Free radical theory of aging

M.Sc. Course in Free Radicals & Antioxidant

For post graduate students

by

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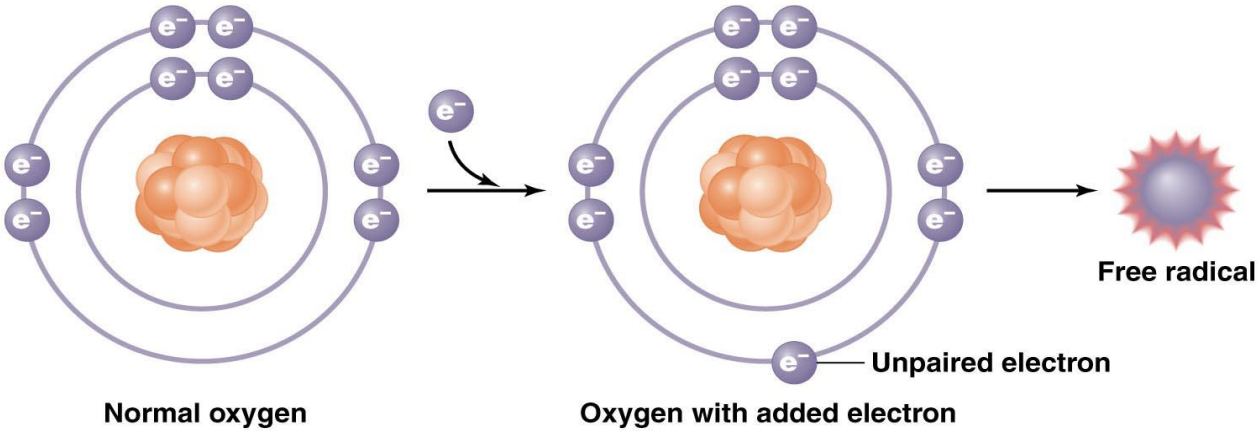
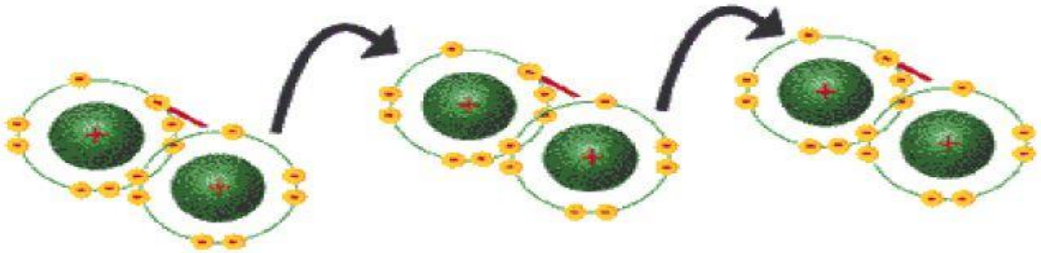
Contents

Introduction

- A free radical is defined as any species that contains one or more unpaired electron occupying an atomic or molecular orbital.



- As they are highly reactive and unstable, they pull electron from other molecules and cause affected molecules to become free radical and then new free radical pull electron to next molecules , so chain is produce .



Examples of free radicals- Superoxide anion, Hydroxyl radical , Peroxynitrite, Hydrogen radical, Nitric oxide , Lipid peroxyl .

Postulates of free radical theory of aging

In 1956s Dr. Denham Harman studied -

- The rate of living theory, which holds that lifespan is an inverse function of metabolic rate which in turn is proportional to oxygen consumption .
- Rebbeca Gershman's observation that oxygen toxicity and radiation toxicity could be explained by the same underlying phenomenon: oxygen free radicals.

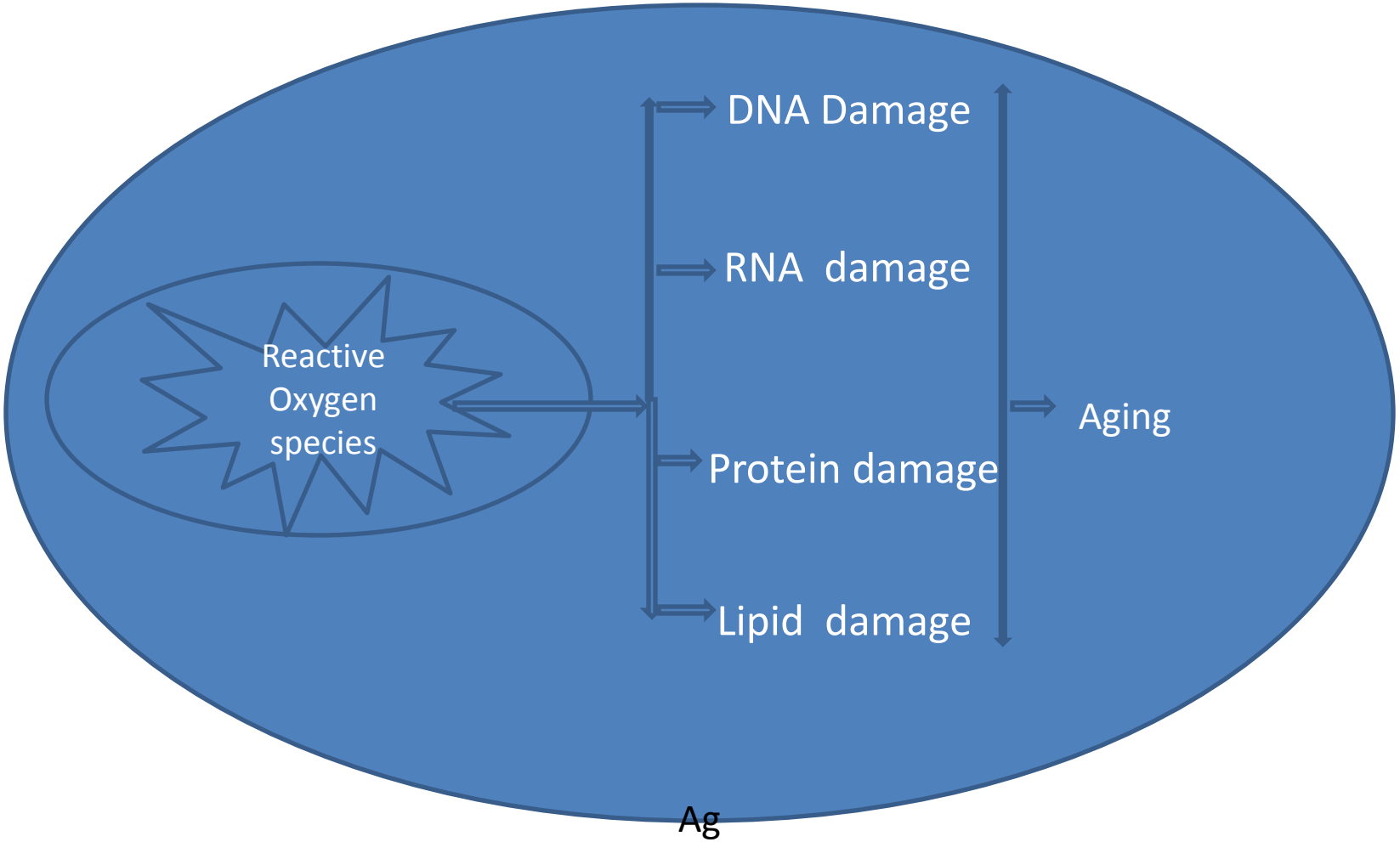
On basis of these , he proposed that-

Cells continuously produce free radicals by normal metabolism and oxidation of organic compounds and these free radicals damage cellular macromolecules (like DNA , lipid , proteins) and due accumulation of these damage over time period cause aging.

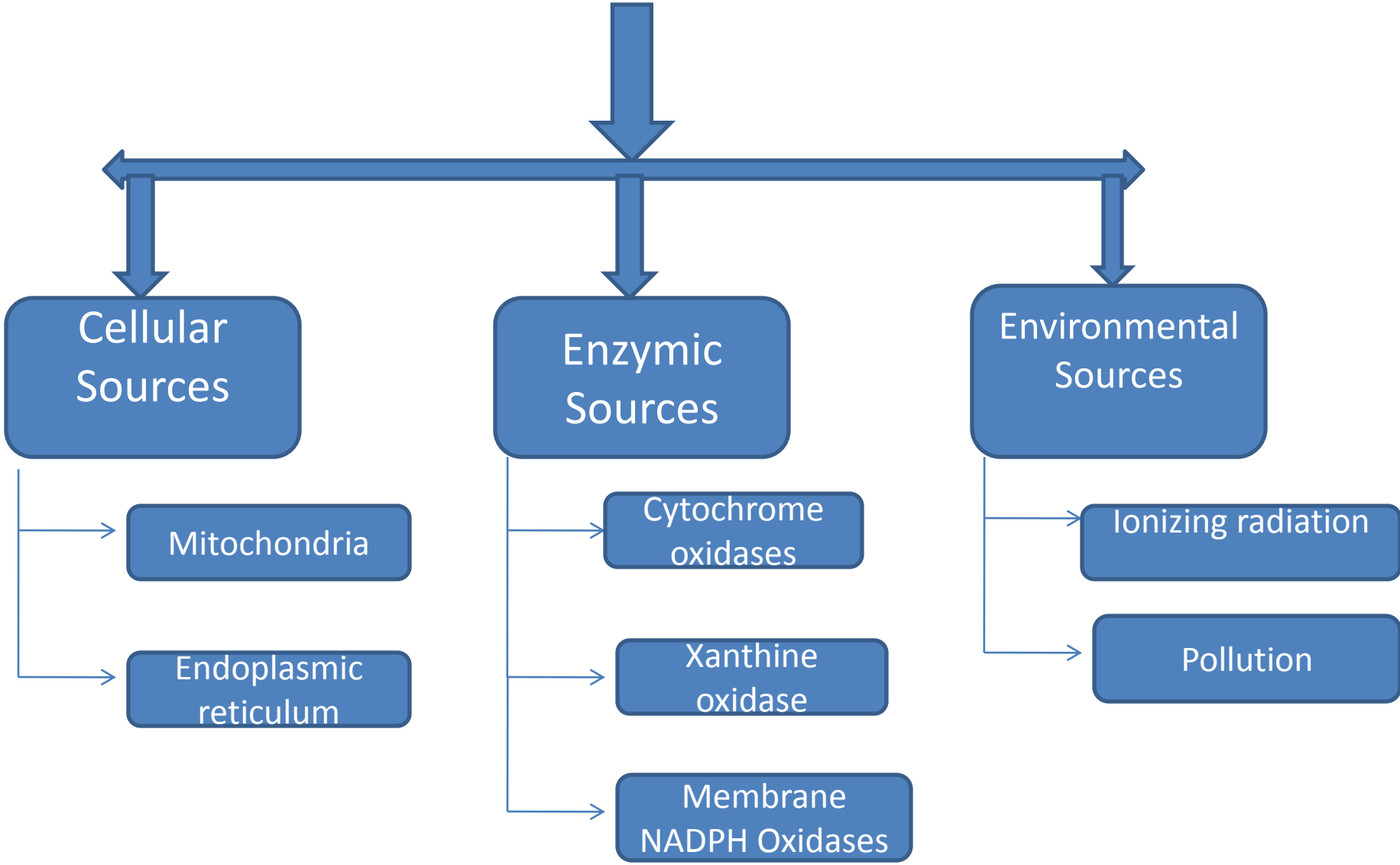
Mitochondrial free radical theory of aging

In 1972s, Denham Harman modified his theory-

- About 95% energy of a cell is produce in mitochondria and about 97% - 99% of oxygen is use in energy formation and 1%- 3% oxygen is utilize in reactive oxygen species formation.
- It states that reactive oxygen species (ROS) are produce in mitochondria during electron transport chain -ETC cycle and they cause damage to macromolecules including lipid , protein, DNA of mitochondria and nucleus which lead to aging .

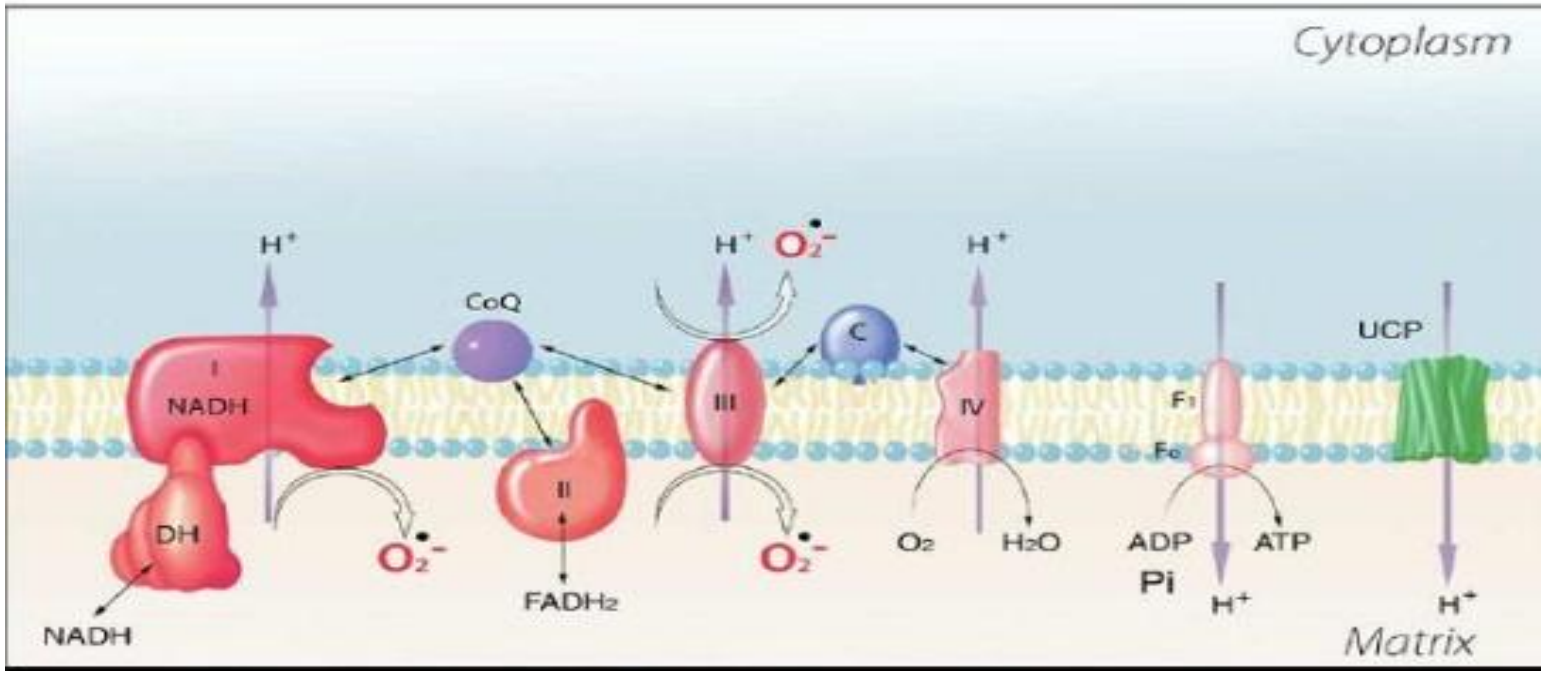


Sources of free Radicals



Mitochondria غير مطلوب

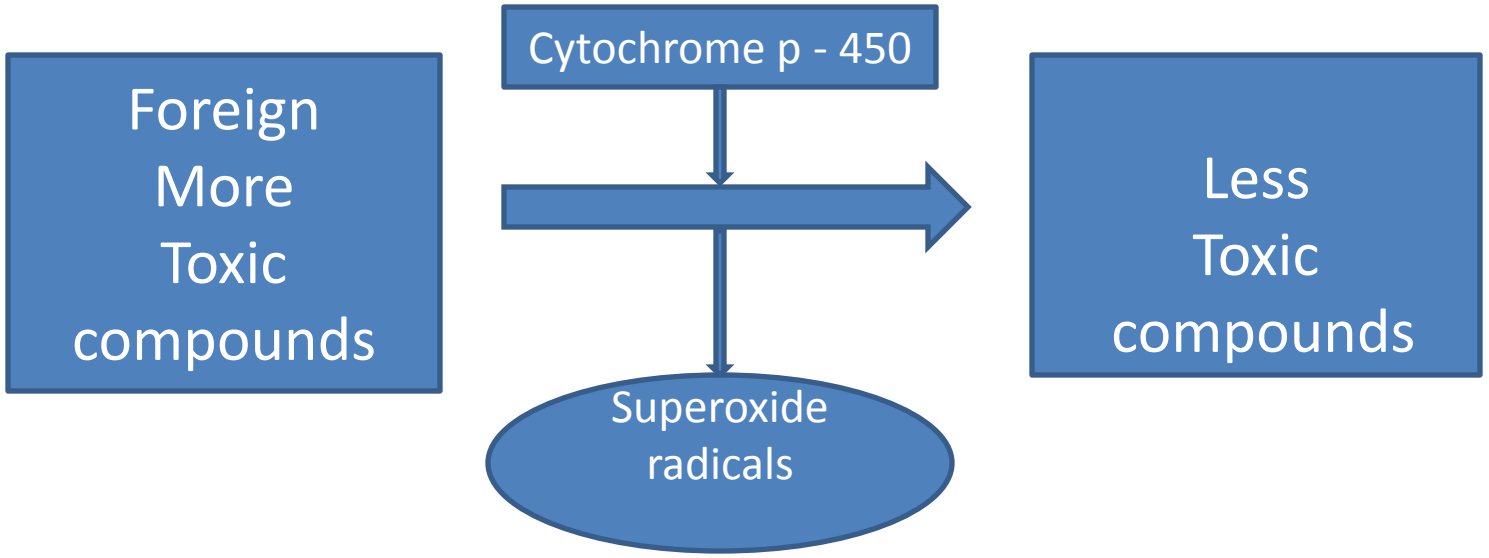
- **Mitochondria are major cellular sources of reactive oxygen species.**
- **1-3% of the total oxygen consumed by mitochondria, is associated with the generation of oxygen radicals**
- **The passage of electrons from QH_2 to complex III . and passage of electrons from complex I to QH_2 , involve $Q^{\cdot -}$ as an intermediate the $Q^{\cdot -}$ can ,with low probality, pass an electron to O_2 in the reaction**
- **Intermediate Ubisemiquinone donates one electron to molecular oxygen yielding superoxide anion and ubiquinone; this is known as autooxidation of Ubisemiquinone.**



- $O_2^{\bullet -} + O_2^{\bullet -} + H^+ \longrightarrow H_2O_2 + O_2$

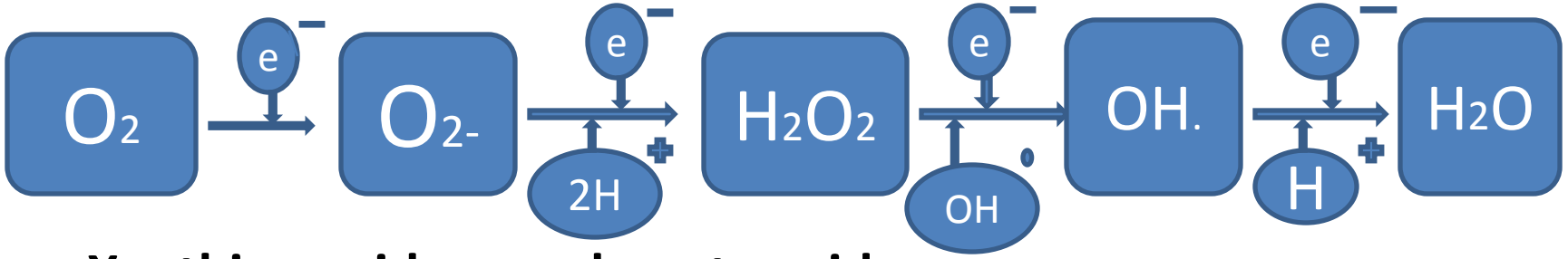
Endoplasmic reticulum

- Oxidation of toxic compounds

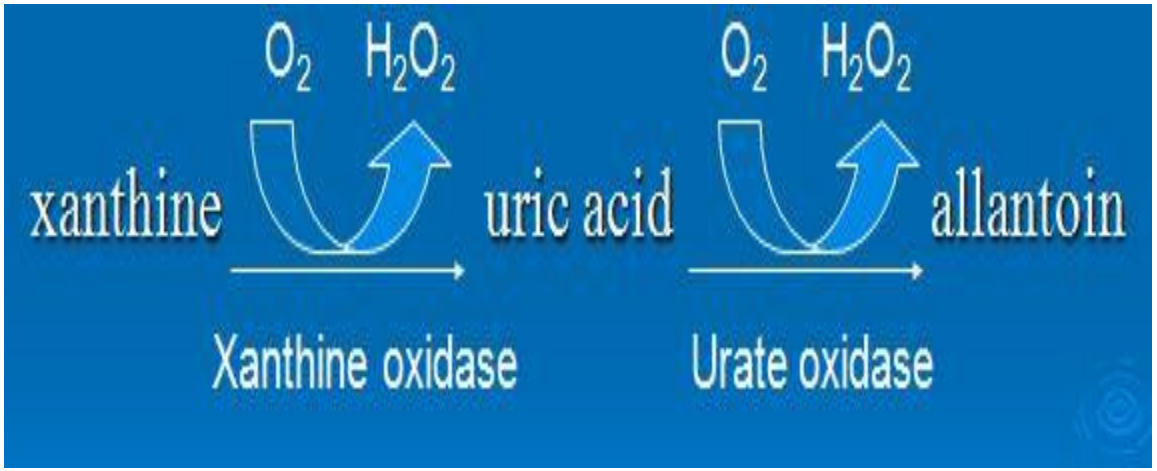


Enzymic sources

- **Cytochrome oxidase** adds four electrons onto a molecule of dioxygen in a series of reduction reactions . Each of these reduction reactions may potentially have superoxide radicals as a byproduct.

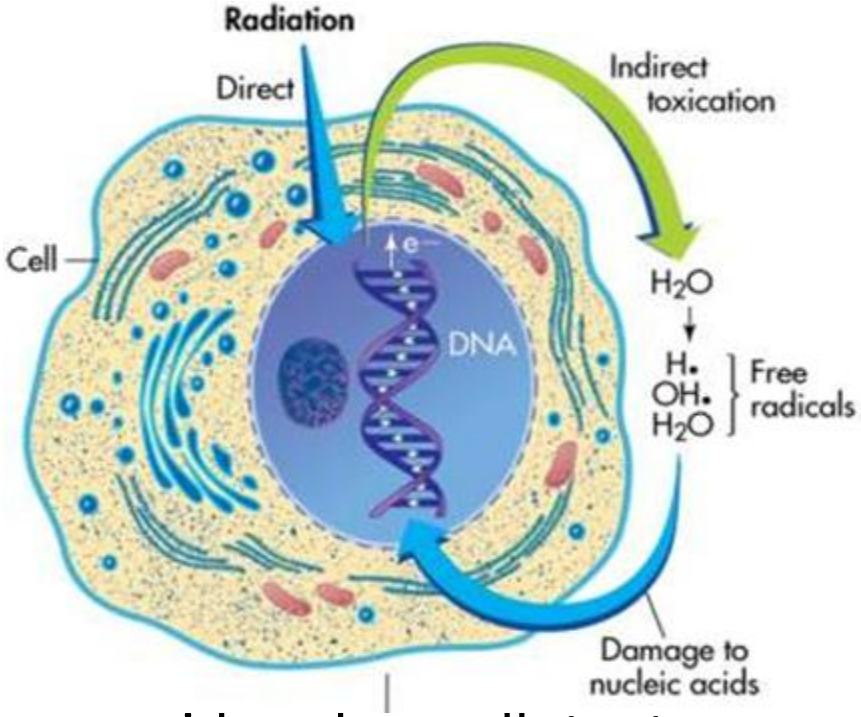


- **Xanthine oxidase and urate oxidase**



Environmental sources

- Exposure to ionizing radiations like gamma rays, x-rays, and ultraviolet rays excite the electrons in many atoms, thereby generating large amounts of free radicals.

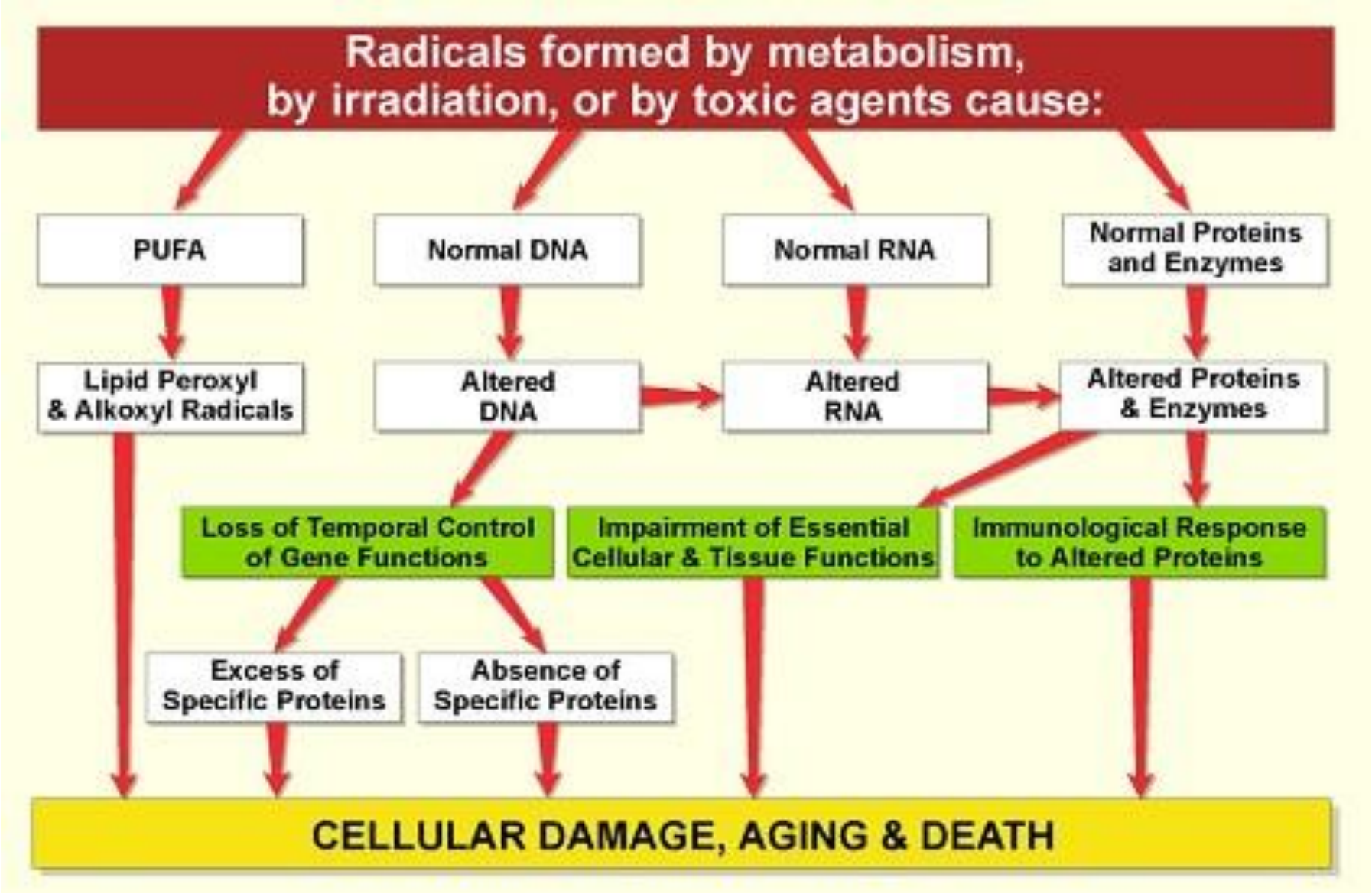


$$H_2O \xrightarrow{\text{U.V. Rays}} HO^{\bullet} + H^{+}$$

- Oxygen free radicals in the atmosphere considered as pollutants.
- Interaction with chemicals, automobile exhausts fumes, smoking of cigarettes, cigars, beedie.

How free radicals cause aging

PUFA: Poly Unsaturated Fatty Acids



Free radicals affect three components of cell غير مطلب

- **lipid degradation –**

Lipid peroxidation- Biomembranes and subcellular organelles are particularly sensitive to oxidative attack due to the presence of polyunsaturated fatty acids (PUFA) in their membrane phospholipids.

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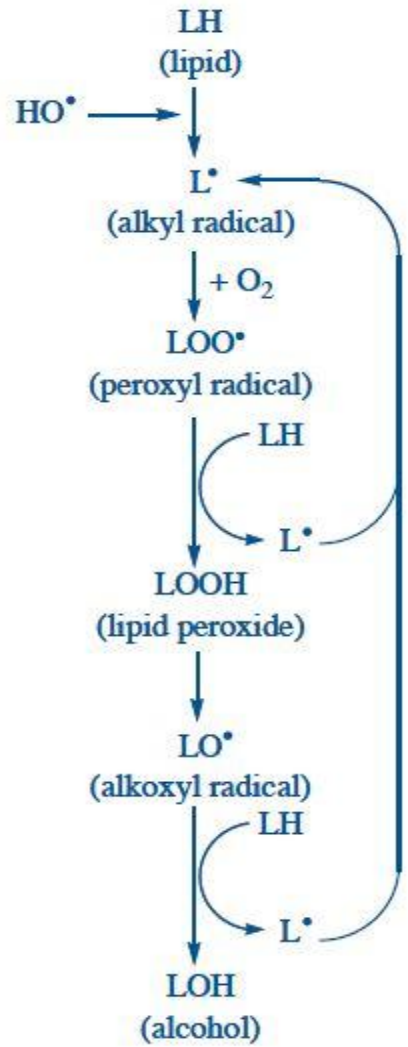
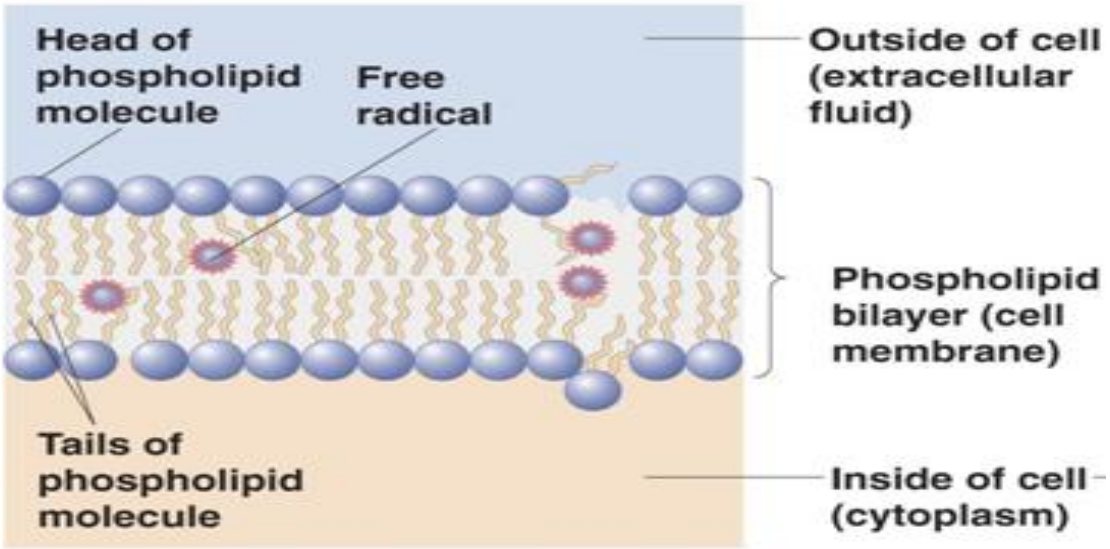




DNA damage غير مطلب

Free radicals can damage by following ways –

- Oxidation –

- Nitration –

Guanine —nitro oxide→ 8-nitroguanine

Guanine —peroxyl nitrite→ 8-nitrodioxideguanine

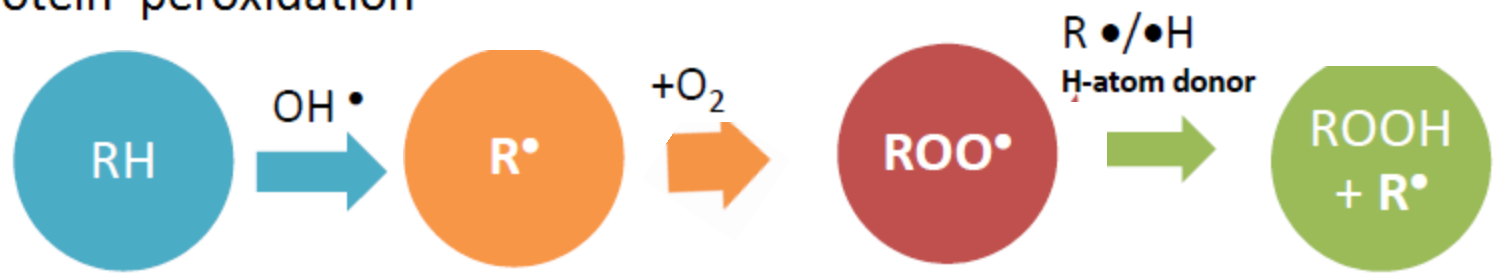
- Inter and intra stand cross linking-

Inter and intra stand cross linking are formed due covalent bond formation between opposite and same stand . Covalent bond is formed between second nitrogen in one stand with second carbon of another guanine located opposite stand

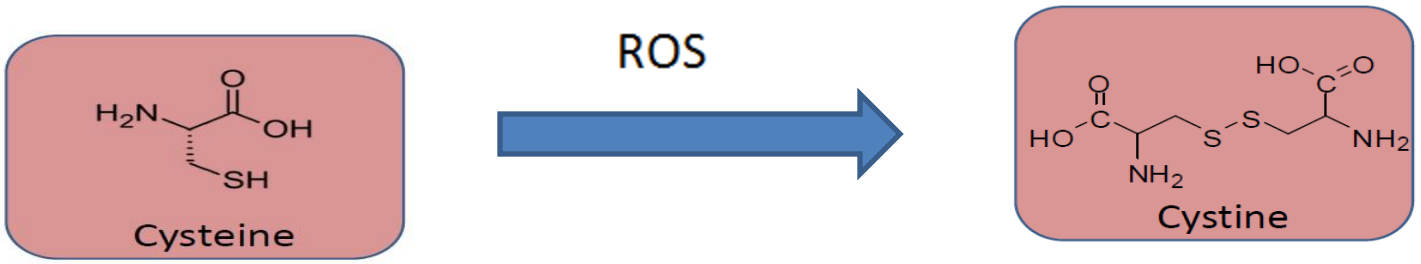
Protein degradation

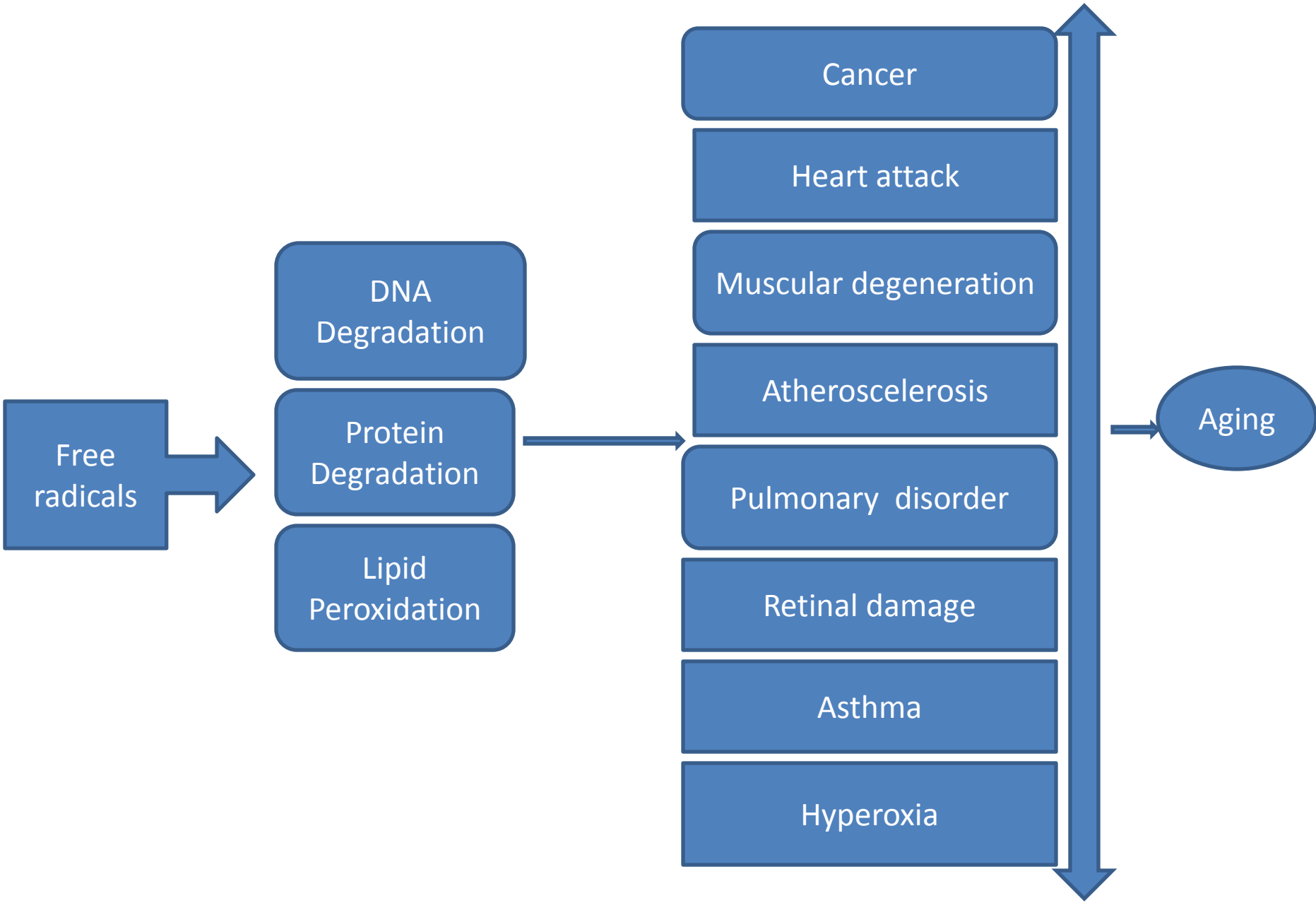
- Peroxidation of protein
- Cabonyl formation
- Cross linking Proteins

Protein peroxidation



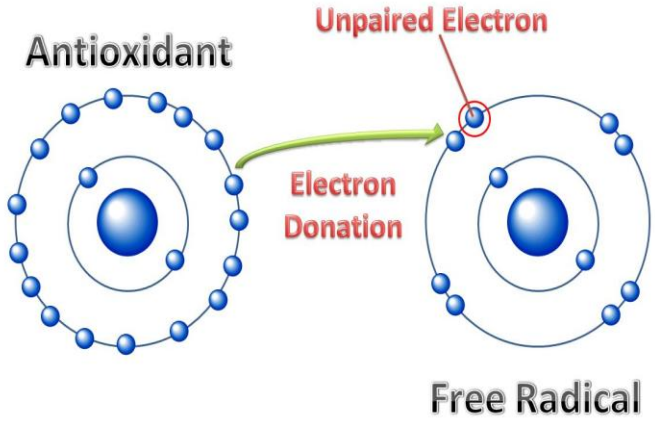
Cross linking -

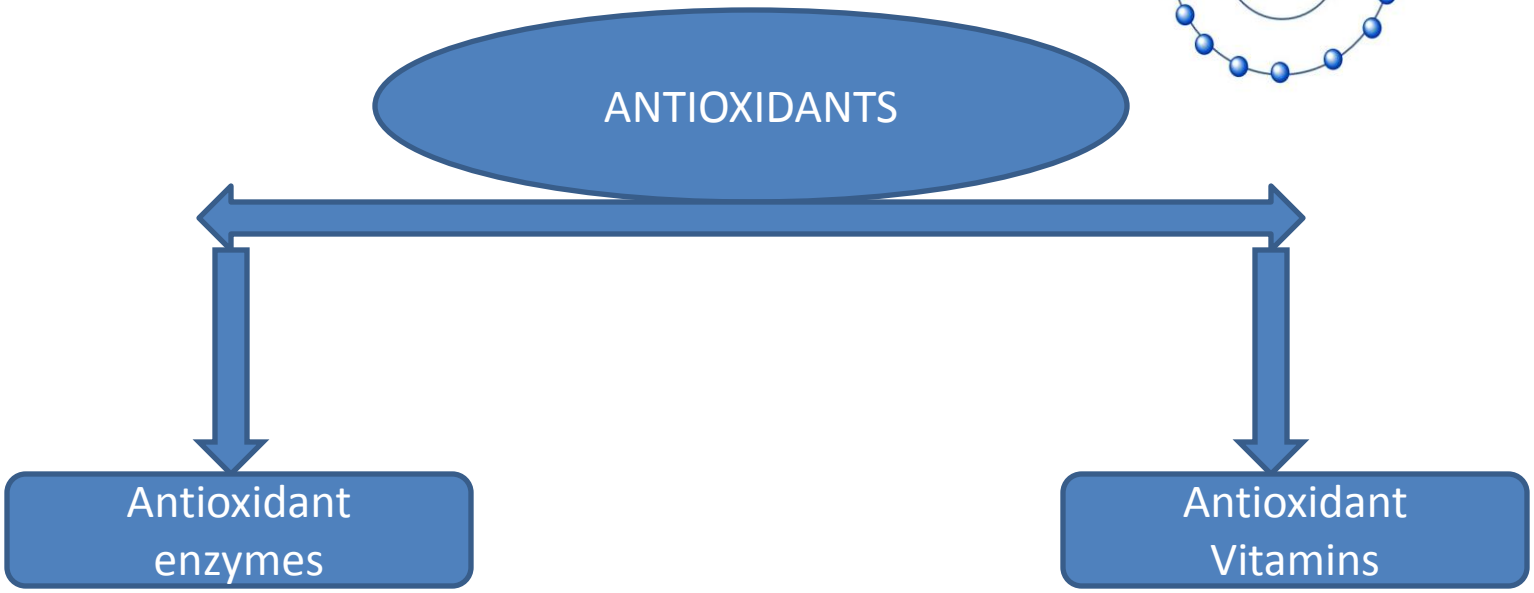



Free radicals
DNA Degradation
Protein Degradation
Lipid Peroxidation
Cancer
Heart attack
Muscular degeneration
Atheroscelerosis
Pulmonary disorder
Retinal damage
Asthma
Hyperoxia
Aging

Antioxidants

- Any synthetic or natural substance that delay or inhibits oxidative damage to a target molecule and capable to neutralize free radicals by donating electron or hydrogen molecule. They prevent cell damage and tissue damage and act as scavenger.



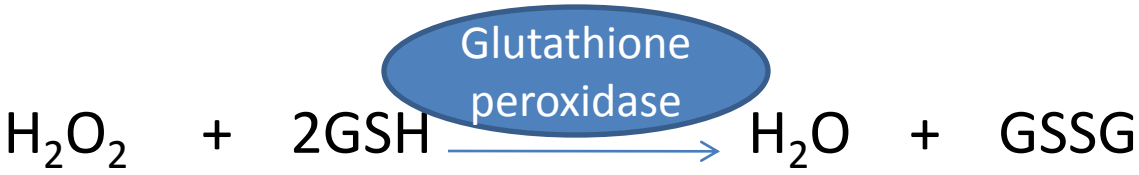


Antioxidant enzymes

- Superoxide dismutases- It catalyze the rapid dismutation of superoxide radical to hydrogen peroxide and oxygen.

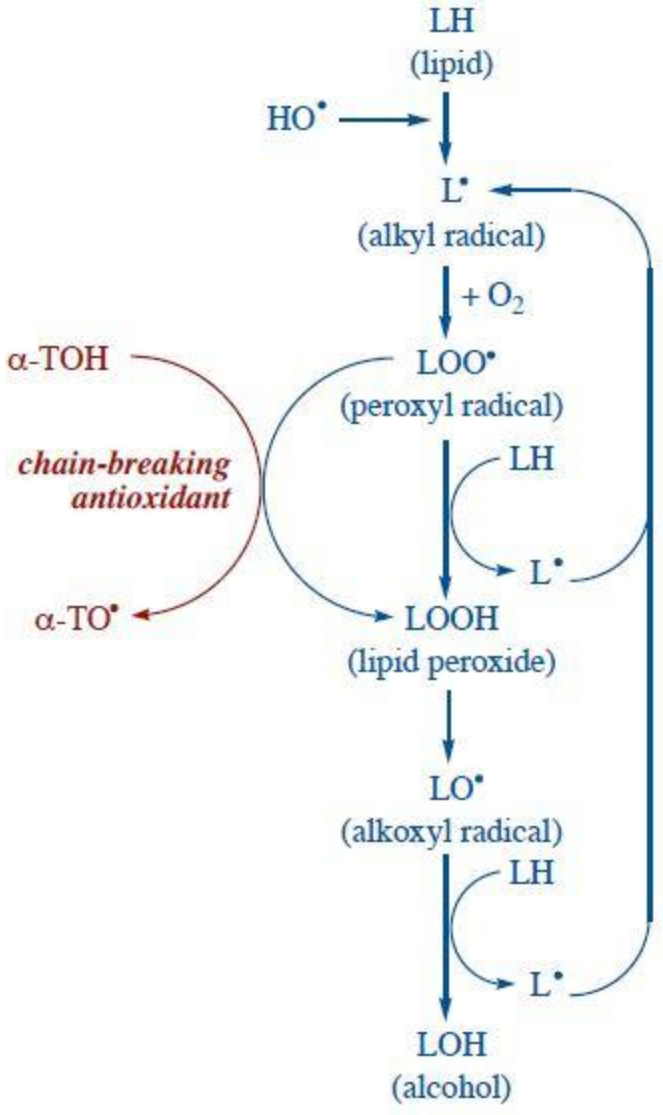
- Catalase- It reduces peroxide (H_2O_2) to water.

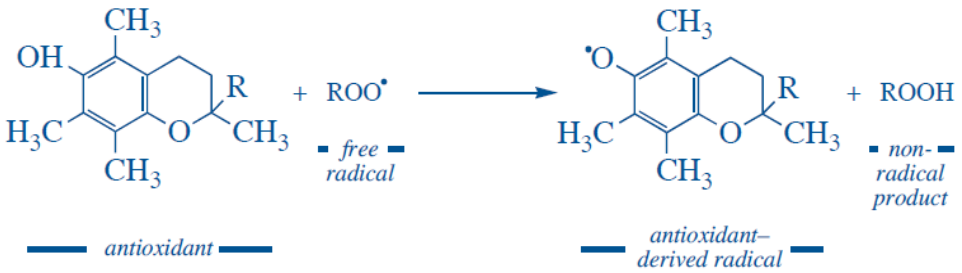
- Glutathione Peroxidase.

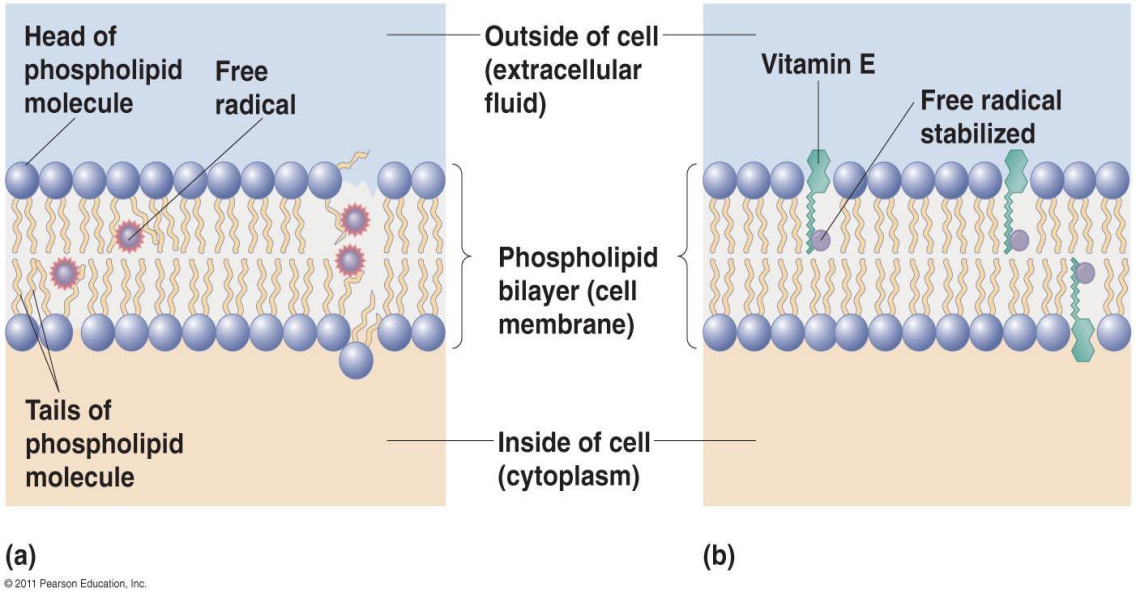


Antioxidant Vitamins --

- **Vitamin E-**It is a fat soluble vitamin and prevent peroxidation of lipid by donating of electrons to free radicals







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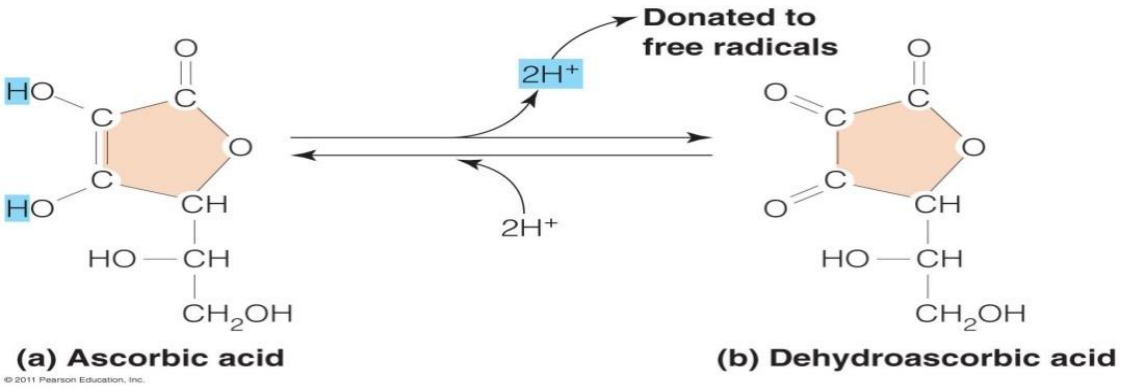
- **Vitamin C-** It is a water-soluble vitamin that reacts with several radical species producing semidehydroascorbic acid or ascorbyl radical ($A^{\cdot -}$). Ascorbyl radical or semidehydroascorbate radical back to ascorbate by dehydroascorbate reductase and NADH-semidehydroascorbate reductase

$$AH^- + HO^{\bullet} \longrightarrow A^{\bullet} + H_2O$$



- **Vitamin A –** Vitamin A works as an antioxidant in form of carotenoids. Mainly beta carotenoids (CAR) react with free radicals and prevent lipid oxidation

$$LOO^{\bullet} + CAR \longrightarrow LOO\text{--}CAR^{\bullet}$$

$$LOO\text{--}CAR^{\bullet} + LOO^{\bullet} \longrightarrow LOO—CAR—LOO(\text{non radical product})$$

Evidences supported to free radical theory of aging

- Schriner, N.J.Linford – Transgenic mice that over express human catalase lived longer than control.

- R.S. Sohal , S. Cadenas ,C. Rojas -Comparing birds with mammals with similar metabolic rates, the much longer life spans of birds are related to a smaller diversion of O_2 to SO by the bird mitochondria.

- Don Beal -Protein can be converted into carbonyl derivative through reaction with lipid peroxidation product by free radical and these protien cabonyl derivative increase with age in multiple tissue.

- Rebrin -Glutathione is one of most abudant intracellular antioxidant. The ratio of reduce /oxidize glutathione decline with aging in multiple tissue.

- Corbisier and Remacle perform a experiment in support of mitochondria free radical theory of aging . They inject micro injected isolated mitochondria from fibroblast of old rat old into cells of young ones so who had recieve old mitochondria rapidly entered senescence .

Criticisms of free radical theory of aging

- Main criticism of this theory is that all free radicals are responsible for damage biomolecules which must be major reason for cell aging but it is not true because –

  Many reactive oxygen species participate in signaling pathway.

  Many free radicals kill and inject harmful bacteria .

  Many free radicals are co facter of enzyme and protein derivatives.

- Zintel , Luce , Hamann are suggested fungal aging model Podospora anserina the over expression of antioxidative enzyme MnSOD led to lifespan shortening.

- Goto and Radak are suggested that we do physical exercise which is good for healthy life but also accompanied by overproduction.

- In 2007 Barja discussed an increase in longevity during dietary restriction that can occur together with the enhancement of oxygen consumption.

  He concluded that increasing oxygen consumption should not always associate with an increase in the rate of mitochondrial oxygen radical generation.

Conclusion

Free radical theory of aging is only concerned with all free radicals in our body cause cumulative damage which would eventually lead to loss of functionality, and ultimately death. This theory is supported by a vast number of experiments and observations .This provide important view about free radicals. There is no doubt that reactive free radicals such as hydroxyl and peroxy radicals can damage biomolecules and their activities can be suppressed by some antioxidants (free radical scavengers) such as α-tocopherol (vitamin E) and ascorbic acid (vitamin C). But this theory could not find differences between various free radicals .However many free radicals help to regulate many functions in cells like cell-cell signaling, killing of harmful bacteria , co-factors of enzymes. Free radical theory of aging must be broaden and modify