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Aging Mechanisms: Linking oxidative stress, obesity and inflammation

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ABSTRACT

Aging cannot be defeated in anyway in the world even having new and advanced technology. But molecular mechanism is a successful method to control aging. Many complex and multifunctional factors are the main cause of aging.
It is evident that the studies regarding cellular, genetic, and pathological and biochemical changes are exploring more and more pathways linking various diverse mechanism explaining aging. Implications of basic mechanisms of aging for improving both longevity and quality of life in human needs a clear understanding and takes a long time. However, reactive oxygen species (ROS) indicate a growing body even in the presence of fundamental mechanisms. According to oxidative stress theory, advanced and permanent addition of oxidative damage on critical aspects of aging process instigated by ROS influences. Telomeres theory is another, new aging theory that holds many promising possibilities for the field of anti-aging medicine. The theory was originated from the surge of technological breakthroughs in genetics and genetic engineering. Telomeres have also been found related to obesity. Obesity also leads to accelerated cellular processes. A "causative agent in aging" is considered inflammation that underlies a mechanism showing that for survival acute inflammatory response is necessary but long term exposure to different antigens than predicted by evolution cause low-grade inflammatory status which intern contributes to age-associated illness and death. The condition known as "inflammaging".

1. Introduction

Aging defined by Harman as the "progressive harmful variations in the cells and tissues with age that increase the risk of ailment and demise" (14). According to this, there are two basic aspects of aging process: 1) progressively loss of biological functions with age, and 2) consequently reduction in fighting with numerous forms of stress and increased exposure to many diseases.

Well defined, descriptive and definitive characteristics are significant to express process of aging but still remains poorly understood, largely because of its integrative and fundamentally complex nature and undefined normal aging from pathological aging. Aging has also been defined by many theories introduced by large variety from many disciplines such as physiology, genetics to epidemiology and demography (26).

The aging is one of the best examples of deterioration of homeostasis, as it is accompanied by an impairment of the physiological systems including immune system (2). The complex and multifactorial sources are important in aging. It is evident that the studies regarding cellular, genetic, and pathological and biochemical changes are exploring more and more pathways linking various diverse mechanism explaining aging. It is strongly believe that the cellular aging is mostly affected by increase in the oxidative stress and ROS formation. The Figure explains the integrative situation that contribute exogenous and endogenous factors at all levels to aging introduced by ROS and oxidative stress.

Aging causes the macromolecular damage which affects the signal transduction pathways at cellular level and cause organelle dysfunction, inflammation leading to cell death. This in turns manifest at systemic levels, including increased incidence of diseases, decline in organ function, death and reduced oxidative stress tolerance. While increased oxidative stress with other factors cause a range of modifications at molecular levels that contributes to genetic factors, aging and life style. Sensitizing or preventing and repairing defects can also reverse the aging process.

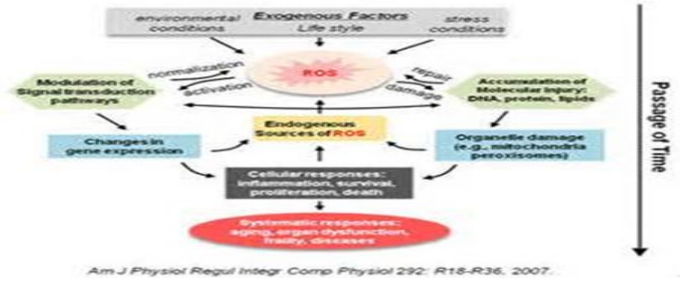


Fig: Explains the effects of endogenous and exogenous ROS on signal transformation, DNA repair, gene expressions and macromolecules with the passage of time

OXIDATIVE STRESS AND AGING: One of the most widely accepted theories well explain the aging process is Oxidative stress. Oxidative stress is the imbalance between the production and destruction of ROS (reactive oxygen species). ROS are metabolites of molecular oxygen. Reactive oxygen species are highly unstable because they have an unpaired electron; they try to achieve stability by accepting electrons from nearby molecules. The later become unstable and therefore chain reaction starts. ROS includes unstable oxygen radical superoxide radicals (O2) and hydroxyl radical(HO) and non-radical molecules like hydrogen peroxide(H2O2).These are byproduct of aerobic respiration or taken up from external environment. Their production is increased in stress and pathological states

Over the past decades many articles have been published that explains the role of oxidative stress in aging (2, 4, 6, 9, 10, 14, 24). In spite of many evidences explaining the notion that ROS are produced in the cells and manifest damage, an exact link explaining how damage occur is still not been clear.

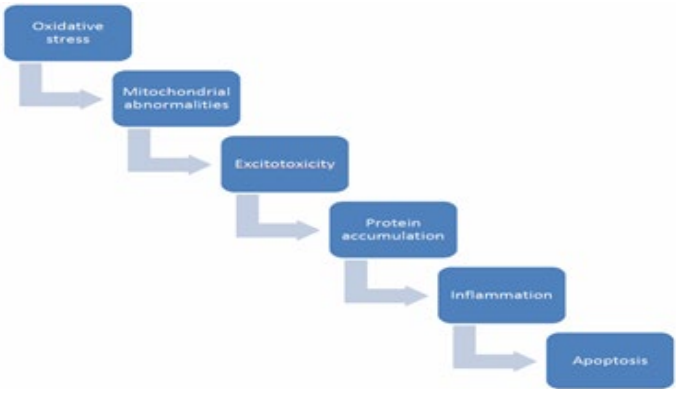


Fig: shows cascade of Oxidative stress

Mitochondrial theory is one of the extensively studied theory in aging regarding ROS component. Hypothesizing mitochondria plays a dynamic part in process of aging as it is the primary site for aerobic respiration. It produces ATP through different steps of oxidative phosphorylation reducing four electrons to water. Mitochondrial DNA and its structure is damaged by the ROS which is generated by electrons released from electron transport

Thain, leading to decrease in mitochondrial function and as a result more and more ROS are produced (35). Evidences to support mitochondria theory of aging suggest that mitochondrial DNA damage is directly related to aging (12,13).

Intracellular production of ROS includes peroxisomal oxidases (31), cytochrome p-450 enzymes (36), NADPH oxidases (25), or, Xanthene – Xanthene oxidases (28). Additionally, several environmental stresses like herbicide/insecticide contamination and heat stress (3), ultraviolet light exposure (31) and environmental toxins (32).

EFFECT OF ROS ON MACROMOLECULES: macromolecules such as nucleic acid, proteins and lipids are directly damaged by increased levels of ROS. Once these macromolecules become instable because of these ROS a chain of reactions starts until termination products are produced. For example, cellular membrane permeability and even membrane leakage changes can be manifested when lipid peroxidation occurs (30). ROS oxidation is very vulnerable by DNA bases and as a result they get either mutated or deleted (both in nuclear and mitochondrial DNA).

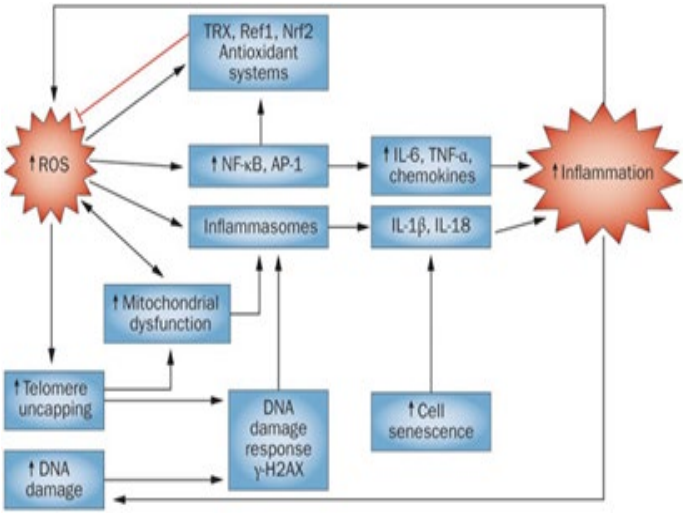


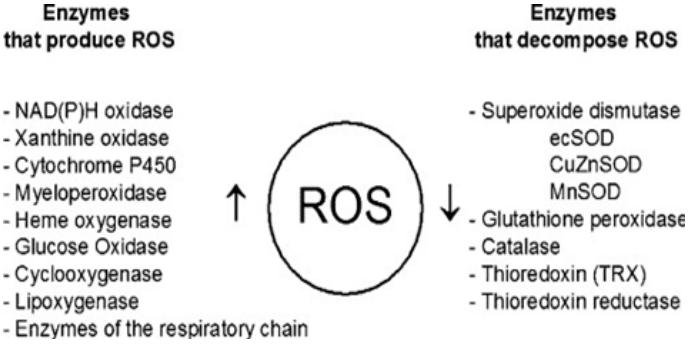
Fig: Showing mechanisms linking ROS with inflammation and DNA damage

Functional changes occur in proteins affected by these ROS producing substantial physiological impact e.g enzymes and transcriptional factors. Latter can produce a drastic effect by affecting the gene expression ultimately regulating the cell survival, death and aging.

ROS also affects apoptosis (programmed cell death).

Intrinsic and extrinsic apoptotic pathways involve ROS modulated molecules (27). Intrinsic apoptotic pathway, proteins that control mitochondrial membrane potential in the mitochondrial permeability transition pore complex, are the direct target for ROS (20). While some exogenous ROS generating stressor, will promotes apoptosis such as proinflammatory cytokines treatment, radiation, growth factors withdrawal and physiological challenges such as heat stress (3, 11, 18, 27).

ANTIOXIDANT SYSTEM: Various sophisticated antioxidant systems are distributed within cytoplasm and organelles to equalibirize the cellular production of ROS. Catalase, SOD and peroxidases are the chief antioxidant enzymes, whereas secondary enzymes acts as co factors like NADPH, vitamins E and C, thioredoxin and GSH, trace metals like selenium, which help primary enzymes in scavengering the ROS.



Attempts to use antioxidants to delay the process of aging were unsuccessful to enhance the life span in most cases (7, 33). Studies conducted by Keaney et al. (11) presented no increase in life span in dose dependent administration of synthetic antioxidant enzymes whereas, the experiments of Melov et al. (27) revealed significant increase in life span of cells treated with both synthetic SOD and catalase. These controversial and contradictory outcomes of both pharmacological and genetic effects of antioxidant on life span provide that aging as a multifaceted and complicated phenomenon hardly explained by a single theory. Another theory widely accepted to explain the cellular aging is "senescence theory of aging". This theory mainly focuses on the role of cellular signaling response to anxiety and injury. This signaling arouse the paths regulating cell senescence and leading to death (5). At cell stage, ROS can modulate signals speeding up the mitogenesis and premature cellular senescence (16).

Until now different studies have focused on the oxidative stress and aging processes but still there is a need to investigate more and have insight look in modulating the gene expression using redox sensitive transcription. Humans, mice, rats and flies have been under limited observation for potential changes in gene expression while most of the other studies focuses on the accumulation of oxidative markers with increase in age (15,22,23,29,37,39).

According to DNA damage theory, damaged and unrepaired naturally occurring DNA accumulate in the form of aging. Change in the structure of DNA results in abnormal development. Irreparable DNA damage is caused by many factors such as food additives, environmental pollutants, low dose ionizing radiation and, particularly nitrites and nitrates responsible for pre-mature aging and cancer. Two major types of DNAs contribute towards aging. One is called mitochondrial while other is called nuclear DNA. of these two, nuclear DNA is of major concern as it affects aging either directly (by increasing cell dysfunction) or indirectly (by increasing apoptosis or cellular senescence) by blocking and preventing transcription, translation as well as replication leading to cell death. The damage of expression of some specific genes can be noticed at both the mRNA level and protein level.

2. TELOMERES AND AGING:

Telomeres have been found existing at the ends of eukaryotic chromosomes and considered major in determining biological aging rate. Main role of telomeres lies in balancing metabolic dysfunctions related to age and integrity of genome. Telomere is mostly affected by inflammation and increase in oxidative stress. Loss of longevity and cellular senescence is directly related to erosion of telomere and destruction to healthy cells. Shorter telomere have been associated with increased adiposity, high body mass index, and extra visceral fat buildup. In in vitro cultured somatic cells, it has been shown that oxidative stress is directly proportional to erosion with each replication cycle (10).

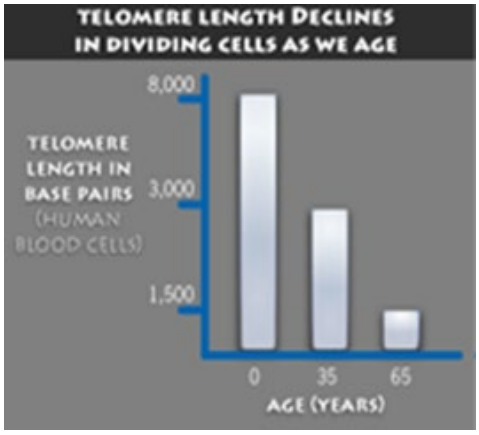
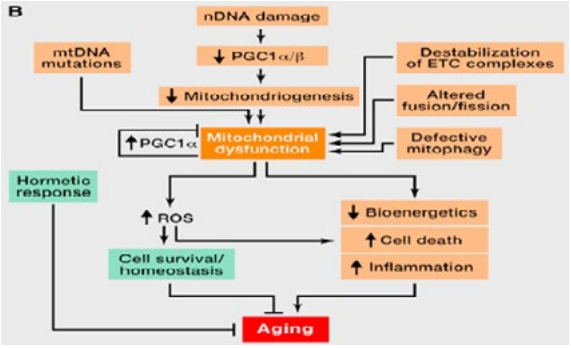


Fig: shows the decrease in length of telomere cap of DNA with advancing age in term of number of base pairs

Telomeres exist at the ends of mammalian chromosomes as non-coding double stranded repetitive structures (7). Their size reduced with each cell division (Harley et al.,1990). Incomplete replication of lagging strand (von Zglinicki and Martin-Ruiz,2005) with associated proteins are responsible for shortening in size. They protect play a role to protect chromosome ends (Wong and Collin,2001).

Close association between shorter telomeres and obesity is related with inflammation and oxidative stress (Valdes et al., 2005). Repairing capacity

reduced in telomeric DNA which ultimately increase loss of telomeres and replicative senescence in each cell cycle. Oxidative stress breaks single strands in DNA (von Zglinicki, 2002). This is increased with increase in adiposity intensifying oxidative stress, release of inflammatory cytokines and obesity (Furukawa et al., 2004).



A study conducted by Furukawa et al (2004) conducted in obese mice showed increased levels of ROS in adipose tissues and high oxidative stress in fats which have been found as key mechanisms for insulin resistance against obesity (Furukawa et al ., 2004). Study also suggested obesity as an abnormal character affected by inflammation, aging, short telomeres and increased oxidative stress.

Obesity has become a major concern in life these days. It is a condition with excess or abnormal fat and reduced life expectancy. Many age related problems and cancerous diseases have been highlighted due to accumulation of fats in adipose tissues and increased body weight. Metabolic changes such as insulin resistance, diabetes mellitus, increased pro-inflammatory cytokines and CVD and aging of adipose tissues are mainly determined by obesity (Epel, 2009; Scaglione et at., 2010).

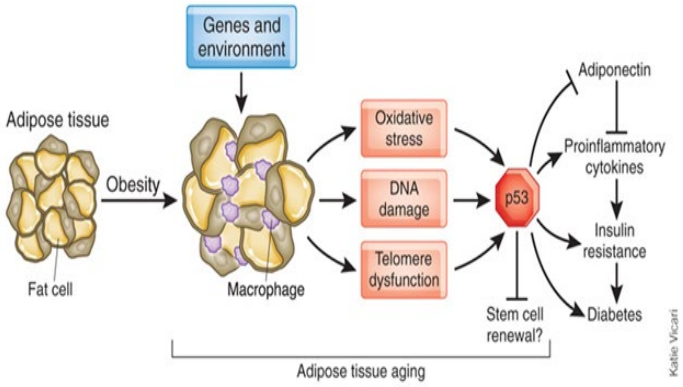


Fig: shows schematic representation of effects of obesity on increase production of oxidative stress, defective DNA repair and telomerase dysfunction leading to release of proinflammatory cytokines causing insulin resistance.

The obesity and obesity-mediated aging are influenced by p53 pathways in adipose tissue which play a key role in enhancing inflammation and aging of adipose tissues (Minamino et al., 2009). Oxidative stress is supposed to affect the telomerase attrition. Compared to non-obese patients, telomere length calculated from subcutaneous adipocytes is significantly lower.

Previous animal studies showed an inverse relation between telomerase length and levels of C-reactive proteins (Aviv et al.,2006). Systemic inflammation and profound insulin resistance are promoted by local pro-inflammatory cytokines which are ultimately produced and increased by adipose tissue (Aviv et al.,2006). Obesity cause chronic systemic inflammation (Garden et al.,2005Hotamisligil,2006), which put impacts on telomerase length by increased cellular proliferation, irrespective to age,. A lot of studies are currently going on to discover the means for adiposity, insulin resistance, diet, chronic stress, systemic inflammation and adipose derived hormones that are related to telomerase length.

3. Inflammation and aging:

Inflammation is considered as a "causative agent in aging". This phenomenon covers the facts for survival in acute inflammatory responses and to control and reduce infectious agents and healing processes in the susceptible host. Inflammation is important for our productive years to manage acute inflammation, damaging agents and crucial for survival while morbidity and mortality associated with age are caused by chronic low-grade inflammatory status which in turn occurs due to long term exposure to antigens such as cytomegalovirus. Such condition known as inflammaging. Pro- inflammatory markers and anti-inflammatory markers are unique to reduce disease onset, called as centenarians. Reduced exposure to pathogens and decreased chronic inflammation plays a key in making aging successful and longevity.

Discussion:

Above discussion shows different theories about aging and it is very important to know its cause. This is quite similar to the sense of knowing about the problem first to proceed with remedy. It is believed that all theories about aging are correlated to each other and may be originated from one another. Most of them are interlinked, affected by many factors and arranged in the way as biological process are associated in the body.

However, these theories with special treatment protocol can help to figure out problem at different levels and also to reduce and stop pillar of aging. Mitochondrial theory of aging describe production of energy and free radicals within the body (see the Mitochondrial Theory of Aging). Universal energy molecules are known as Adenosine Triphosphate (ATP) which produce energy during energy production cycle and assisted by simple process such as eating, drinking and breathing. These free radicals attacks the cell membrane causing metabolic waste products (see the Membrane Theory of Aging). Accumulation of these toxic substances put negative impacts on the normal functioning of cell activities, DNA, RNA, energy and many important chemical process.

However, it is well said that free radicals can be distorted by free-radical scavengers (otherwise known as anti-oxidants). Stability can be achieved by particular anti-oxidants after binding to particular free radicals. At the top in the list free radicals come in a order (according to their potential for damage) with the hydroxyl-radical and the superoxide-radical. Therefore a cross-section of anti-oxidants is necessary for the process of elimination of the free radicals; if this is not done, then large number of damage free radicals may be changed into a greater number of lower damage free radicals. Such a broad cross-section of anti-oxidants includes substances such as vitamin C, beta carotene, grape seed extract, and vitamin E and hydergine, melatonin and vinpocetine as strong chemical substances.

Chemically speaking, mitochondria are fiery furnaces under normal conditions and undergo a lot of free radical damage (see the Free Radical Theory of Aging). Their immune system is very low in the body and with age the mitochondria become less efficient, fewer in number and larger in size and reduced ATP. To repair and function properly, each organ need a specific amount of energy through their mitochondria. If any organ cannot be supported we called it as organ failure which leads to the death.

Aging can be reduced by enhancing and protection of the mitochondria. ATP supplements and above mention nutrients can themselves cause enhancement whereas protection may be afforded by a broad spectrum of anti-oxidants substances and Idebenone and Pregnenolone substances.

Obesity has become a major concern in life these days. It is a condition in which excess or abnormal fat accumulation may present with adverse effects on health and decreased life expectancy. Many age related problems and cancerous diseases have been highlighted due to accumulation of fats in adipose tissues and increased body weight. A lot of studies are currently going on to explore metabolic changes such as insulin resistance, diabetes mellitus, increased pro-inflammatory cytokines and CVD and aging of adipose tissues which are mainly determined by obesity.

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