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OXIDATIVE STRESS AND LONGEVITY

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Abstract: **Reactive oxygen species (ROS), unavoidable by products of aerobic metabolism, are known to cause oxidative damage to cells and molecules. This in turn is widely accepted as a fundamental determinant of both life and life span. Harman was the first to put forward that the damaging effects of ROS may play a key role in the mechanism of aging. Genetic studies of such abstractedly related species of *Caenorhabditis elegans, Drosophila melanogaster*, and mice support this hypothesis. However, ROS are not only a cause of structural damage, but also physiologically signally processes. Abnormally high levels of ROS may therefore lead to dysregualtion of redox-sensitive signaling pathways. This paper gives an overview of the positive and negative functions of reactive oxygen species, the oxidative stress, rate of living and ROS signaling theory of aging, mechanism of aging, effect of oxidative stress and the interaction of aging and age-related disease and the effect of antioxidants supplementation on aging and longevity.**

Keywords: **Reactive oxygen species (ROS), longevity, oxidative stress, antioxidants and supplementation.**

1. INTRODUCTION

The development of life on earth came about alongside the formation of free radicals [1]. Free radicals play a role in major biological processes such as cell division, cell decay and death [2]. Endogenous production of ROS is mainly linked to cellular metabolism. During cellular respiration, O_2 is used by the mitochondria to produce the necessary energy in the form of Adenosine Triphosphate (ATP), which is entwined with the formation of ROS, especially within the mitochondrial electron chain (part of oxidative phosphorylation) [3, 4].

Mitochondrial supplies are represented by the electron chain and the nitric oxide syntheses reaction. The rate of mitochondrial respiration is responsible for the rate of production of reactive oxygen species (ROS). Therefore, the higher the metabolic rate of an organism, the shorter is its maximum life span with few exceptions [5, 6].

Cells use antioxidants to neutralize ROS. The superoxide anion (O_2^*) the direct product of mitochondrial metabolism, is neutralized by superoxide dismutase, producing hydrogen peroxide H_20_2. This ROS is not very reactive; however, in the presence of some substances, it may activate the formation of highly reactive free radical; for instance, H_20_2 is catalyzed by the free iron bivalent ions and leads to the generation of hydroxyl radical (OH*) in the Fenton reaction.

ROS may have a productive use as well [7]. The beneficial physiological cellular use of ROS is now being demonstrated in different fields, including intracellular signally and redox regulation. Thus our cells also produce some hydrogen peroxide consciously for use as a chemical signal that regulates everything from glucose metabolism to cellular growth and proliferation [8]. The main ROS that are synthesized are, O_2^{*-} (Superoxide radical) and NO (Nitric Oxide), which are produced by Nicotinamide Adenine dinucleotide phosphate hydrogen oxidase (NADPH oxidase) and nitric oxide syntheses (NO syntheses) in different places of the organism [9]. These enzymes are very reactive in most of the reproductive tissues, signifying that ROS are indeed crucial for reproduction for example, a certain level of NO is necessary for mammalian spermatozoid maturation and activation, [10], the functioning of immune system sense (sight) and other subsystems depends on the use of ROS. Oxidation also allows obtaining energy for living and reproduction from different sources that were not available prior to the great oxidation [2, 1]. Thus the dilemma is not the existence of ROS in living systems but the imbalance between the ROS and antioxidants that is oxidative stress.

Aging is an intrinsic, universal, multifactorial and progressive process characterized as degenerative in nature, accompanied by continuous loss of function and eventually increased mortality rate [11-14]. It can also be viewed as a dynamic, time-dependent process characterized by the gradual ever increasing cell damage, the progressive reduction in cell functions, and the increased susceptibility to morbidity [15]. Although aging is relatively well preserved process among all organisms, the underlying molecular mechanisms differ between species and are still an active field of investigation [16-19, 4]. Aging is one of the risk factors for several chronic diseases. The accumulation of disease associated toxic materials like [ROS], an excess amount of pro-inflammatory cytokines can accelerate the aging process [20]. The severity of the disease conditions and candidate immune players could be biomarkers for the measurement of aging [20]. Among the theories that elucidate the aging process, the free radical theory, of aging is long established [21] this theory hypothesize that aging is a consequence of the failure of several defensive mechanisms to respond to the reactive oxygen species (ROS) induced damage particularly in the mitochondria [22]. Age- related diseases are related to structural changes in mitochondria, accompanied by the alteration of biophysical properties of the membrane including alteration in the electron transport chain complexes activities, decreased fluidity, and subsequently resulted in energy imbalance and mitochondrial failure. These perturbations damage cellular homeostasis mitochondrial function and increase vulnerability in oxidative stress [23, 24]. Elderly people are vulnerable to a decline in the efficiency of their endogenous antioxidant systems. Organs such as brain and heart, with high rates of oxygen consumption and limited respiration levels, are particularly vulnerable to this phenomenon, hence partly explaining the high prevalence of cardiovascular diseases (CVD) and neurological disorders in elderly [25].

Oxidative stress plays a fundamental role in the development of age-related diseases including; ischemia, heart failure, and diabetic cardiomyopathy [26-28]. ROS excess can also provoke CVD and irreversible damage to the mitochondria. Oxidative stress is also involved in the development of neurodegenerative diseases, such as Alzheimer's disease, Parkinson disease and Huntington's disease and can cause retinal degeneration. The pathophysiology of diseases such as respiratory, obesity, metabolic syndrome, recurrent aphthous stomatitis and diabetes mellitus is associated with oxidative stress [28-30]. ROS are produced within the biological system to modulate the cellular activities such as cell survival, stress or response and inflammation [31, 32]. Elevation of ROS has been associated with the onset and progression of aging however they may not be an essential factor for aging. [12], they are more likely to exacerbate age-related diseases progression via oxidative damage and interaction with mitochondria [33]. Due to their reactivity high concentration of ROS can cause oxidative stress by disrupting the balance of antioxidant and pro-oxidant levels [32]. Emerging research evidence has suggested that natural compound can reduce oxidative stress and improve immune function [34]. Indeed oxidation damage is highly dependent on the inherited or acquired defects in enzymes involved in the redox mediated signaling pathway.

Therefore the role of antioxidants in preventing age related diseases and in promoting healthy aging should be considered.

2. OXIDATIVE STRESS (FREE RADICAL) THEORY OF AGING

The free radical theory of aging [35] was originally described by Harman in the 1950s [21]. It proposes that organisms age because they accumulate oxidative damage. This damage comes from ROS which are partially reduced metabolites of molecular oxygen generated as products of metabolic reactions or as by-products of diverse cellular processes, such as respiration. For many years till date this theory has been the most popular concept in the area of aging, with thousands of publications every year. There are various studies that reveal that ROS and oxidative damage increase with age [36]. To elaborate on the aforementioned fact, this theory posits that, during aerobic metabolism, the electron transport chain in mitochondria is not only a source of ATP but also of reactive oxygen species (ROS). At moderate concentrations ROS may have important intracellular signaling functions, particularly for the control of ventilation, nerve transmission and immune regulatory processes [37]. ROS are also considered second messengers involved in the activation of NF-Kappa Beta Via Tumor necrosis factors (TNF) and interleukin –1 [38], and in the regulation of Mitogen Activated Protein Kinase (MAPK) pathway [38]. Through these actions, ROS affects cell function, growth and development and are therefore considered "absolutely essential for the regulation of the metabolome" [39]. Contrary to conventional wisdom, ROS are not produced in an unregulated manner, having need of immediate neutralization. Rather rates of production are usually extremely low [~ 0.1 nM. H_20_2 formed min – 1 mg- 1 mitochondrial protein, ~ 0.01 % of metabolic rate [40]. High levels of ROS may be incompletely neutralized by antioxidants within the cell, resulting in indiscriminate damage to cellular lipids, proteins and Deoxyribonucleic acid (DNA). ROS levels may possibly increase in damaged and aged mitochondria and cause accumulation of ROS beyond physiological levels [40].

Oxidative, damage may be inadequately repaired or eliminated this can lead to physiological deterioration and phenotypic changes in the elderly and increased incidence of age-related diseases and death. And this may be a key determinant of Maximum Species Lifespan, (MLS). Oxidative stress could also provide a mechanism upon which other "damage" theories of aging are based. Examples include genomic instability as a result of DNA damage and accumulation of glycated cross links during protein damage that can results in the pathogenesis linked to cardiovascular and neurodegenerative disease: ROS production plausibly fulfills the four key characteristics used in defining the aging process [6]. ROS are endogenously produced under normal physiological conditions; they are produced continuously throughout life; and their deleterious effects on biological macro molecules may cause irreversible damage especially in post-mitotic tissues. Given these circumstances, differential rates of aging among species may be due to differences in oxidative damage accrual, either in response to low rates of ROS production or though enhanced antioxidant defense. Despite the intuitive logic and vast support of this theory [41-43, 6] a causal link between oxidative stress and the rate of aging still has not been clearly established. Not all available data support the oxidative stress hypothesis, begging the question of whether or not this aging theory is in fact still valid [44-46].

3. OXIDATIVE STRESS AND RATE OF LIVING THEORY

In 1778, Lavoisier suggested that oxygen was poisonous after noting that guinea pigs housed in pure oxygen died before the gas was used up [47]. The rate of living theory of aging begins with these findings, as well as studies on resting metabolic rate in various animal species [48]. This theory asserted that lifetime oxygen consumption is rigidly fixed; therefore, metabolic rate determines longevity.

Free radicals were first regarded as the reason for oxygen toxicity in 1954 [49] Gerschman *et al.*, and soon afterwards Denham Harman integrated the "rate of living theory", proposing that aging is due to the harmful activities of free radicals endogenously formed during normal metabolic processes [21] . Since then, the free radical theory has been repeatedly modified, renamed and constantly propounded [42, 50-52].

The oxidative stress theory and rate of living theories are iterations of the same hypothesis, if one presumes that higher levels of ROS are generated at faster metabolic rates than of lower metabolic rates [53, 54]. Animals with high mass specific metabolic rates ought to have short life spans, but this assertion is not supported in all cases with published data [53, 54].

a. Species lifetime energy expenditure based upon average daily metabolic rate is not constant but rather declines by more than 20% for every doubling of body or body mass.

b. Although dietary control extends lifespan, this process is not accompanied by attenuation in mass specific metabolic rate [55];

c. Significant species variations in MLS in both birds and mammals cannot be explained by divergent metabolic rates. Even within specie those individuals with the highest metabolic rates can live longest and those that exercise more do not automatically have shorter lives [56]. With the above mentioned facts, therefore the initial iteration of this theory while still often proposed [52] (Ishii, 2007), is no longer considered plausible.

4. TELOMERE SHORTENING

Replicative senescence (irreversible loss of division potentials) is a suitable model for aging. The replicative potentials *in-vitro* and the age of the donor/maximal lifespan are correlated [57]. Telomeres are sensors for oxidative damage in the genome. These segments of repetitive nucleotide sequences at each end of the chromosome protects the chromosome against deterioration at the chromosome ends. Oxidative stress and inflammation are the basic reasons for telomere shortening, which induces cellular senescence and apoptosis. Cell senescence provokes mitotic arrest and the Senescence-Associated Secretory Phenotype (SASP).

A large quantity of proinflammatory and growth factors are secreted. This triggers inflammation and production of ROS. Consequently there is even further cellular senescence, resulting in a vicious cycle. Telomere shortening has the potential to be a biomarker of aging, as it reflects the cumulative amount of oxidative damage to the organism [29, 57]. ROS can increase the speed of telomere shortening, as telomere are very rich in guanine nucleotide, which is the reason why they are particularly sensitive to oxidative stress, followed by DNA damage response and senescence. Senescence results to further ROS generation via SASP. A characteristic of cellular renascence is proliferative arrest [57].

Cellular senescence can be categorized into two types: replicative or stress-induced premature senescence. Replicative renascence is determined by cell division, while stress-induced premature renascence is induced by oxidative stress, mitogens, oncogenes, irradiation and other factors and is normally not related to telomere attrition [29]. SASP results in degenerative and proliferative age-related tissue alterations. These leads to chronic inflammation, remodeling and tissue repair. This provokes more oxidative stress, and therefore, more cells become premature renascent cells.

Telomere shortening and dysfunction are not only affected by age (oxidative stress and inflammation); there are a lot of other factors that have influence on telomere shortening. Some example of environmental factors that promote telomere shortening are; smoking, alcohol abuse, obesity, air pollution and mental stress. Divergent metabolisms, vitamins C, D and E, omega-3 fatty acids and estrogen treatment are examples of environmental factors countering telomere shortening. These factors are modifiable. Endogenous factors that counteract telomere shortening are telomerase, estrogen and endogenous antioxidants. Telomerase replaces telomere repeats by catalyzing (DNA) synthesis, preventing the shortening of telomeres in stem and germ cells, In addition, in cancer cells a high activity of telomerase is noticeable. Adversely in somatic cells there is low or undetectable telomerase activity. Estrogen stimulates telomerase. Additionally, telomerase shortening is linked with CVD, genetic and genomic perturbation, cell division, mitogenic signals and nontelomeric damage [29].

5. EFFECTS OF ANTIOXIDANTS SUPPLEMENTATION ON AGING AND LONGEVITY

The oxidative damage theory of aging seems to deal with a key component of intrinsic biological instability of living systems [58, 59]. The fundamental idea of the oxidative stress theory of aging is that free radicals and other ROS, formed unavoidably in the course of metabolism and occurring due to the action of various exogenous factors, destroy bio-molecules and accumulation of this damage are the cause of age-related diseases and aging.

If this theory is true antioxidants should slow down aging and prolong lifespan. This apparently obvious conclusion has encouraged enormous number of studies aimed at finding a relationship between levels of endogenous antioxidants and lifespan of various organisms or the effects of addition of exogenous antioxidants on the course of aging and lifespan on model organisms. Pub med provides more than 13300 hits for conjunction of terms “antioxidant and aging” [60]. However, in spite of the plethora of studies the answer to the question if exogenous antioxidants can prolong life is far from being clear.

6. EFFECTS OF SOME EXOGENOUS ANTIOXIDANTS ON THE LIFESPAN OF MODEL ORGANISM

Antioxidants protects the body against oxidative damage. They can prevent formation of ROS or they can quench ROS before they reacts to other biomolecules [28, 30]. Many studies have tackled the question of whether supplementation with antioxidant vitamins C and E, and synthetic compounds can prolong the lifespan of model animals. Vitamin C (ascorbic acid) is the major hydrophilic antioxidant and a powerful inhibitor of lipid per oxidation. In membranes, this molecule rapidly reduces α – tocopheroxyl radicals and Low Density Lipoprotein (LDL) to regenerate α - tocopherol and inhibits propagation of free radicals. Vitamin E (α–tocopherol) is the main hydrophobic antioxidant in cell membranes and circulating lipoproteins. Its antioxidant role is strongly supported by regeneration promoted by vitamin C. Vitamin E is thought to prevent atherosclerosis through inhibition of oxidative modification. Coenzyme Q (ubiquinol, CoQ) and lipoic acid in their reduced forms and melatonin are also efficient antioxidants. [60].

Novel endogenous indoles, indole propionamide, another endogenous antioxidant is comparable in structure to melatonin, binds to the rate limiting components of oxidative phosphorylation in complex 1 of the respiratory chain and acts as a stabilizer of energy metabolism, thus reduction ROS production [61]. A synthetic tetra peptide (Epitalon) Ala - Glu - Asp-Gly, showing antioxidant activity [62], (S,S) - 6 - hydroxyl - 2, 5, 7, 8, tetramethylchroman - 2 - carbonyl beta - alanyl - L - histidine (S, S - Trolox - carnosine) is a synthetic analogue of carnosine containing a trolox (water - soluble analogue of vitamin E) residue [63].

Recently, the anti-aging effect of resveratrol (RSV) has become a topic of great interest [64]. RSV a polyphenolic compound synthesized in many plants such as peanuts, blueberries, pine nuts and grapes which protects them against fungal infection and ultraviolet irradiation. It is largely build up in a glycosylated state (pieced). Some dimethoxylated RSV derivatives (Pterostilbene) are also present as well as RSV oligomers. Fascinatingly RSV plays a number of protective roles in animals, although it is rapidly metabolized in a conjugated form (glucorono - or sulfo) [65]. Since the early 1990’s it has been

suggested that RSV could be the molecule responsible for the French paradox that is the low occurrence of coronary heart diseases and cardio-vascular diseases in South- Western France, despite the consumption of a high saturated fat diet. The French paradox was connected to some extent with the regular consumption of red wine, which contains high levels of RSV [66].

Curcumin, the main constituent of the yellow extract from the plant *Curcuma longa* (turmeric), is a main bioactive polyphenol, which has been used extensively as a spice, food additive and herbal medicine in Asia [67]. Tetra hydrocurcumin (THC) is an active metabolite of curcumin. Orally ingested curcumin is metabolized into THC by a reductase situated in the intestinal epithelium. THC possesses extremely powerful antioxidant activity compared to other curcuminoids. The antioxidant role of THC has been implicated in recovery from renal injury in mice and anti-inflammatory responses [68].

Some researchers are optimistic that development of new means of introduction of antioxidants into cells or construction of new antioxidants can make a breakthrough in antioxidant modulation of aging and longevity. If mitochondria are the main source of ROS in the cell, mitochondrially targeted antioxidants could be more effective than traditional ones. This idea was the starting point of synthesizing positively charged derivatives of plastoquinone and other antioxidants which are retained in the mitochondria due to the high negative potential of the inner mitochondrial membrane [69].

Ascorbic acid partially rescued the lifespan of Superoxide Dismutase (SOD) deficient yeast- *Saccharomyces cerevisiae* which was considerably reduced as a result of lack of this vital antioxidant enzyme [70]. However, this effect should be seen rather as a partial restoration of the redox status seriously unbalanced in these cells rate compared to life extension of normal yeast cells. Another study, using D-erythro ascorbic acid showed little upshot of this antioxidant on the replicative lifespan of wild-type yeast [70]. Similar reports have been published for multicellular organisms, in which antioxidants had life-prolonging effects on mutant deficient in anti-oxidant defense or were subjected to oxidative stress but did not have an effect on the lifespan of healthy wild type animals.

Supplementation of the growth medium of *S. cerevisiae* with the lipophilic antioxidants α – tocopherol and CoQ alone or in combination increased oxidative stress and decreased cellular lifespan [71]. However, *S. cerevisiae* is not capable of producing polyunsaturated fatty acids[72] so lipid oxidative damage may be of lower significance and lack of protective effects of hydrophobic antioxidants located mainly in cell membranes may be the cause of this finding [71].

Effect of Vitamin E (on the lifespan of several multicellular model organisms (*Caenorhabditis elegans, Drosophila melanogaster*, mice, rats and guinea pigs) has been recently reviewed by Pallauf *et al.,* no consistent picture came into sight from the summary of data, some studies demonstrating prolongation of lifespan and others showing no effect [73]. Ernst *et al.*, conducted a comprehensive literature review as regards the effect of vitamin E on lifespan in model organism, including single- cell organisms, rotifers, *C. elegans, D. melanogaster* and laboratory rodents. The findings of their review suggest that there is no consistent beneficial effect of vitamin E lifespan in model organisms, which corresponds to the outcome of meta- analysis of mortality in human intervention studies [74].

[75] Hector *et al.*, (2012) quantified the current knowledge of life extension of model organisms by RSV. These authors used meta- analysis technique to evaluate the effect of RSV on survival, using data from 19 published papers, including species; yeast, nematodes, Mexican fruit flies, and Turquoise kill fish. While the lifespan of the turquoise Kill fish was positively affected by the RSV treatments, results are less clear for flies and nematodes, and there was important variability between the studies [75].

The rapid expansion of Nano-technology provided a huge assortment of Nanoparticles (NPs) that differ in chemical composition in size, shape surface charge, chemistry, and coating and dispersion status.

Antioxidant delivery can be significantly improved using various NPs [76], some NPs possess antioxidant properties and are able to efficiency attenuate oxidative stress by penetrating specie tissues or organs, even when administered at low concentrations and found to increase the lifespan of model organism [77, 78]. Nevertheless there is an increasing concern about the toxicity especially gene toxicity of NPs, and this question field requires thorough studies.

It has been argued that antioxidant mixtures, such as those found in natural products, are healthier than simple antioxidant formulas that are due to synergism between antioxidants. KPG-7 is a commercially available herb mixture containing *Thymus vulgaris*, *Rosmarinus officinalis*, *Curcuma longa*, *Foeniculum vulgare*, *Vitis vinifera* (polyphenol), *Silk protein*

Taraxacum officinale and *Eleutherococcuss senticosus*, which have been reported to contain a variety of anti-oxidant, antitumor and anti-inflammatory bioactivities. Positive effects of such extracts on the lifespan of model organisms have been reported but other studies showed no significant effect [79].

7. CONCLUSION

This paper presents some explanation in the role of free radical in major biological processes and how the imbalance between ROS and antioxidants results to oxidative stress. It further explains the free radical theory of aging as established by [21] which speculate that aging is a consequence of the failure of several defensive mechanisms to respond to ROS induced damaged. Although ROS generation may not be an essential factor for aging [12], they are more likely to exacerbate age-related diseases progression via oxidative damage and interaction with mitochondria [33]. The free radical theory of aging and the rate of living theory are iterations of the same hypothesis; the only difference is that the rate of living theory further postulates that larger animals outlive the smaller ones due to their slower metabolic rate [53, 54]. It is important to mention that oxidative stress is one of many mechanisms that drives the aging process. ROS signaling is one of the mechanisms responsible for the development of cell senescence and organismal aging. ROS signaling is considered to be a further development of the free radical theory of aging [80]. Considering the effect of antioxidants supplementation on aging and longevity from the summary of data, there seemed to be no consistent findings. Some studies demonstrates prolongation of lifespan others shows no effect or even negative effects on lifespan.

However beneficial effects of antioxidant supplements seem undoubtful in cases of antioxidant deficiencies. Additional studies are required to further investigate, the association between antioxidants and longevity.

AUTHOR'S CONTRIBUTION

Yocy Yohana Izam; (First and corresponding author); Conception, design, and critical revision of the manuscript for intellectual content.

Kennedy Iliya Amagon; Encouraged and assisted the corresponding author to carry out a critical review of the manuscript.

Prof. Nenman Noel Wannang; Supervised the work and gave the approval for the manuscript to be submitted for publication.

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