Review Article

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Biochemistry

ROLE OF FREE RADICALS IN AGEING PROCESS

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ABSTRACT Ageing is defined as progressive loss of tissue and organ function over time. Among the various theories proposed to explain aging, the role of free radicals has gathered significant attention. free radicals play a crucial role in the aging process by promoting oxidative stress and cellular damage. These reactive molecules can damage DNA, shorten telomeres, disrupt gene expression, induce epigenetic modifications, and activate aging-related signaling pathways. These effects can contribute to the gradual decline in physiological functions and tissue homeostasis observed during aging. Minimizing free radical-induced damage and supporting antioxidant defense mechanisms through a healthy lifestyle can help mitigate these effects and promote healthy aging. Antioxidants prevent free radical induced tissue damage by preventing the formation of radicals, scavenging them, or by promoting their decomposition. Synthetic antioxidants are recently reported to be dangerous to human health. Thus the search for effective, nontoxic natural compounds with antioxidative activity has been intensified in recent years. By understanding the mechanisms of free radical-mediated aging, it may be possible to develop interventions and therapeutics to slow or prevent age-related diseases and promote healthy aging.

KEYWORDS : Ageing, Antioxidant, Free Radicals, Oxidative Stress

INTRODUCTION

Ageing is defined as progressive loss of tissue and organ function over time. The aging process is a complex phenomenon influenced by various factors, including genetic predisposition and environmental influences. Among the various theories proposed to explain aging, the role of free radicals has gathered significant attention. Free radicals are natural byproducts of normal cellular functions. When cells generate energy, they inevitably produce unstable oxygen molecules known as free radicals. These molecules possess unpaired electrons, rendering them highly unstable and reactive. Consequently, free radicals can bind to other molecules within the body, disrupting the proper functioning of essential proteins and other molecules. While the body naturally generates free radicals through its metabolic processes, external factors such as diet, stress, smoking, alcohol consumption, exercise, inflammatory drugs, and exposure to sunlight or air pollutants can also contribute to their formation.[2]

Fig.1: Diagram representing a Stable Atom and a Free Radical.

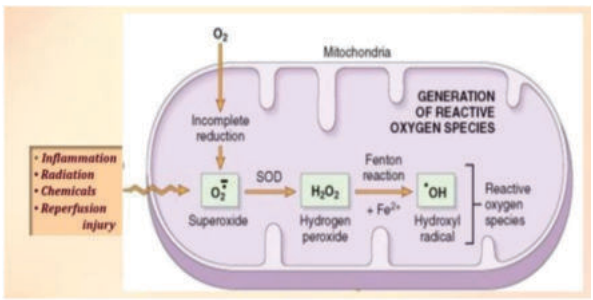

Fig.2: Free radical generation

Understanding Free Radicals:

One significant category of free radicals is referred to as reactive oxygen species (ROS). These highly reactive molecules, possessing unpaired electrons, play a prominent role in various cellular processes and can exert both beneficial and harmful effects depending on their concentration and location within the body. These are produced when food macro-nutrients are broken down in our bodies, along with the oxygen we breathe in, to produce energy in a microscopic part of the cell called mitochondria. Mitochondria are known to become faulty with growing age, resulting in more ROS production. ROS are short lived but can cause damage to DNA, lipids and other various parts of cells all over the body. The availability of free radicals creates oxidative stress in the body. It's called "stress" because the chemical reactions that let free radicals to get an electron occurs in presence of oxygen. Under normal circumstance, this small amount of ROS is greatly beneficial for the cell to support physiological function and to the body's defence system, as free radicals are involved in destroying pathogens to ward off disease. Free radicals can cause the cross-linking of proteins, leading to the formation of aggregates and impairing their normal function. Protein cross-linking is associated with age-related diseases such as Alzheimer's and Parkinson's.

Free radicals can cause oxidative damage to DNA, leading to mutations and genetic instability. This can impair cellular function and contribute to age-related decline.

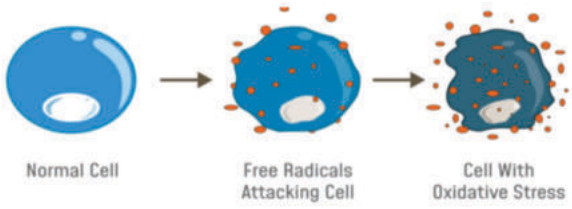

Fig.3: Change of a normal cell due to free radical attack producing oxidative stress in the cell.

Aging is marked by a decline in maximum function and the gradual accumulation of mitochondrial DNA mutations, particularly notable in organs with post-mitotic cells, such as the brain. Oxygen radicals are widely believed to contribute to these aging processes.

During normal aging, the brain suffers both morphological and functional modifications affecting dendritic trees and synapses, neurotransmitters, brain circulation and metabolism, motor and sensory systems, sleep, memory and learning, and lipofuscin accumulation. According to the free radical theory of aging, the progressive build-up of oxidative radicals plays a pivotal role in cellular aging by inducing damage to cellular components. Almost every investigation in this area has shown that the rate of ROS production of mitochondria which have been isolated from post-mitotic tissues including brain is indeed lower in long-lived than in short-lived species.

The detrimental effects of free radicals include DNA damage, protein cross-linking, and other alterations within the body. An important area where damage can cause problems is in tumour suppressor genes. As time passes, this cumulative damage ultimately leads to the experience of aging.[3] External factors that can elevate ROS include poor diet, alcoholism, smoking and some prescription medication.

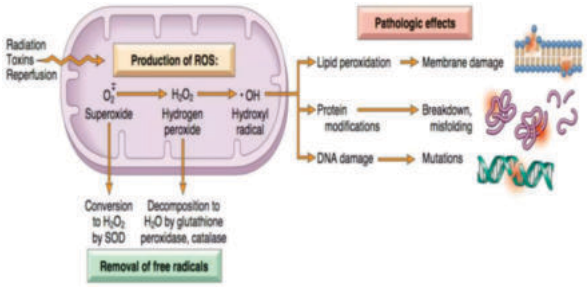

Fig.4: Various Cell Injuries caused by Free Radicals

The body possesses a natural defense mechanism to counteract the harmful effects of reactive oxygen species (ROS) and oxidative stress. This defense mechanism involves the production of antioxidants, which aid in restoring the balance by neutralizing free radicals. Antioxidants are present in various plant-based substances and have the ability to absorb free radicals, acting like sponges, and are believed to mitigate the damage caused by these unstable molecules.[2]

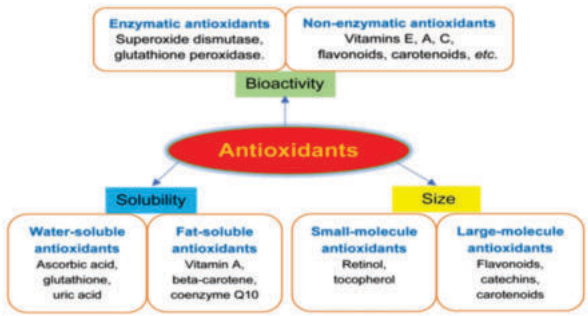

Fig.5: Different types of Antioxidants

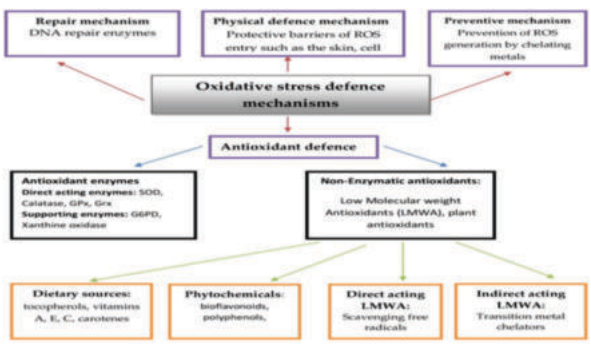

Fig.6: Antioxidants- Oxidative Stress Defence Mechanisms

To promote overall health and also slow down the production of free radicals, it is advisable to maintain a healthy diet like consuming a diet rich in antioxidants, including fruits, vegetables, and whole grains. Refrain from smoking, limit alcohol consumption, engage in regular exercise, and minimize exposure to air pollution and direct sunlight. These measures not only support general well-being but also help reduce the generation of free radicals.[2]

A study performed in 2010 focused on determining the antioxidant content of foods and supplements which are used worldwide found that spices and herbs were among the most antioxidant-rich foods, and berries, fruits, nuts, chocolate, vegetables also have high antioxidant content.

Further research in this area can provide insights into potential interventions for age-related diseases and strategies for extending healthy lifespan.

Types of free radicals

There are various types of free radicals that can form within the body or be encountered from external sources.

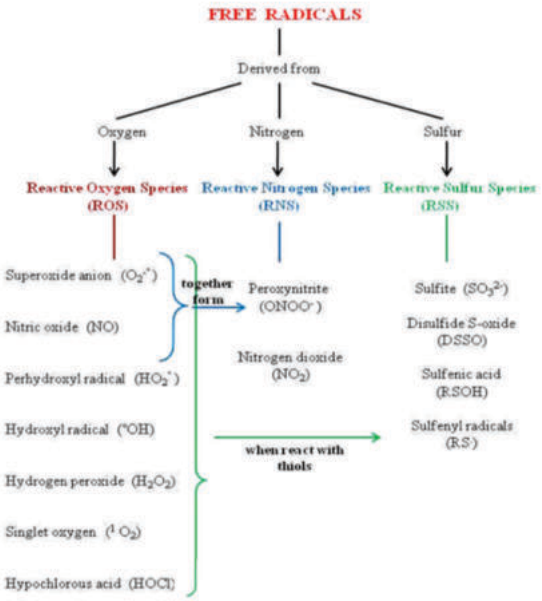

Fig 7: Types of free radicals

Reactive Oxygen Species

They are oxygen containing, highly reactive molecules which can be grouped into – superoxide, hydroxyl and hypochlorite radicals.

They are formed as a result of the inter and intra cellular signalling enzymatic reactions. The non radicals under reactive oxygen species (ROS) are - single oxygen, lipid peroxides, hydrogen peroxide, etc.

Radicals:
- $NO^{\bullet}$ Nitric oxide
- $NO_2^{\bullet}$ Nitrogen dioxide

Non-radicals:
- $ONOO^-$ Peroxynitrite
- ROONO Alkyl peroxynitrites
- N_2O_3 Dinitrogen trioxide
- N_2O_4 Dinitrogen tetroxide
- HNO_2 Nitrous acid
- NO_2^+ Nitronium anion
- NO^- Nitroxyl anion
- NO^+ Nitrosyl cation
- NO_2Cl Nitryl chloride

ROS are produced in two ways – exogenously and endogenously. They can initiate autocatalytic reactions, as they are the major by-product formed in the cells of aerobic organisms. They set off a chain reaction by reacting with the surrounding molecules like protein, enzymes and membrane lipids, thereby converting them into free radicals, resulting in damage. [19]

The exogenous sources are environmental agents, ions, metals, chlorinated compounds, radiation and xenobiotics. And the endogenous sources are peroxisomes, microsomes, mitochondria, inflammation caused by cell activation and cytochrome P450 metabolism,[21] neutrophils and eosinophils.

The other sources are – certain reactions that are catalysed by metals, X-rays and UV light irradiation, mitochondrial catalysed electron transport reactions, macrophages and neutrophils during inflammation, and various pollutants in atmosphere.

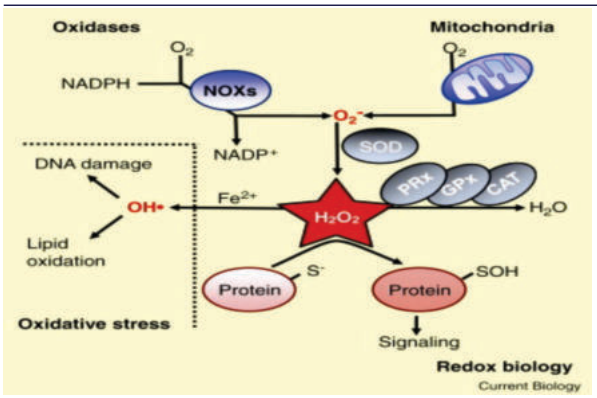

Fig 8: Basics of ROS

Reactive Nitrogen species

Reactive Nitrogen species (RNS) are free radical species that are linked with septic shock, asthma, atherosclerosis etc. Nitric oxide and nitrogen dioxide are the two examples of reactive nitrogen species. Nitric oxide produced by the enzyme nitric oxide synthase (NOS) is highly reactive free radical, causing damage to the carbohydrates, lipids, proteins and nucleotides resulting in inflammation, adhesions and tissue damage. It also inhibits platelet aggregation, relaxes the muscles of arteries and veins and the nitric oxide donors play characteristic role in therapeutics as they are vasodilating agents.

Radicals:	Non-radicals:
$O_2^{\cdot-}$ Superoxide	H_2O_2 Hydrogen peroxide
$OH^{\cdot}$ Hydroxyl	$HOCl^{-}$ Hypochlorous acid
$RO_2^{\cdot}$ Peroxyl	O_3 Ozone
$RO^{\cdot}$ Alkoxyl	$^1O_2$ Singlet oxygen
HO_2 Hydroperoxyl	$ONOO^{-}$ Peroxynitrite

Reactive Sulfur species

These types of free radicals are formed by the oxidation of thiols and disulfides. They are active in nature and consist of sulphur at a high oxidation state. Disulfide, sulfenic acid and thiyl radicals are few examples. They result in the inhibition of thiol proteins and enzymes due to the rapid oxidation they undergo. Certain invitro studies predict that sulphur may exist in different oxidation states in the range of 2 to 6. The electrons necessary for the complete reduction to thiol, imply the number of thiols that can be reduced by these species. Sulphite radicals and Disulfide-S-oxide (DSSO) are two such species that result in higher level of secondary oxidation products. After several tests on muscle homogenates, it was noticed that sulphite causes a steady and slow oxidation of lipids. Experimental studies suggest that the factors that are responsible for the production of reactive sulfur species could be a factor in the oxidation of lipids, and can play a significant role in therapeutics, being vasodilating agents. [24]

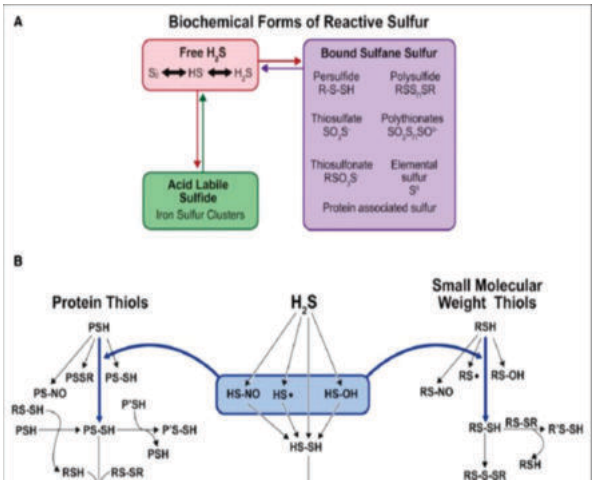

Fig 9: Biochemical nature and species of reactive sulfur species (RSS)

Figure A- Various biochemical forms of reactive sulfur including free hydrogen sulfide (H 2 S), acid-labile sulfide (eg, iron-sulfur clusters), and bound sulfane sulfur.

Figure B- Various sulfide species associated with different biochemical sulfur-containing molecules. Three categories of sulfur containing molecules involve protein thiols, H 2 S itself, and small-molecular-weight thiols (R designates molecules such as GSH or cysteine).

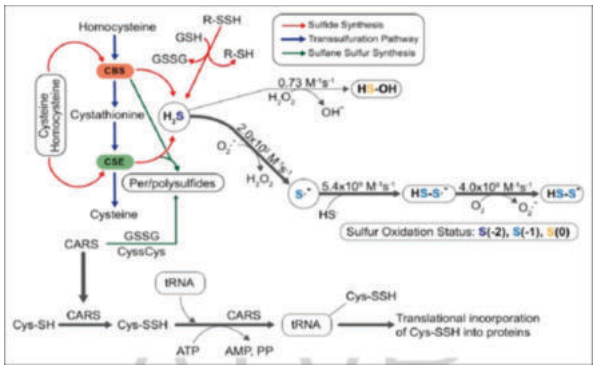

Fig 10: Formation and metabolism of reactive sulfur species.

Transsulfuration enzymes CBS (cystathionine beta-synthase) and CSE (cystathionine gamma-lyase) use substrates homocysteine, cystathionine, or cysteine to generate hydrogen sulfide (H 2 S). H 2 S may subsequently react with reactive oxygen species (eg, superoxide) resulting in sulfide radical formation leading to persulfide formation. Rate constants (M −1 s −1) are shown for each reaction indicating that H 2 S reacts more quickly with superoxide vs hydrogen peroxide. CARS (cysteinyl-tRNA synthetase) enzyme activity also contributes to cysteine persulfide formation that may be translationally incorporated into nascent polypeptide formation. tRNA indicates transfer RNA. [34]

Mechanism of action of free radicals in ageing process

The mechanism of action of free radicals in the aging process involves several interconnected pathways and processes. Here are some key mechanisms by which free radicals contribute to aging:

Oxidative Stress:

The free radical theory of aging, which later termed as oxidative stress theory of aging, is based on the structural damage-based hypothesis that age-associated functional losses are due to the accumulation of oxidative damage to macromolecules (lipids, DNA, and proteins) by RONS (Reactive Oxygen Nitrogen Species).

The exact mechanism of oxidative stress-induced aging is still not clear, but probably increased RONS levels lead to cellular senescence, a physiological mechanism that stops cellular proliferation in response to damages that occur during cell replication. Senescent cells acquire an irreversible senescence-associated secretory phenotype (SASP) involving secretion of soluble factors (interleukins, chemokines, and growth factors), degradative enzymes like matrix metalloproteases (MMPs), and insoluble proteins or extracellular matrix (ECM) components.

Oxidative stress, cellular senescence, and consequently, SASP factors are engaged in several acute and chronic pathological processes, such as CVDs, acute and chronic kidney disease (CKD), neurodegenerative diseases (NDs), macular degeneration (MD), biliary diseases, and cancer. Cardiovascular risk factors like obesity, diabetes, hypertension, and atherosclerosis are associated with the inflammatory pathway mediated by IL-1α, IL-6, IL-8, and increased cellular senescence. [29]

DNA Damage:

DNA damage drives aging by activating signalling responses blocking transcription and other DNA metabolism, altering the epigenome, mutagenesis, triggering cells senescence and apoptosis.

DNA damage occurs stochastically but the amount and types of DNA damage one experiences is influenced by the expression of

genes which codes antioxidant enzymes, genes linked to energetics and mitochondrial function, and a myriad of other factors such as histones, methylases, sirtuins, transcription, and replication factors. Every aspect of how DNA damage might drive aging is also genetically determined via the cellular response to DNA damage. The surprising finding is that DNA damage has far-reaching effects on many aspects of cellular metabolism which are tied to aging, known as **pillars of aging**.

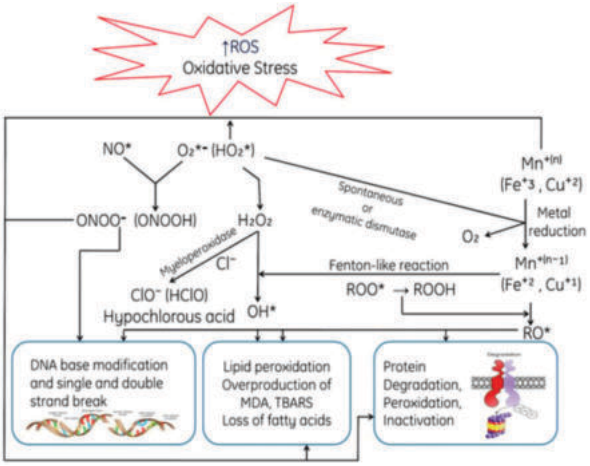

Fig 11: ROS-mediated toxic manifestations such as ROS-mediated DNA damage; peroxidative damage of membrane lipids, degradation of proteins caused ROS, Base modifications of Bases, where MDA: Malondialdehyde, TBARS: Thiobarbituric acid-reactive species, *, unpaired electron

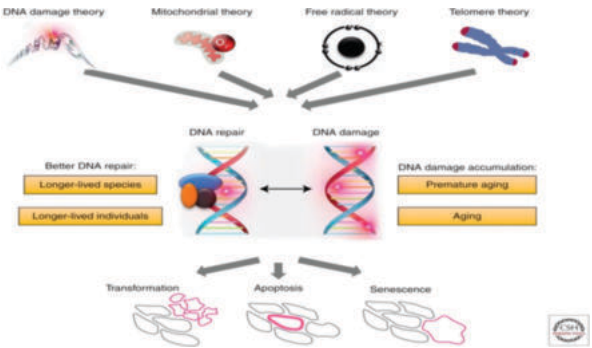

Fig 12: Four major theories of aging

Each theory has DNA damage accumulation and DNA repair as a major component. A variety of evidence, not always consistent, indicates that DNA damage accumulation is associated with aging.

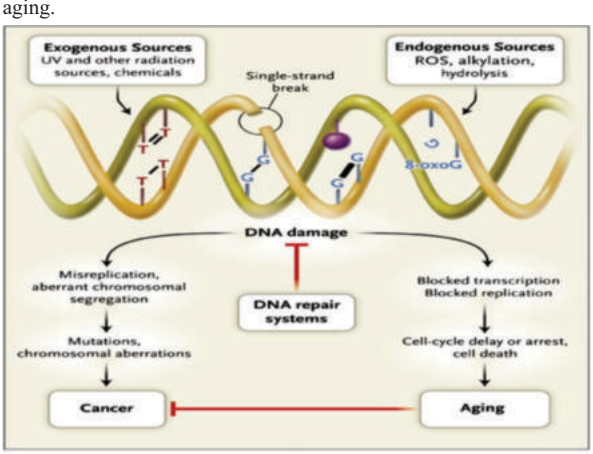

Fig 13: Sources and Consequences of DNA Damage.

DNA damage can be induced by exogenous physical agents, by endogenous chemical genotoxic agents that are the products of metabolism, such as reactive oxygen species (ROS), or by spontaneous chemical reactions, such as hydrolysis. Examples of DNA damage are ultraviolet (UV)-induced photoproducts (left), interstrand and intrastrand crosslinks, bulky chemical adducts (purple sphere), abasic sites, and oxidative damage such as 8-oxoguanine (8-oxoG). The consequences of DNA damage are essentially twofold. After misrepair or replication of the damaged template, surviving cells may be subject to permanent changes in the genetic code in the form of mutations or chromosomal aberrations, both of which increase the risk of cancer. Alternatively, damage may interfere with the vital process of transcription or induce replication arrest, which may trigger cell death or cellular senescence, contributing to aging. Damage-induced cell death protects the body from cancer. G denotes guanine, and T thymidine.

Protein Oxidation and Cross-linking:

Proteins are most abundant in cells, and are major targets for oxidative modifications. ROS can attack proteins in different ways: directly at the protein backbone, amino acid residue side chains or they can lead to the formation of protein carbonyls. An indirect damage of proteins by secondary by-products (oxidatively modified sugars, aldehydes and lipids) can also occur. As a result of this damage, the affected proteins lose their biochemical function, protein expression is altered and finally, aggregate formation occurs, which results in different consequences for the cells. In past few years, increasing evidence has shown that protein oxidation is accompanied by various neurodegenerative diseases like Huntington's disease Parkinson's disease, Alzheimer's disease and a wide variety of age-related disorders. Accumulation of protein aggregates in long-lived postmitotic cells are dramatic, since they are not able to eliminate this waste material by cell division. So, the muscle tissue, neurons and the retinal pigment epithelium are mostly affected. Generally oxidized proteins can be eliminated by degradation systems (lysosomal or proteasomal) or undergo repair mechanisms. As both of these mechanisms decline within aging and also protein synthesis is negatively affected during the aging process, the susceptibility for oxidative modifications increases. So, the hallmark of aging is the disturbed balance between ROS production and ROS clearance, which leads to an accumulation of oxidized proteins, lipids, and aggregates such as lipofuscin and advanced glycation end-products (AGEs). Free radicals can oxidize proteins, which leads to structural changes and loss of function. They can also cause protein cross-linking, which results in the formation of aggregates and impaired protein turnover. Accumulation of oxidized and cross-linked proteins contributes to cellular dysfunction and age-related diseases.

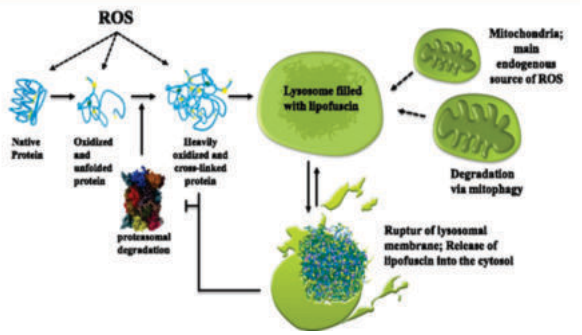

Fig.14:– Formation of lipofuscin.

Lipofuscin formation starts with oxidative damage to proteins. In case of failing of damage removal or repair systems, oxidized proteins cross-link and become functionally impaired and change their structure. Cross-linked proteins are taken up via autophagy by lysosomes where they are processed further leading to lipofuscin formation. Eventually, lysosomes are overloaded and rupture. Lipofuscin is then released into the cytosol and able to inhibit the proteasome. To prevent this, lipofuscin is taken up again and the cycle repeats. Furthermore, it is assumed that mitochondria increase oxidant production during aging and that this is a side effect of mitochondrial declining function. Mitochondrial turnover is regulated via macro autophagy, also called mitophagy, leading to degradation within the lysosome.

Lipid Peroxidation:

The cell membrane is a target that is particularly rich in lipids,

which are easily accessible to free radicals in the cell and susceptible to peroxidising reactions mediated by free radicals. For example, free radicals react with membrane fatty acids and phospholipid components to form lipid peroxides, which induces an irreversible impairment of membrane fluidity and plasticity and thereby lead to irreversible damage to the cell's integrity. All of these changes are particularly important in long-lived postmitotic cells, because the rate of lipid turnover in these cells is lower than in dividing cells. Furthermore, some of the breakdown products of lipid peroxidation reactions are believed to contribute to the production of lipofuscin, a structurally heterogeneous yellowish-brown granular pigment that accumulates in the cytosol with age and appears to be a universal correlate of senescence or ageing. The accumulation of lipofuscin is particularly evident in postmitotic cells. For example, up to 7% of the intracellular volume of human myocardial cells derived from 90-year-old individuals might be occupied by this pigment. In contrast, lipofuscin is completely absent or almost undetectable in cells derived from young individuals. Indeed, lipofuscin provides strong evidence to support the theory that lipid oxidative processes occur in vivo and, it has been hypothesized that its accumulation compromises vital cell functions, such as respiration and energy production.

Mitochondrial Dysfunction: Mitochondria, the cellular organelles responsible for energy production, are both sources and targets of free radical damage. Mitochondria generate ROS during the electron transport chain as a byproduct of energy production. Over time, accumulated free radical damage can impair mitochondrial function, decrease energy production, and lead to further ROS production, creating a vicious cycle of oxidative stress and mitochondrial dysfunction. This mitochondrial dysfunction contributes to aging processes and age-related diseases.

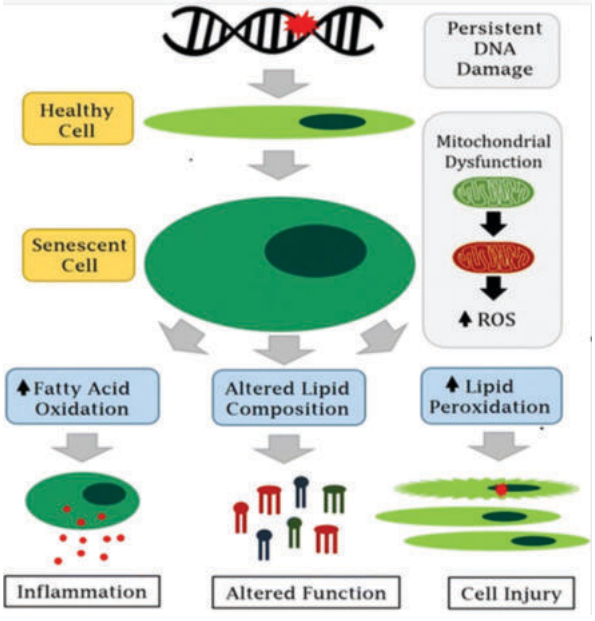

Fig.15: Free radical leading to lipid peroxidation induced cell injury

Inflammation and Immune Activation:
Free radicals can trigger and sustain chronic inflammation, leading to the release of inflammatory mediators and activation of immune responses. Memory and learning declines are consequences of normal aging which is associated with hippocampus. It has been observed that the impairments induced by normal aging are associated with synaptic remodelling, and that they are more likely to affect functions that are associated with the hippocampus, i.e several areas of memory and learning. This suggests that chronic inflammation and immune system over-activity may underlie the aging process of the human brain, and the potential anti-inflammatory treatments targeting those genes that were the most significant in terms of differential expression may slow down this process and alleviate its symptoms.

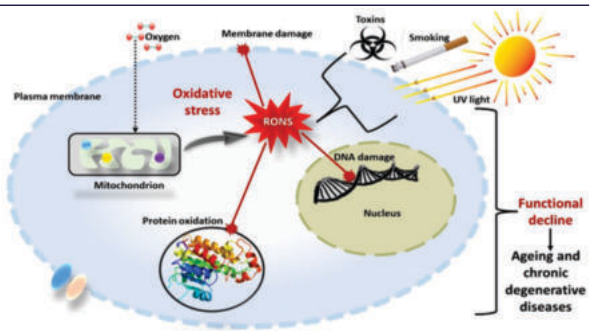

Fig: 16: Schematic representation of oxidative stress

It is a phenomenon elevated with ageing and degenerative diseases. It involves the accumulation of reactive oxygen and nitrogen species (RONS) in cells and tissues, harmfully modifying deoxyribonucleic acid (DNA), proteins and lipids and triggering ageing and chronic degenerative diseases.

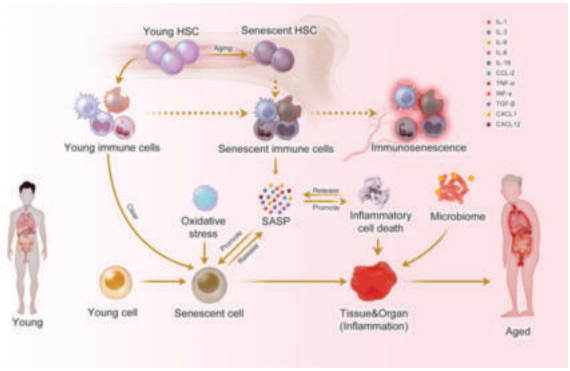

Fig: 17: Inflammation at the molecular, cellular, and organ levels

During the aging process, almost all cells in the body undergo senescence, a state characterized by a dysfunctional state and senescence-associated secretory phenotype (SASP). While immune cells play a crucial role in recognizing and eliminating these senescent cells, they are also affected by SASP, leading to a phenomenon called immunosenescence. Immunosenescence can impair the immunity to respond to infections and diseases, making the organism more vulnerable to illnesses. Moreover, the accumulation of senescent cells can trigger inflammation in organs, leading to organ damage and an increased risk of age-related diseases. This process is exacerbated by positive feedback loops that drive the accumulation of inflammation and organ damage, leading to further inflammation and an even higher risk of aging-related diseases.

Therapeutic uses
The body possesses a natural defense mechanism to counteract the harmful effects of reactive oxygen species (ROS) and oxidative stress. A balance between free radicals and antioxidants is necessary for proper physiological function. This defense mechanism involves the production of antioxidants, which aid in restoring the balance by neutralizing free radicals.[19]Antioxidants are present in various plant-based substances and have the ability to absorb free radicals, acting like sponges, and are believed to mitigate the damage caused by these unstable molecules.[2]

Fig.5: Different types of Antioxidants [20]
Fig.6: Antioxidants- Oxidative Stress Defence Mechanisms [21]

To promote overall health and also slow down the production of free radicals, it is advisable to maintain a healthy diet like consuming a diet rich in antioxidants, including fruits, vegetables, and whole grains. [22] Refrain from smoking, limit alcohol consumption, engage in regular exercise, and minimize exposure to air pollution and direct sunlight. These measures not only support general well-being but also help reduce the generation of free radicals.[2] These antioxidants delay or inhibit cellular damage mainly through their free radical scavenging

property.[62] These low-molecular-weight antioxidants can safely interact with free radicals and terminate the chain reaction before vital molecules are damaged. Some of such antioxidants, including glutathione, ubiquinol, and uric acid, are produced during normal metabolism in the body.[63] A study performed in 2010 focused on determining the antioxidant content of foods and supplements which are used worldwide found that spices and herbs were among the most antioxidant-rich foods, and berries, fruits, nuts, chocolate, vegetables also have high antioxidant content. the principle micronutrient (vitamins) antioxidants are vitamin E (α-tocopherol), vitamin C (ascorbic acid), and B-carotene. The body cannot manufacture these micronutrients, so they must be supplied in the diet.[64]

CONCLUSION

In conclusion, free radicals play a crucial role in the aging process by promoting oxidative stress and cellular damage. These reactive molecules can damage DNA, shorten telomeres, disrupt gene expression, induce epigenetic modifications, and activate aging-related signaling pathways. These effects can contribute to the gradual decline in physiological functions and tissue homeostasis observed during aging. Minimizing free radical-induced damage and supporting antioxidant defense mechanisms through a healthy lifestyle can help mitigate these effects and promote healthy aging. By understanding the mechanisms of free radical-mediated aging, it may be possible to develop interventions and therapeutics to slow or prevent age-related diseases and promote healthy aging.

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