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A Glance on Ageing, Longevity & the Roles of Free Radicals

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Abstract

This paper explores the intricate relationship between aging, cellular dynamics, and oxidative stress, emphasizing the role of free radicals and reactive oxygen species (ROS) in the aging process. It traces the historical context of longevity, highlighting the significant increase in life expectancy over the centuries and the biological mechanisms underlying aging, including mitochondrial DNA mutations and cellular senescence. Recent findings from the Okinawa Institute of Science and Technology reveal a crucial link between cell membrane integrity and aging, demonstrating how mechanical damage to membranes can influence cell fate and senescence. The research further investigates the impact of free radicals generated during metabolic processes and their contribution to cellular damage, leading to accelerated aging. The role of thiol groups, particularly in biomolecules like cysteine and glutathione, is examined for their antioxidant properties and significance in maintaining cellular health. The paper concludes that aging is a cumulative response to various stressors, both internal and external, underscoring the need for future research focused on therapeutic interventions that enhance cellular repair mechanisms and promote healthy longevity. Understanding these molecular underpinnings can inform strategies aimed at improving the quality of life and extending health spans in aging populations.

Keywords: Ageing; oxidation; antioxidants; free radicals.

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1.Introduction

Longevity refers to the pursuit of a longer and healthier life, encompassing both the duration of life and the quality of health experienced. At the close of the 18th century, life expectancy at birth in North America and Northwestern Europe was approximately 35 to 40 years. By 1970, this figure had risen to nearly 70 years, and it reached almost 78 years by 2015 [1]. Aging is a universal phenomenon observed in various multicellular organisms, including humans, dogs, and mice. Biologically, aging can be characterized as a gradual, event-dependent decline in the capacity to sustain biochemical and physiological functions. This intrinsic deterioration manifests over time, affecting cellular processes across both unicellular organisms, such as yeast, and more complex multicellular systems [2]. We posit that the concept of longevity is intricately linked to the health of biological organs and cells.

The aging process is marked by a decline in maximum functional capacity, coupled with the accumulation of mitochondrial DNA mutations, particularly evident in post-mitotic cells found in the brain [3]. Increasingly, oxygen radicals are implicated in the mechanisms underlying cellular aging. Comparative studies across species with varying lifespans have demonstrated that the rate of mitochondrial oxygen radical production correlates directly with the level of oxidative damage to mitochondrial DNA, while exhibiting an inverse relationship with maximum longevity in higher vertebrates [33]. Additionally, the degree of unsaturation in tissue fatty acids shows an inverse correlation with maximum lifespan [34]. Notably, caloric restriction has been shown to reduce the rate of aging, concomitantly lowering mitochondrial oxygen radical generation.

1.1. Aging and Cell Membrane Dynamics

Recent research conducted by scientists at the Okinawa Institute of Science and Technology (OIST) has unveiled a significant relationship between cell membrane integrity and cellular senescence, a key aspect of aging. The cell membrane, a delicate structure measuring approximately 5 nanometers in thickness—equivalent to one-twentieth of a soap bubble—surrounds each cell, rendering it vulnerable to damage from various physiological activities, such as muscle contraction and tissue injury. To mitigate this damage, cells possess intrinsic repair mechanisms capable of addressing membrane disruptions to a certain extent.

Historically, mechanical damage to the cell membrane was thought to result in straightforward cellular responses: either recovery, senescence, or cell death. However, the determination of cell fate is contingent upon the severity of the damage and the subsequent influx of calcium ions. Minor damage to the cell membrane can be effectively repaired, enabling continued cell division. Conversely, severe damage typically leads to cell death. Interestingly, moderate damage can induce a state of senescence several days post-injury, despite apparent successful membrane resealing.

Aging cells undergo a series of morphological and functional changes, including increased cell size and a diminished capacity for division and proliferation. Additionally, there is often an accumulation of pigments and lipids within the cellular environment. Many aging cells exhibit a decline in functional capacity, leading to abnormal cellular behaviors.

1.2. Free Radicals and Aging

Research conducted on rodent models indicates that free radicals generated within mitochondria contribute to cellular damage, impairing the essential functions necessary for cellular viability [5]. This oxidative damage can lead to mutations that further amplify free radical production, thereby accelerating cellular deterioration. Additionally, the cumulative stress and damage over time can induce a state known as cellular senescence, characterized by the cessation of cell division, loss of original function, and the release of deleterious molecules. Ongoing investigations aim to elucidate the key factors influencing the aging process, including the organism's response to various stressors, immune system functionality, the role of cellular senescence, and responses to macromolecular damage.

The most well-established trigger for cellular senescence is repeated cell division; however, other stressors—such as DNA damage, oncogene activation, and epigenetic modifications—also induce senescence in controlled laboratory settings. Traditionally, it has been posited that various stressors activate cellular senescence primarily through the DNA damage response. Recent findings suggest that cell membrane damage may induce senescence through alternative mechanisms involving calcium ions and tumor suppressor genes. These insights could pave the way for strategies aimed at promoting healthy longevity.

Accumulating evidence suggests that free radical-induced cellular damage underlies the pathological changes associated with aging [6]. Free radicals and other reactive oxygen species (ROS) originate from both normal metabolic processes and external sources, such as exposure to X-rays, ozone, cigarette smoke, air pollution, and industrial chemicals. The generation of free radicals occurs during aerobic respiration when cells utilize oxygen to produce ATP (adenosine triphosphate) in mitochondria. These by-products predominantly consist of reactive oxygen species (ROS) and reactive nitrogen species (RNS), resulting from cellular redox processes. Free radicals are formed through the homolytic cleavage of molecules, yielding fragments with equal numbers of electrons.

There is a growing body of evidence indicating that the cumulative effects of harmful free radical reactions throughout cellular and tissue environments contribute significantly to the aging process. In mammalian systems, these reactions primarily involve oxygen. As individuals age, mutations and deletions accumulate in the mitochondrial genome at a rate surpassing that of nuclear genes, which have been linked to various aging symptoms. Notably, many mutations have been identified that extend lifespan across diverse organisms, from yeast to mammals. The investigation of metazoan model organisms, such as Caenorhabditis elegans, has proven invaluable in elucidating the genetic underpinnings of cellular aging. Longevity mutants across a spectrum of model organisms suggest that aging rates are regulated by genetic control of cellular processes, with the regulation and eventual breakdown of these processes reflecting a cellular decision to either maintain or forgo maintenance functions as aging progresses.

Furthermore, evidence indicates that ultraviolet (UV) radiation and sunlight exposure can accelerate skin aging, a phenomenon termed photoaging, which accounts for approximately 90% of visible skin changes. UV light damages skin cells, leading to premature changes such as age spots. Oxidative free radicals, including hydroxyl

radicals and superoxide radicals, are implicated in DNA damage, which may play a critical role in the aging of essential tissues [5].

Cellular aging can also result from interactions between radiation-induced free radicals and sensitive cellular targets. Radiation affects cells through two mechanisms:

- Direct Effects: This mechanism involves the interaction of radiation with critical biological targets within the cell. Sufficient energy transfer to atoms or molecules can disrupt the cell's life-sustaining processes, potentially leading to cellular destruction.
- Indirect Effects: This mechanism involves radiation interacting with water molecules, resulting in ionization and excitation processes that can break molecular bonds. This interaction produces reactive fragments, such as hydrogen (H) and hydroxyl radicals (OH). While low-energy transfers may result in harmless recombination of these fragments, intermediate to high-energy transfers can yield toxic substances, such as hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and hydrogen radicals (H•) [7], contributing to cellular damage.

In the field of radiobiology, the loss of reproductive capacity and colony formation is often classified as cell death. This phenomenon can be attributed to the interaction of free radicals generated by radiation with one or more sensitive (critical) targets within the cell. Among the most significant chemical components present in cells is the sulfhydryl group, also known as the thiol group (-SH) [8-9]. The interactions between free radicals and biological molecules containing thiol groups can significantly influence cellular functions. The thiol group is a highly reactive component in biological systems, primarily characterized by its propensity to ionize into the thiolate anion, which is typically the reactive species. Notably, the thiol group exhibits weak hydrogen-bonding capabilities, allowing it to readily donate hydrogen in various chemical reactions:

$RH_1 \bullet + R_2SH \rightarrow R_1H + R_2S \bullet$

1.3. Role of Thiol Groups

The thiol group can be considered a primary target for free radicals. This property facilitates the repair of biological molecules, represented by the reaction:

$R_1 \bullet + R_2SH \rightarrow R_1H + R_2S \bullet \quad R_1 \bullet + R_2SH \rightarrow R_1H + R_2S \bullet$

Thiol groups can effectively neutralize attacking free radicals and ions through the following reactions:

$RSH + [\![OH]\!] \bullet \rightarrow [\![RS]\!] \bullet + H_2O$

$RSH + H \bullet \rightarrow [\![RS]\!] \bullet + H_2O$

$RSH + H \bullet \rightarrow R \bullet + H_2S$

$RSH + e\_aq \rightarrow R\bullet + [SH]^-$

$RSH + e\_aq \rightarrow [RS]^- + H\bullet$

Most thiol groups within cells are associated with larger protein molecules and amino acids such as cysteine. However, their abundance is often insufficient to prevent radiation-induced damage or facilitate effective repair Reference [10]. Certain fatty molecules, such as glutathione (GSH), which also contain thiol groups, can be administered externally to enhance repair mechanisms by scavenging free radicals [11]. Conversely, substances like diazene dicarboxylic acid can diminish GSH levels within cells, thereby increasing radiation sensitivity. Primarily, thiol groups function as antioxidant agents, mitigating the effects of free radicals and protecting the body from damage. Furthermore, biological molecules or cells that incorporate thiol groups in their structural framework may perform essential functions within the cell. The removal of thiol groups due to reactions with free radicals or ions can impair cellular functions, a phenomenon observed in various biomolecules and biochemical reactions. This phenomenon is observed in various biomolecules and biochemical processes, including:

1.3.1. Cysteine Amino Acid

Cysteine is one of over 300 amino acids found in nature, with approximately 20 being essential for the synthesis of mammalian proteins. As an uncharged polar amino acid, cysteine contains a sulfhydryl group (–SH) in its side chain. Two cysteine molecules can undergo oxidation to form a covalent disulfide bond, resulting in the formation of cystine.

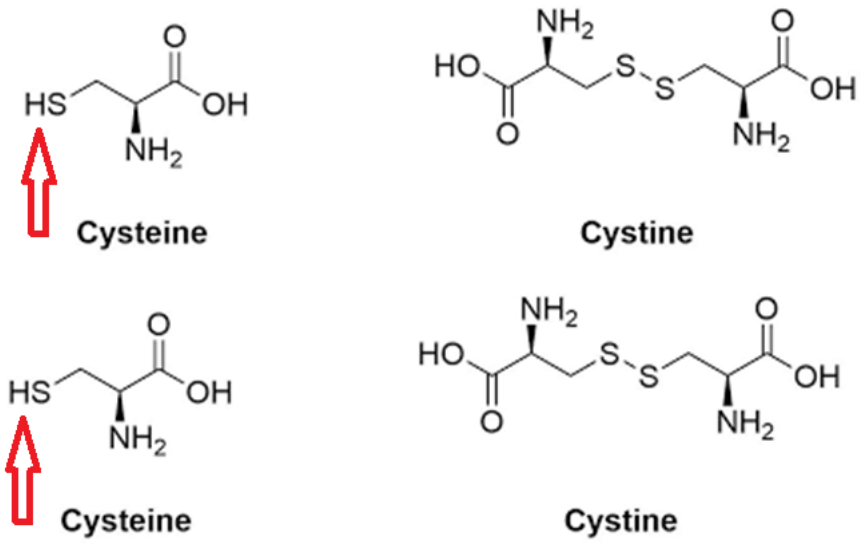

Figure 1: The structure of cysteine and cystine

Cysteine is a critical component of proteins in nails, skin, and hair, and plays a vital role in collagen synthesis, influencing skin elasticity and texture. Its antioxidant properties stem from the thiol group, which is unique among coded amino acids due to its high reactivity and redox chemistry. Cysteine is the only amino acid capable of forming covalent disulfide bonds in oxidative environments, which can be reversibly dissociated under reductive conditions. Although cysteine is not considered an essential dietary amino acid—since it can be synthesized from methionine—it is crucial within the cell for protein synthesis and the production of various other molecules, including glutathione (GSH), coenzyme A (CoA), taurine, iron-sulfur clusters, and hormones such as insulin and vasopressin. The formation of disulfide bridges from cysteine residues is essential for proper protein folding into secondary and tertiary structures, and these bonds also stabilize large proteins like albumin, a key transporter in the body. The reactivity of free thiols often results in cysteine binding with other molecules, and it is worth noting that cysteine is a glucogenic amino acid that can be catabolized to pyruvic acid and glucose, ultimately liberating energy.

1.3.2. Coenzyme A (CoA)

Fatty acid synthesis is a complex, multi-step process that begins with the formation of malonyl-CoA from acetyl-CoA. The fatty acid synthase complex, which consists of two arms (Pan-SH and Cys-SH), facilitates this process. The Pan-SH arm holds malonyl-CoA, while the Cys-SH arm accepts incoming acetyl-CoA. Following the removal of both CoA groups, the acetate from the Cys-SH arm attacks the molecule on the Pan-SH arm, leading to the formation of saturated butyric acid, which is then transferred to the free end of Cys-SH. This cycle repeats, ultimately producing 16-carbon fatty acids such as palmitic acid.

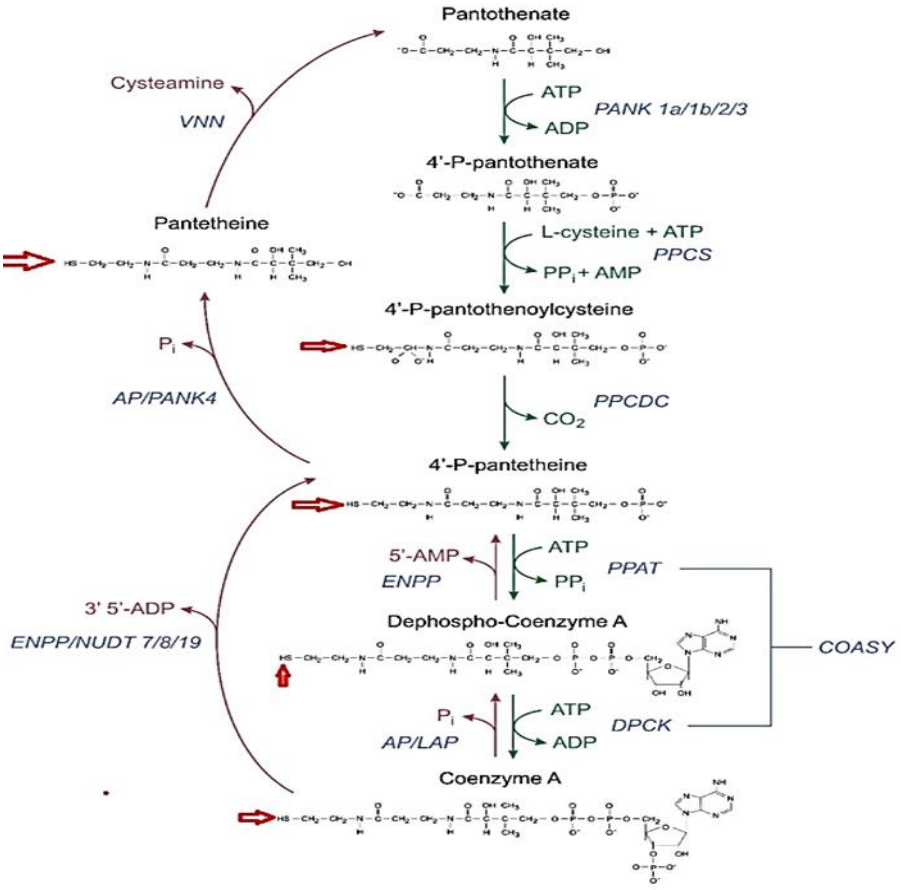

Figure 2: The Synthesis of Co-A

The thiol group plays a pivotal role in the production of CoA and the functionality of the fatty acid synthase enzyme complex, which are crucial for lipid biosynthesis. During CoA production, cysteine reacts to form 4-phosphopantetheine, a fundamental molecule in fat synthesis. Any interference from free radicals with cysteine or the thiol group can hinder CoA production.

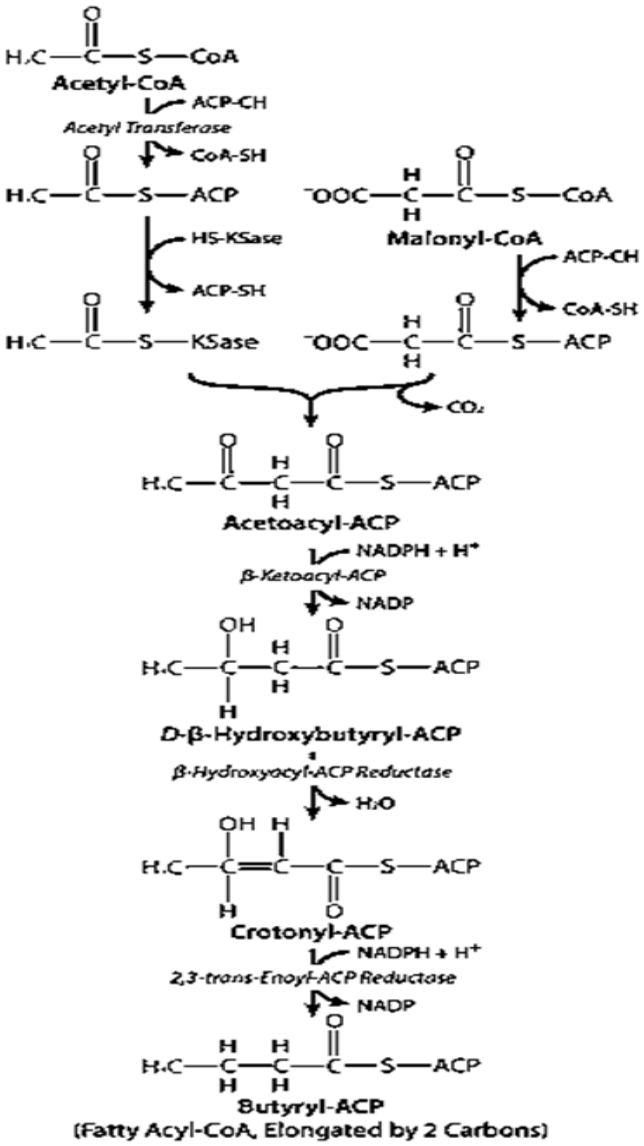

Figure 3: Fatty Acid Synthesis

CoA is also integral to energy liberation, combining with pyruvate to form acetyl-CoA, which initiates the citric acid cycle. Furthermore, radiation exposure may adversely affect CoA production, potentially damaging acetyl-CoA and disrupting mitochondrial Krebs and citric acid cycles.

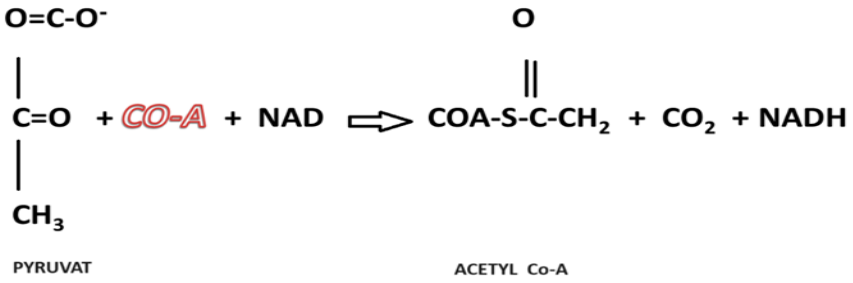

Figure 4: The reaction of Co-A to form Acetyl Co-A

1.3.3. Homocysteine

Homocysteine, an amino acid derived from the demethylation of methionine, plays a crucial role in synthesizing several amino acids, facilitated by its thiol group. It can interact with other molecules to form cystathionine, which is subsequently hydrolyzed into cysteine.Cysteine is essential for cellular function, contributing to the synthesis of various proteins and CoA. Homocysteine is also involved in producing tetrahydrofolate, the active form of folic acid, which is vital for hemoglobin production.

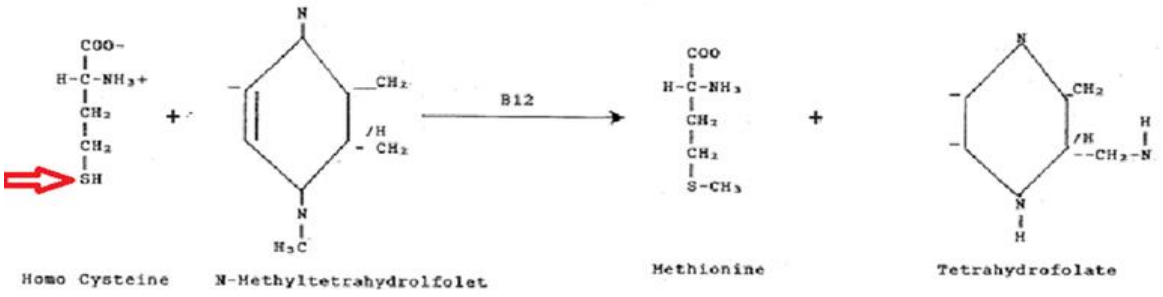

Figure 5: The Production of Tetrahydrofolate

1.3.4. Pantothenic Acid (Vitamin B5)

Pantothenic acid, found abundantly in both plant and animal sources, is essential for human health. It aids in the utilization of carbohydrates, proteins, and lipids, and is crucial for maintaining healthy skin. Pantothenic acid is synthesized via peptide linkage to β-mercaptothion amine, derived from cysteine. The terminal thiol group of β-mercaptothion amine serves as the reactive site for CoA. This sulfur bond possesses high energy, comparable to that of high-energy phosphate molecules like ATP, facilitating numerous metabolic reactions.

1.3.5. Beta-Oxidation of Fatty Acids

Beta-oxidation is the metabolic process by which fatty acids are degraded to produce energy. Long-chain fatty acids enter cells via specific transporters and are subsequently activated by the addition of a CoA group. Any disruption of CoA or acetyl-CoA production by free radicals can impede the initial stages of beta-oxidation.

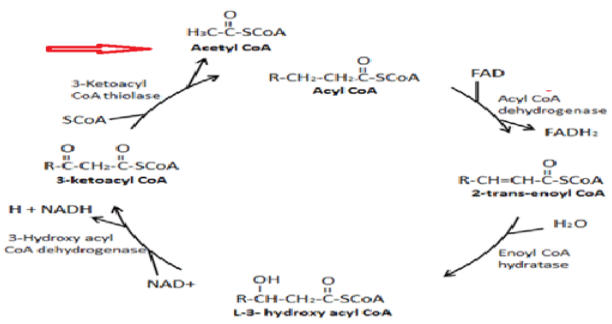

Figure 6: Key regulation sites of fatty acid β-oxidation

1.3.6. Cholesterol Synthesis and HMG-CoA Formation

HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) serves as a precursor for cholesterol synthesis, formed through the condensation of acetyl-CoA and acetoacetyl-CoA, catalyzed by HMG-CoA synthase. The rate-limiting step in cholesterol synthesis is catalyzed by HMG-CoA reductase, an enzyme containing a thiol group, which can be affected by radiation.

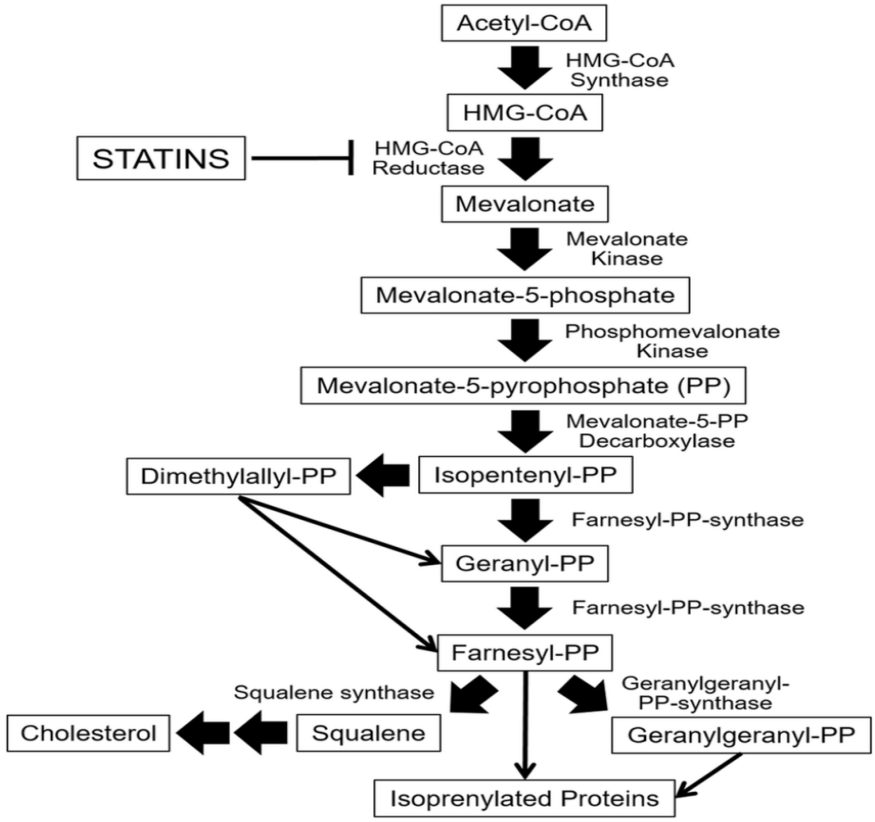

Figure 7: The Mevalonate pathway

1.3.7. Iron-Sulfur Proteins

Iron-sulfur proteins, integral components of the electron transport chain, transfer electrons during cellular respiration. Various forms of non-heme iron-sulfur clusters exist, distinguished by their iron and thiol group content.

- FeS→has four SH group & one iron atom
- Fe_2S→has four SH group & 2 iron atoms
- Fe_4S→has four SH group & 4 iron atoms
- Fe_3S→has four SH group & 3 iron atoms

1.3.8. Synthesis of Glutathione

Glutathione is synthesized through the sequential addition of cysteine to glutamate, followed by glycine. The reduced form, GSH, contains an active thiol group, while the oxidized form, GSSG, is crucial for cellular protection against oxidative stress. Ionizing radiation can stimulate endogenous ROS production, leading to mitochondrial dysfunction.

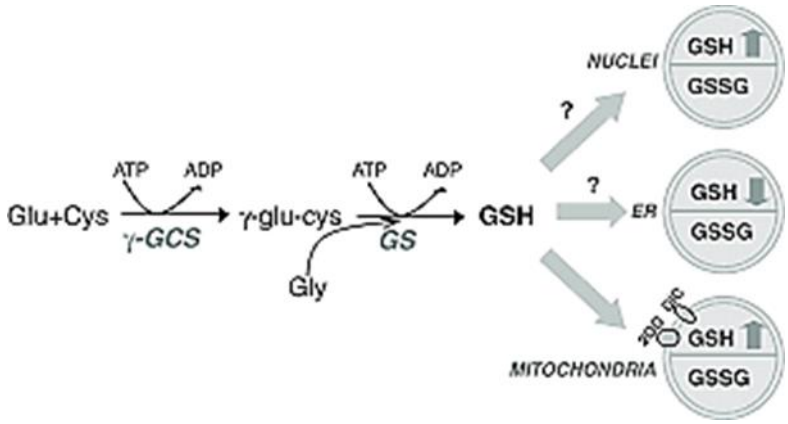

Figure 8: Glutathione synthesis and compartmentation [20]

1.4. The Effect of Free Radicals on Thiolate Biological Molecules

The interactions between free radicals and thiolate biological molecules can lead to several detrimental cellular effects, including:

•Early Cell Death: The oxidative damage caused by free radicals can initiate apoptotic pathways, leading to premature cell death.

•Delayed or Stopped Cell Division: Reactive species can interfere with the cell cycle, causing delays or halting division altogether.

•Cell Aging: Accumulation of oxidative damage over time contributes to the aging process at the cellular level.

•Unbalanced Cell Division and Cancer Development: Disruption in normal cellular signaling can lead to unregulated cell division, fostering the development of cancerous cells.

•Genetic Mutation: Free radicals can induce mutations in DNA, which may result in long-term genetic consequences.

Hypothetically, if cells could efficiently eliminate free radicals within a very short timeframe, the likelihood of these reactive species interacting with critical biological molecules would significantly decrease. Cellular mechanisms for the removal of free radicals and waste products include biological excretion processes. This involves transporting waste to the cell membrane, expelling it, and subsequently sealing the membrane to isolate

the remaining cellular components. This excretory process is vital for maintaining a stable chemical environment within the cell.

Typically, cells require minutes or hours to eliminate small waste materials, including free radicals, and hours to days for larger waste molecules. However, the average lifespan of free radicals' ranges from 10−910−9 to 10−610−6 seconds. This brief existence indicates that biological removal mechanisms alone cannot effectively manage the effects of free radicals.

Alternative strategies for mitigating free radical presence include the introduction of external molecules through dietary sources, such as antioxidants. Compounds like glutathione (GSH), which contains a thiol group, can react with and neutralize free radicals.

In recent years, there has been a growing interest in free radical chemistry. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced by various endogenous systems and can be exacerbated by exposure to different physicochemical conditions or pathological states. A delicate balance between free radicals and antioxidants is crucial for maintaining physiological function. When free radicals exceed the body's regulatory capacity, oxidative stress occurs, leading to adverse alterations in lipids, proteins, and DNA, which can trigger a variety of human diseases.

Therefore, the application of external antioxidant sources can help mitigate oxidative stress. Reducing free radical levels or decreasing their production rate may delay the aging process. Certain nutritional antioxidants have shown promise in retarding aging and preventing disease

2.Discussion

The concept of longevity encompasses not only the extension of life but also the enhancement of health quality throughout one's lifespan. Historically, significant improvements in life expectancy have been observed, increasing from approximately 35-40 years in the late 18th century to nearly 78 years by 2015. This trend highlights advancements in healthcare, nutrition, and living conditions, yet it also raises questions about the quality of life during these extended years.

Aging is characterized by a gradual decline in physiological functions and an accumulation of cellular damage. The review emphasizes the role of **mitochondrial DNA mutations** and oxidative stress in this process. Mitochondria, as the powerhouses of cells, generate energy but also produce reactive oxygen species (ROS) that can lead to oxidative damage. The correlation between mitochondrial dysfunction and aging underscores the importance of understanding these cellular processes to promote healthy longevity.

The review extensively covers the impact of **free radicals** on aging. Free radicals, particularly those generated in mitochondria, contribute to cellular damage and aging. The evidence linking oxidative stress to various aging symptoms emphasizes the dual nature of free radicals: while they are byproducts of normal metabolic processes, their accumulation leads to detrimental effects. The concept of **oxidative stress** as a key player in aging opens avenues for antioxidant therapies that may mitigate the effects of free radicals and enhance longevity.

The above discussion on **thiol groups** and their role in cellular repair mechanisms is particularly noteworthy. Thiol-containing molecules like glutathione are central to combating oxidative stress. The review suggests that enhancing the availability of thiol groups through dietary antioxidants could improve cellular resilience against aging-related damage. This aligns with the growing interest in nutritional interventions to promote health span alongside life span.

The limited availability of thiol groups within cells to neutralize reactive oxygen species under stress conditions highlights the necessity of considering external supplementation, especially in situations involving radiation exposure, smoking, or excessive sun exposure, to mitigate their negative effects on health span. Conversely, reducing thiol levels may enhance sensitivity to radiation during therapeutic treatments trial.

3.Limitation of the study

The interplay between various factors influencing aging—such as genetic predispositions, environmental stressors, and cellular responses—necessitates a multidisciplinary approach to research. Future studies should focus on elucidating the mechanisms by which oxidative stress and free radicals' impact cellular functions over time. Additionally, investigating the genetic control of aging processes in model organisms could provide valuable insights into potential interventions for promoting longevity.

4.Conclusion

In summary, the multifaceted nature of aging is intricately linked to cellular dynamics, oxidative stress, and the integrity of biological structures. This research underscores the pivotal role of free radicals and reactive oxygen species in driving the aging process, highlighting their contribution to cellular damage and the decline in physiological functions. The findings from recent studies, particularly those focusing on cell membrane dynamics and mitochondrial health, illuminate the complex interplay between cellular senescence, damage repair mechanisms, and longevity.

The evidence presented affirms that aging is not merely a product of time but a cumulative response to various internal and external stressors, including oxidative damage and environmental factors such as UV radiation. The involvement of thiol groups, particularly in critical biomolecules like cysteine and glutathione, further emphasizes the importance of maintaining cellular health to mitigate aging effects.

Future research should aim to explore therapeutic interventions that bolster cellular repair mechanisms, enhance antioxidant defenses, and promote healthy longevity. Understanding the molecular underpinnings of aging can pave the way for innovative strategies to improve quality of life and extend health span, ultimately contributing to the broader goal of achieving healthier aging in our populations.

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