

- can react with

- **Organic and**
- **Inorganic substances**
  - **Proteins**
  - **Lipids**
  - **Nucleoproteins**

**Making them useless or unstable**

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**Membrane Damage**

- **Free Radicals**
  - **Once this reaction is started**
  - **it continue...**

The diagram illustrates a chain reaction of free radicals. On the left, two atoms are shown with their outer shells and valence electrons. An arrow points to the right, where the atoms have formed a bond, and a radical (represented by a blue dot) is transferred to the second atom. A curved arrow at the bottom indicates that this process continues.

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**Membrane Damage**

- **Carbon tetrachloride (CCl<sub>4</sub>)**

$$\text{CCl}_4 \xrightarrow[\text{Cytochrome P450}]{\text{Mixed function Oxidases}} \text{CCl}_3 + \text{Cl}$$

$$\text{CCl}_3 + \text{Cl} + \text{Lipids} \longrightarrow \text{Lipid radical}$$

$$\text{Lipid Radical} + \text{O}_2 \longrightarrow \text{Lipid peroxy radical}$$

The flowchart shows the metabolic activation of carbon tetrachloride. CCl<sub>4</sub> is converted to CCl<sub>3</sub> and Cl by mixed function oxidases and cytochrome P450. The CCl<sub>3</sub> and Cl then react with lipids to form a lipid radical, which subsequently reacts with O<sub>2</sub> to form a lipid peroxy radical. A curved arrow at the bottom indicates the continuation of the reaction.

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**Membrane Damage**

- **Carbon tetrachloride (CCl<sub>4</sub>)**

$$\text{Lipid Radical} + \text{O}_2 \longrightarrow \text{Lipid peroxy radical}$$

$$\text{Lipid radical} + \text{Lipid peroxide} \longrightarrow \text{Lipid radical} + \text{Lipid peroxide}$$

**Lipid peroxide -- highly unstable -- break down ⇒ aldehydes**

The diagram shows the conversion of a lipid radical to a lipid peroxy radical by reacting with O<sub>2</sub>. Below, a cycle is shown where a lipid radical reacts with a lipid peroxide to produce another lipid radical and a lipid peroxide. A note states that lipid peroxide is highly unstable and breaks down into aldehydes.

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**Membrane Damage**

- **Free Radicals**
  - **Also degrade enzymes**
    - **Fragmentation of polypeptide chains**
    - **Cross-linking sulfhydryl (-SH) groups**
  - **DNA**
    - **Strands break**
    - **Abnormal cross linking**

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### Membrane Damage

- **Lipid peroxidation**
  - Main attack is membrane (especially of organelles)
  - Cu and Fe -- catalyst
    - Mitochondria -- cytochromes
    - ER
- Lysosomal membranes – slightly resistant

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### SOURCES OF FREE RADICALS

- Reduction-oxidation (redox) reactions
  - Normal physiologic activity produces free radicals.
  - At the end of the mitochondrial respiratory chain, O<sub>2</sub> accepts electrons in forming water with protons (hydrogen).
    - During this process, toxic intermediates form: •O<sub>2</sub>, H<sub>2</sub>O<sub>2</sub>, •OH.
  - Cellular (P-450) oxidases also produce free radicals.
- Fenton reaction
  - Ferrous iron catalyzes free radical formation, a major process in areas of hemorrhage.

Not very damaging

$\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \cdot\text{OH} + \text{OH}^-$

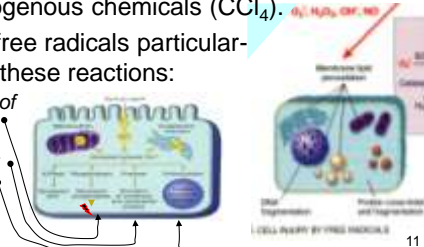
Very damaging

- Most cellular iron is ferric, but •O<sub>2</sub><sup>-</sup> donates an electron → Fe<sup>2+</sup>.

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### SOURCES OF FREE RADICALS

- NO is a widespread chemical mediator
  - Can act as a free radical.
  - Can be converted into peroxynitrite.
    - O<sub>2</sub><sup>-</sup> + NO + H<sup>+</sup> → ONOOH (peroxynitrite) → •OH + NO<sub>2</sub>.
- Ionizing radiation (UV light, X-rays)
  - H<sub>2</sub>O hydrolyzed into •OH and •H (hydrogen) free radicals.
- Breakdown of exogenous chemicals (CCl<sub>4</sub>).
- Cellular injury by free radicals particularly occurs through these reactions:
  - Lipid peroxidation of membranes.
  - Protein cross-linking.
  - DNA fragmentation.
  - All similar to Ca<sup>2+</sup> damage.



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### Membrane Damage

#### ANTI F.R.

$$\text{OH}^\bullet + \text{GSH} \longrightarrow \text{H}_2\text{O} + \text{GSSH (Oxidised)}$$

$$2\text{H}_2\text{O}_2 \xrightarrow{\text{catalase}} \text{O}_2 + 2\text{H}_2\text{O}$$

$$\text{O}_2^\bullet + \text{O}_2^\bullet + 2\text{H} \xrightarrow{\text{SOD (Cu)}} \text{H}_2\text{O}_2 + \text{O}_2$$

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**Membrane Damage**

**ANTI F.R.**

**Vitamin E**

$$\text{ROO}^\bullet + \text{TocOH} \longrightarrow \text{ROOH} + \text{TocO}^\bullet$$

$$\text{ROO}^\bullet + \text{TocO}^\bullet \longrightarrow \text{ROOH} + (\text{non-radical product})$$

ROO<sup>•</sup> = Peroxyl radical  
 ROOH = Hydroperoxide  
 TocOH = (Vitamin E or tocopherol)  
 TocO = Oxidized tocopherol radical

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**Membrane Damage**

**ANTI F.R.**

**Vitamin C**

**Similar to vitamin E**

**Vitamin E**      **Fat soluble places**  
**Vitamin C**      **Water soluble places**

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- Getting rid of free radicals
  - Spontaneous decay.
  - Enzyme systems.
    - Superoxide dismutases.
    - Glutathione peroxidase.
    - Catalase.
  - Vitamins A, C and E, and β-carotene.
- Sequestered heavy metals
  - Free ionized iron and copper are not readily available to catalyze the formation of reactive oxygen species because the cell partitions them in storage and as transport proteins.
    - Ferritin, transferrin, ceruloplasmin.

NEUTRALIZATION OF FREE RADICALS—NO CELL INJURY

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