ALTERED REDOX BALANCE IN AGING PROCESS: GENERAL MECHANISTIC AND CLINICAL ASPECTS

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Abstract:

Introduction: Aging researches have experienced an unprecedented advance over recent years. The comprehension of process leading to age-associated alterations for the development of new treatments for age-associated diseases, such as cancer, diabetes, Alzheimer and cardiovascular accidents but also to encourage healthy gain of years with high standard of quality of life is encouraged. It is widely considered that the accumulation of molecular and cellular damage influenced by reactive oxygen species producing oxidation might orchestrate the progressive loss of control over biological homeostasis and the functional impairment typical of aged tissues.
Objective: The overall aim of this work is review the general and clinical aspects of aging and connects biological at molecular, cellular and organism levels.
Materials and methods: Through general overview of findings reported in consulted literature (132 valid documents-53 selected) is sustained how resulting oxidative stress-redox disruption signal took part in the mechanisms of ageing physiology and physiopathology.
Results: Findings related to aging controlled, at least to some extent, by genetic pathways and biochemical processes conserved in evolution is discussed and integrates to common denominators of aging in different organisms, with special emphasis on mammalian aging. The aspects considered in overview are: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.
Conclusions: Based on the revisited aging associated redox mechanisms causing damage, the compensatory responses leading to homeostasis reestablishment and the interconnection between them are analyzed and explored with the final goal of identifying pharmaceutical targets to improve human health during aging, with minimal side effects.

Keywords: aging, oxidative stress, free radical, reactive oxygen species

INTRODUCTION

Aging is the process of change accumulation by age and it could be defined as a complex chronological and multifactor [1,2]. There are several hypotheses to explain how aging occurs, considering complex physiological alteration in the organism described as: mitochondrial changes, accumulation of aberrant proteins in the cytosol, chemical damage to macromolecules, somatic mutations and enhanced or diminished transcription of specific genes. Historically, theories of aging have been divided into two general categories: stochastic and developmental-genetic. In stochastic theories the free radical (oxidative stress/ mitochondrial DNA) theories are included. In developmental-genetic theories are defined ones that recognized the aging process to be part of the genetically programmed and controlled continuum of development and maturation. Longevity genes, accelerated aging syndromes, neuroendocrine, immunologic, cellular senescence and cell death theories are among them. [3,4,5]. These categories are not mutually exclusive. Indeed there is probably that maturation reflects a spectrum of changes from decreasing influence of active genetic factors and an increasing effect of stochastic events [6].

No theory has been generally accepted. The early observations on the rate-of-living theory by Max Rubner and the report by Gershman [7] that oxygen free radicals exist in vivo culminated in the seminal proposal in the 1954 by Denham Harman that reactive oxygen species (ROS) are a cause of aging (free radical theory of aging). This hypothesis of Free Radicals Theory of Aging [8] was after modified in 1972 [9] and the modern version of this tenet is the oxidative stress (OS) theory with best mechanistic elucidation of the aging process and other age-related phenomena such as age-related diseases.

The OS hypothesis of aging postulates that accrual of macromolecular damage accumulation is due to the redox imbalance, i.e. the net effect of disparity between the amount of ROS generation and the counter-acting antioxidative forces [10,11]. ROS are oxygen derived metabolites that have higher reactivity than molecular oxygen and are continually produced as consequences of normal aerobic metabolism as well as taken up from the external environment [12-14].

They serve as specific signalling molecules in both, normal and pathological conditions, and their transient generation, within boundaries is essential to maintain homeostasis. ROS can inflict oxidative molecular damage to lipids, proteins and DNA when their production overwhelms the capacity of antioxidant systems [12-14]. Age-related diseases are often considered to be distinct pathologies, rather than inevitable part of aging and a consequence of redox deregulation. The OS connotation to aging has been elucidated through previous research in animal's models. The functional consequence of an age related modifications in such biochemical's markers of OS has been little studied and remains therefore largely unknown. In recent years several related theories containing ROS have also been proposed. Mitochondrial theory, senescence theory and molecular inflammatory theory are among extensively studied all of them contributing to aging [15-16]. The overall aim of this work is a current review of theses aspects and connects biological at molecular, cellular and organism level. Recent clinical evidences in humans of OS alterations are finally compared and discussed.

I. MATERIAL AND METHODS

This review is intended to analyze original investigations and reviews articles focused on the effect of oxidative metabolism in antioxidant status during aging also related to findings in clinical researches. ROS, antioxidant and redox biology physiological aspect are considered. This work presents data from around 132 reviews, book chapters and original research about how resulting oxidative stress-redox disruption signal took part in the mechanisms of ageing physiology and physiopathology. In an attempt to identify the relevant literature, a comprehensive search was performed using PubMed and Google Scholar. The following search terms were included in multiple combinations: oxidative stress, agind and antioxidant status, oxidative stress, age-associated events, and clinical research.

Further PubMed search was performed by selecting the "See all related articles" function, thus providing an additional extensive list of publications.

Further search was performed by manual scanning of reference lists of several review articles, as well as original investigations. Search was conducted from December 2016 to September 2017.

II. RESULTS

MITOCHONDRIA AND ROS GENERATION

It is generally accepted that the respiratory chain is one of the most important if not the first source of ROS generation in animal and human body. Interrelationships between ROS generation and effects in mitochondria have been studied in detail [17,18].

This organelle produces ATP through a series of oxidative phosphorylation sequences that ultimately involve a four electron reduction of molecular oxygen to water. During these events one- or two-electron reductions of molecular oxygen can occur, generating ROS as anion superoxide radical and non radical metabolites as hydrogen peroxide [13]. The oxygen metabolites can be converted to others ROS as carbonate radical. Indeed mitochondria generate and are in contact with different oxidants with diverse strength, reactive properties and ability to diffuse and to be removed. This last by specific antioxidants such as: catalase (CAT), peroxiredoxins and theirs associated reductases (glutathione peroxidase (GPx)/ glutathione reductase (GRx) system and thioredoxin peroxidase (TrxP)/ thioredoxin reductase (TRxR) system), NADH/NADP transhydrogenase, matrix Mn superoxide dismutases (SOD) and Cu Zn SOD in intermembrane spaces. Responses to the ROS presence depend on the species, rate, quantity, accumulation, and microenvironment of generation [13].

Progressive decline in mitochondrial function with age associated to OS have been demonstrated in a variety of tissues [19,20]. This decline is related to impairment of electron transport chain, elicited by respiratory inhibitors, mitochondrial DNA (mtDNA) mutation, or gene knock-out [21].

A number of large –scale deletions, point mutations, and tandem duplications of mtDNA have been found in various mammalians aged tissues and usually coexist with the wild type mtDNA termed heteroplasmy. The frequency of occurrence and the type of mtDNA mutation are determined by the interaction between mt DNA polymerase that bear the ROS-induced oxidative damage during DNA replication [20,22,23].

These finding and others evidences have been supported the notion that OS is an important contributor to decline of mitochondria functions during aging [21].

ROS serve as specific signalling molecules under both physiological and pathophysiological conditions involved in: modulation of transcription factors as AP-1, p53, Forkhead transcription factors

and NF-κB, modulation of kinases (protein kinase C, MAP, ERK), phosphorylation (protein tyrosine, protein ser/thr) adenylyl and guanylyl cyclases activation, modulation of cell adhesion molecules expression, endonucleases and proteases activation, DNA synthesis and repair, modulation of apoptosis, telomere shortening, autophagy and cellular senescence [24,25,26,27].

The importance of mitochondria in both aging and age related disease is testified by research from Tanaka 1998 [28]. They showed that two-tends of Japanese centenarians have a mitochondrial gene variant known as Mt5178A. This variant codes for a subunit of NADH dehydrogenase, at complex I of the respiratory chain and it is associated with a low leakage of ROS generation. These people not only survive to hundred but they were half as likely to be hospitalized for any age –related disease as people without the variant: a strong link between aging and age related disease [28].

However these findings it remains unclear whether the decline in mitochondrial functions during aging mainly results from OS or consequences of synergistic effects of many factors associated.

ANTIOXIDANT DEFENSE

During lifetime, an antioxidant sophisticated network counteracts the deleterious action of ROS on macromolecules [16,29]. Cells synthesize some of their antioxidants, as the enzymes SOD, CAT and GPx, as well as the peptides with thiols groups, as glutathione (GSH) and thioredoxin (TRX) family. Other antioxidants are obtained from nature through nutrition, as vitamin C, vitamin E, and carotenoids. Several repair systems contribute to recovery the damaged molecules. Together these systems play an important role in the ability of the body to respond to the oxidant challenge of using molecular oxygen to drive reactions that yield the necessary energy [1,10].

In eukaryotic organism, several ubiquitous primary antioxidant enzymes, such as SOD, CAT, and different forms of peroxidases work in a complex series of integrated reactions to convert ROS to more stable molecules, such as water and molecular oxygen. Secondary enzymes act in concert with small molecular-weight antioxidants to form redox cycles that provides necessary cofactors for primary antioxidant enzymes functions.

The small molecular weight antioxidants (e.g. GSH, NADPH, TRX, vitamins E and C, trace metals, such as selenium) can also function as direct scavengers of ROS. This complex system has the ability to both maintain an intracellular redox balance and prevent or reduce molecular damage by ROS [29,30].

All are strategically compartmentalized in subcellular organelles within the cell to provide maximum protection. Generally almost antioxidants are specialized in removing or react with certain ROS. Considerable overlap and cooperation are demonstrated among antioxidants. Some antioxidants are obtained from diet and others from endogenous origin are heavily influenced by nutritional factors. Some are mandatory in the diet, and trace elements (as selenium) for the biosynthesis, or other functions which require special aminoacids [29]

Longevity has been associated with higher rate of antioxidants capacity. It is generally accepted that the activities and capacities of antioxidant systems are declined with age, leading to the gradual loss of prooxidant/ antioxidant balance and accumulation of oxidative damage in the aging process [1,16].

Evidences from populations' studies are contradictory. Previous works showed plasma and red blood cell SOD activity and plasma GPx activity increased or not change or decline with increasing age.

Simultaneously a decline in nutritional antioxidants was observed. Mn SOD located in the mitochondria is most significantly elevated during aging in various human tissues [31,32]. The modifications of

antioxidants activities could be associated with dysfunctional shift, oxidative DNA damage of specific genes, protein altered expression, post transcriptional oxidative damage and consumption of basic pools [33]. Different animals model have been developed to argue the functional consequence of decreased antioxidant capacities for aged cells [34]. In others, overexpressions of specific antioxidant enzymes were evaluated. The constructs modified or not the life span overall, although there were sex and genotypes specific effects. Pharmacological treatment can also used in appraisal investigation.

The Repair antioxidant system has received less attention than ROS scavenging or respiration efficiency. Some research explored the ability to repair oxidized proteins in animals' models. Results drive observation that an age related decrease expression of the system involves short life span [34].

OXIDATIVE STRESS AND BIOMOLECULES DAMAGE

ROS reacts with lipids, proteins, peptides, and nucleic acids. Oxidative damage to macromolecules is detectable under normal physiological conditions in healthy individuals suggesting that the efficiency of antioxidant and repair mechanisms cannot avoid completely the oxidation reaction mediated by ROS [4,16,29]. During aging the cellular homeostatic machinery becomes progressively impaired. Those increase vulnerability to oxidative damage. Oxidative process cause reversible or irreversible alteration to macromolecules [35]. Accumulation of oxidative and deleterious change overtime is associated to senescence [36,37].

DNA oxidative damage is a common mediator for both replicative senescence, which is triggered by telomere shortening, and premature cellular senescence induced by various stressors such as oncogenic stress and OS [33,38,39]. Extensive observations suggest that DNA damage accumulates with age and this may be due to an increase in ROS production and a decline in DNA repair capacity with age. Mutation or disrupted expression of genes that increase DNA damage often result in premature aging. Different methods and parameters have been used in animal models producing variety of ranging concentrations and contradictory data [11,40]. As a consequence it was assumed that same patron could occur also in humans.

It is important to note that the oxidative damage to macromolecule varies greatly among different tissues, species and detection methods.

The functional consequences of an age related increases in such oxidative damage have been little studied. It is possible that the concentration of this cumulative damage reported with age may fall below the threshold that a cell or tissue may tolerate with little or not direct impact on functional efficiency. Conversely oxidative damage to key genes and proteins may results in the efficiency of cell functioning [10,41,42].

INFLAMMATORY PROCESS AND DISEASE

In evaluating the Free Radical theory of aging and its possible link to numerous age related maladies, investigators have focused attention on the possibility that an increase in ROS generation, along with a concomitant disruption in redox balance, leads to a state of chronic inflammation [20,43-46]

By enhancing the intracellular signalling pathways of lymphocytes, ROS from activated macrophages and neutrophils may contribute decisively to the activation of the antigen-specific immune response and may allow immune system to respond to minute amounts of invading pathogens [43,44]. During physiological, redox regulation is implicated in gain or loss of functions or outright destruction, but an excessive stimulation by inflammatory mediator's increasingly relevant ROS production. Both acute and

chronic inflammations are physiological protective mechanism that acts in response to cellular injury or tissue destruction [44,47]. Inflammatory reactions are well-orchestrated events, known to be extremely complex but essential designed to limit insult and promote repair. Expressions of certain genes that encode several inflammatory proteins, including IL-1, IL-6, IL-8, and TNFα are enhanced in these conditions. These cytokines contain redox-sensitive NF-κB, specific, DNA binding sites in the promoter regions and their production is greatly influenced by oxidative status [80]. They have been shown to stimulate more OS condition, leading to further NF-κB activation. In this scenario, a positive feedback loop is also activated with the generation of ROS, which serves to further augment of the inflammatory processes cascade and exacerbate inflammation induced cellular and tissue damage. Chronic pro-inflammatory stages are likely pursued [24,43,47].

In aged organism, inflammatory reactions combined with the disruption of the organism's control could lead to a persistent pro-inflammatory state as, evidenced in a wide range of diseases that involve no-resolving or re-occurring reactivities [43,44]. Consistent changes in redox responsive cascades and in the expressions of corresponding target genes may have a similar or even greater impact on senescence as the direct radical inflicted damage of cellular constituents [4,10,48].

OS' CLINICAL EVIDENCES DURING AGING

A large amount of data about OS implications in tissues damage, diseases, biological variables and life habits has been shown [11,16,34,35]. The oxidative cumulative values in healthy humans related with aging and sex have been shown in biological fluids too [49]. There exist some reports on human erythrocytic, blood and plasmatic GSH, GSSG MDA, protein carbonyls, HNE, glutathione disulfide (GSSH), uric acid (UA), SOD, CAT and GPx values and others redox indexes in blood and plasma samples of healthy women and men of ages ranging from 9 to 99 years and centenarians [30,50-55]. In 2000 data from Italy [51], in 2002 data of USA [52], and Turkey [53], in 2004 data from Brazil [56], in 2006 from Germany [54], and in 2007 data from USA [55] and Mexico [30] healthy populations have been published. In those investigations tendencies for some parameters also significant correlations were established showing an increase of prooxidative capacities and a decrease of antioxidant capacities [52,56,54]. Further studies which were carried out previously present conflicting and contradictory results, e.g. concerning total antioxidative capacity of human blood plasma, which increased in one study, but decreased with age in another study [30,49,57]. Authors carried out in general cross sectional and comparative studies. In order to test whether the age dependence of redox parameter are gradually or seems to be a continuous process, authors divided cohorts of healthy subjects in smaller groups (decenniums preferentially) according to their ages. The results indicate that the balance of oxidant and antioxidant systems in plasma shifts in favour of accelerating oxidation during aging. One of the characteristic of aging is that the levels of non enzymatic antioxidant components decline during senescence. Linear dependence with age of some variables was considered reflecting a positive and significant correlation for E-GPx, P-SOD, E-SOD, MDA, HNE, PCO, and GSSG. A negative and significant correlation was found in GSH, Se [51,54,55]. In some studies data were transformed for statistical analyses. Correlation between some parameters is few reported .In that cases association were found between HNE:MDA, MDA:GSH and HNE:MDA. Analyses show general trends of oxidation as functions of age related to decreased antioxidant capacity. Cross sectionals study design lend itself to limitations because it is not possible to know who from the individuals recruited in each group of age will live beyond 80 years or more. In the articles refereed authors did not directly measured free radical production so it is not possi-

ble to determine if older persons produce more free radicals but also have an enhanced capacity to defend against them [54].

Centenarians represent a highly selected group of successfully aged people. They apparently escaped the age-related disease during their lives and show some distinct immunologic or metabolic features. It would conceivable to expect their antioxidant status to be better than that of normally aged subjects [51]. As results of different studies a quite peculiar antioxidant profile was finding. It is probably that this is not linked only to their antioxidants properties but also to their functions in other homeostatic mechanism such as immunomodulation.

III. CONCLUSIONS

Taking into account that causes of ageing are complex and multifaceted, the recognition of molecular and cellular concert involved are crucial. A causal relationship between some elements such as oxidative macromolecules modifications, mutations of mtDNA, mitochondrial dysfunction and aging has emerged but the mechanism by which these molecular and biochemical events occur remain to be established. Contribution of elements and basic mechanistic aspect should be research for more comprehensive understanding of in vivo metabolism and repercussion to human health. Cross longitudinal studies is needed to confirm existing evidences and support the related aging hypothesis. Despite these concerns, substantial progress has been made toward an integrative understanding of living senescence and attempts to delineate mechanism considering oxidative stress and ROS as potential key participants. Gaining in knowledge of specific aging pathway, investigators will be provided with additional opportunities to impact both life span and age related diseases in humans and others species. Nevertheless a strong possibility is previously suggested that the wasting process related to aging and diseases, at least to some extent, may not be irreversible in principle.

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