Chronic Inflammation and Oxidative Stress as a Major Cause of Age-Related Diseases and Cancer

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Abstract: Chronic inflammation is a pathological condition characterized by continued active inflammation response and tissue destruction. Many of the immune cells including macrophages, neutrophils and eosinophils are involved directly or by production of inflammatory cytokine production in pathology of chronic inflammation. From literatures, it is appear that there is a general concept that chronic inflammation can be a major cause of cancers and express aging processes. Moreover, many studies suggest that chronic inflammation could have serious role in wide variety of age-related diseases including diabetes, cardiovascular and autoimmune diseases. Inflammatory process induces oxidative stress and reduces cellular antioxidant capacity. Overproduced free radicals react with cell membrane fatty acids and proteins impairing their function permanently. In addition, free radicals can lead to mutation and DNA damage that can be a predisposing factor for cancer and age-related disorders.

This article reviews the antioxidant defense systems, free radicals production and their role in cancer and age related diseases and also some of the recent patent relevant to the field. Study of the role of free radicals in human diseases can help the investigators to consider the antioxidants as proper agents in preventive medicine, especially for cancer and aging processes.

Keywords: Chronic inflammation, cancer, age-related diseases, free radicals, DNA damage, antioxidant, angiogenesis.

INTRODUCTION

Inflammation is a protective mechanism employed by tissues against endogenous and exogenous antigens. The relationship between chronic inflammation and many cancers has been recognized [1]. Chronic inflammation is a prolonged pathological condition characterized by mononuclear immune cell infiltration [monocytes, macrophages, lymphocytes, and plasma cells], tissue destruction and fibrosis. However, chronic inflammation exerts its cellular side effects mainly through excessive production of free radicals and depletion of antioxidants [2]. Aging may be defined as a progressive decline in the physiological functions of an organism after the reproductive phase of its life. The idea that, aging is the result of free radical damage, is often credited to Denham Harman, who proposed this theory based on this observation that, irradiation induces the formation of free radicals, shortens life span, and produces changes that resemble aging processes [3]. His work has gradually triggered intense researches into understanding the role of free radicals in biological systems. The main aim of this review is to analyze the role of free radicals, which are by products of chronic inflammation, in carcinogenesis and aging.

GENERAL CONCEPTS OF FREE RADICALS

In the last two decades, there has been a considerable amount of interest in the role of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in clinical medicine. A free radical is defined as any chemical species that contains unpaired electrons. This unpaired electron usually produces a highly reactive free radical.

In biological systems, the most common source of free radicals is oxygen.

The harmful effects and biological damage caused by ROS and RNS is termed oxidative stress and nitrosative stress [4]. Unfavorable side effects occur when there is an imbalance between overproduction of ROS/RNS and decrease of antioxidant molecules in body. Generally, ROS and RNS play dual roles in body: deleterious and beneficial effects [5]. Usually the beneficial effects of ROS involve defense against microbial pathogens. This role occurs by low concentration of these molecules. However, overproduction of ROS or RNS can damage and inhibit the normal functions of lipids, proteins and DNA. This effect is due to intracellular reduction of O_2 into ROS or free radicals, which is toxic to cells and tissues [6].

ROS can be produced from both endogenous and exogenous cellular substances. Potential endogenous sources include mitochondria, cytochrome P_{450}, peroxisomes, and inflammatory cells activation [7]. Mitochondria generate significant quantities of hydrogen peroxide and use ~90% of cellular O_2. During the mitochondrial process of reducing oxygen for production of water, several short-lived intermediates are produced, including superoxide (O_2), hydrogen peroxide (H_2O_2) and the hydroxyl radical [OH]. Superoxide and hydroxyl radicals are toxic to cells. Cell destruction also causes further free radical generation [6].

Additional endogenous sources of cellular reactive oxygen species are neutrophils, eosinophils and macrophages. Activated macrophages initiate increase in oxygen

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uptake and give rise to a variety of reactive oxygen species, including O_2, nitric oxide (NO) and hydrogen H_2O_2 [8]. Liver macrophages {Kupffer cells} participate in free radical-induced hepatotoxicity and liver cancer by producing inflammatory cytokines [9]. Recent investigations suggest that there is a direct relationship between Kupffer cells, inflammatory cytokines, and liver tumor promotion [10].

In addition, intracellular formation of free radicals can occur by environmental sources including ultraviolet light, ionizing radiation, and pollutants such as paraquat and ozone. All of these sources of free radicals, both enzymatic and nonenzymatic, have the potential to inflict oxidative damage on a wide range of biological macromolecules [11].

TARGETS OF FREE RADICALS

The cell membrane is one of the most susceptible sites to ROS damage. Free radicals can react with cell membrane fatty acids and form lipid peroxides. Lipid peroxides accumulation can lead to production of carcinogenesis agents like malondialdehyde [12]. Cell membrane damage via lipid peroxidation can permanently impair fluidity and elasticity of the membrane, which can lead to the cell rupture. These changes are particularly significant in long-lived cells such as neurons [13].

The proteins are another main targets for free radicals attack. Overproduced radicals can react with protein aminoacids to oxidize and cross-link them. Radical-protein reactions can impair the function of important cellular and extracellular proteins like enzymes and connective tissue proteins permanently. Based on many investigations, accumulation of tissue and cell damage is much higher in aged individuals. In fact, it has been estimated that oxidized protein in old animals may compose 30-50% of the total cellular protein [14].

DNA is also highly susceptible to free radical attacks. An oxygen radical interaction with DNA can break its strands or delete a base. This DNA damage can be a lethal event for an organism. The rate of DNA damage inflicted by free radicals is considerably high; it is estimated that in average more than 10,000 oxidative hits occur each day in the DNA of a human cell [15]. Although cellular repair system corrects much of these damages, but the radical induced DNA lesion that accumulate with age, can be an important etiology aging of processes [6].

FREE RADICALS IN MITOCHONDRIA

Mitochondria are the main cellular organelles that are involved in free radical production. Mitochondria consume about 90% of the cellular oxygen and are the most susceptible organelles to oxidative damage. Mitochondrial DNA contains histone that is highly susceptible to reactive oxygen damage. Moreover, mitochondria contain more than 100 different enzymes, involved in ATP production, which continuously interact with free radicals. Decrease activity of some of these enzymes during the aging process might be due to the long time interaction of these enzymes with free radicals. It has been estimated that the number of oxidative-induced damages in mitochondrial DNA is ten times higher than nuclear DNA. It has been shown that mitochondrial DNA damage accumulates with age and can have an important role in cellular aging too [15]. It should be also noted that DNA repair is much less efficient in mitochondria than in the nucleus [16].

The lack of equilibrium between free radical production in mitochondria and anti-oxidant defense mechanisms in this organelle may leads to leak of these harmful reactant to cytoplasm or connective tissues, hence damaging tissues and/or cells. Based on these facts, mitochondria can have a very important intermediatory role in age-related tissue degradation and aging processes [17].

DEFENSE MECHANISMS AGAINST FREE RADICALS

In order to neutralizing the threat of free radicals to the tissues and cells, a wide variety of antioxidant and repair systems has been evolved. Defense mechanisms against oxidative stress can be divided into: antioxidant, preventative and repair mechanisms, and physical defenses. Many enzymes participate in free radical neutralizing processes include: glutathione peroxidase, superoxide dismutase (SOD), and catalase. The non-enzymatic antioxidants that participate in oxidative stress defense include: ascorbic acid (Vitamin C), alpha-tocopherol (Vitamin E), glutathione (GSH), carotenoids, and flavinoids. In the normal and healthy cells, there is a precise balance between free radicals production and the level of antioxidant molecules, but under oxidative stress condition, the balance has been tilted towards excessive of oxidative radicals.

It is well understood that reduced-glutathione is an important cellular antioxidant molecule in the mitochondria and cell nucleus. Glutathione is considered to be the most powerful, versatile, and important antioxidant in the body. Glutathione is synthesized in the body from three amino acids: Cysteine, glutamine and glycine. Cysteine is one of the sulfur containing amino acids used for the synthesis of glutathione (this amino acid is very critical in detoxification). When an electron of the GSH is lost then it becomes oxidized. When the level of oxidized form of this molecule is increased then they linked with each other by a disulfide bridge to form glutathione disulfide or oxidized glutathione (GSSG).

The main protective roles of glutathione against oxidative stress are: [i] glutathione is a cofactor for other detoxifying enzymes like glutathione peroxidase (GPx), and glutathione transferase [ii] GSH participates in amino acid transport through the plasma membrane; [iii] GSH scavenges hydroxyl radicals and singlet oxygen directly, detoxifying hydrogen peroxide and lipid peroxides by the catalytic action of glutathione peroxidase; [iv] Glutathione is able to reduce oxidized Vitamin C and Vitamin E back to their unoxidized state. Moreover, GSH in the nucleus involves in mechanisms that are necessary for DNA repair and expression [18].

FREE RADICAL PRODUCTION DURING INFLAMMATION

The interaction of the cellular immune system with endogenous and/or exogenous antigens results generation of ROS and RNS, leading to signaling cascades that trigger the production of proinflammatory cytokines and chemokines [19]. Inflammation is the primary immune system reaction to

eliminate pathogens or other stimuli in order to restore the cells to normal state or replace destroyed tissue with scar [20]. After activation, innate immune system cells secrete proinflammatory cytokines and chemokines that induce ROS/RNS production [21]. In the innate immune system, macrophages play a pivotal role in eliminating the pathogen through the generation of reactive oxygen species including superoxide, nitric oxide, hydrogen peroxide, hydroxyl radical, peroxynitrite and hydrochlorous acid (Hocl) [22]. Inflammation reaction continues until the pathogens are eliminated and the tissue repair process be completed [23].

Continued active inflammation response can lead to cell damage or cellular hyperplasia following ROS overproduction from inflammatory cells. During inflammation ROS can interact with DNA in mitotic cells resulting in permanent genomic mutation such as point mutations, gene deletions, or gene rearrangement [24]. During inflammation cellular antioxidant systems respond to free radical overproduction by activating genes involved in DNA repair [25]. In chronic inflammation the rate of ROS induced DNA damage is extensive because this condition leads to depletion of cellular antioxidants. Chronic inflammation predisposes cells for transformation due to induction of recurrent DNA damage by inflammatory cells, hence higher frequency of mutation [26]. In addition, chronic inflammation induces increase of growth factor production and growth-supporting stimuli.

Over all, it seems that chronic inflammations facilitates cellular malignancy and transformation [27]. Based on these facts, inflammation is considered to be a major precursor for cancer development. To further elucidate the relationship between chronic inflammation and ROS content in tissues, we will review the role of inflammatory cytokines in production of free radicals.

Cytokines are soluble mediators of intracellular communications. They contribute to a chemical signaling language that regulates development, tissue repair, haemopoiesis, inflammation, and the specific and non-specific immune responses. Binding of cytokines to their receptors initiates transmission of extracellular information into the cytoplasm and the nucleus [28]. Cytokine receptors are usually directly linked to the ion channels or G proteins. The information is transmitted by various signaling pathways like nuclear factor κB and mitogen-activated protein kinase (MAPK) [29]. It has been recognized that a variety of cytokines induces ROS production in nonphagocytic cells by binding to their specific receptors. Some of the well-known activated growth factor receptors that induce ROS include: epidermal growth factor (EGF) receptor, platelet-derived growth factor (PDGF) receptor and vascular endothelial growth factor (VEGF) receptor [30]. Inflammatory cytokines such as IL-1, IL-6, TNF-α, and IFN-γ have been shown to generate ROS in nonphagocytic cells too [31]. The ROS produced by cytokine induction can be an important signal for other biological effects in cells such as proliferation and programmed cell death [23]. For instance, TNF-α enhances ROS production by neutrophils, while IL-1-β, TNF-α, and IFN-γ stimulate the expression of inducible nitric oxide synthase (iNOS) in inflammatory and epithelial cells [32]. In animal models of multiple myeloma, plasma cells require IL-6 for growth, which is provided by macrophages in the chronically-inflamed tissue [33]. IL-6 is stimulated by PGE2 derived from cyclooxygenase-2 (COX-2), which is elevated in inflammatory macrophages. This process can be inhibited by anti-inflammatory drugs [34, 35]. TNF-α is another important inflammatory cytokine that is secreted mainly from activated macrophages and induces ROS production in many types of cells. TNF-α Knockout mice show significant decrease of skin tumor development in response to DMBA [36]. IL-8 is an inflammatory chemokine, derived from monocytes, macrophages, and endothelial cells, that has important role in tumor angiogenesis. In addition, its role in many types of tumors including: colon, bladder, lung, and stomach cancer has been described [37].

CHRONIC INFLAMMATION AND CARCINOGENESIS

Many studies have demonstrated the direct relationship between chronic inflammation and cancer [32]. It has been estimated that chronic infection and the associated inflammation contribute to approximately one-quarter of all cancer cases worldwide [38-40].

A wide variety of chronic inflammatory conditions predispose susceptible cells to neoplastic transformation [41]. Inflammation is a multistep process that includes injury, repair, and resolution. Inflammation process exerts its effects on other cells through messenger molecules such as cytokines, prostaglandins, chemokines and angiogenic factors [42]. ROS/RNS and inflammatory cytokines, like TNF-α activate a transcription factor called nuclear factor kappa-B (NFκB) by phosphorylation and subsequent proteasomal degradation. After that, NFκB migrate to nucleus and activates specific gene transcription [23]. NFκB induces the expression of genes involved in cell proliferation, apoptosis and carcinogenesis [43]. NFκB can also induce production of proinflammatory cytokines, which will enhance the inflammatory responses. In normal state NFκB is inhibited by its inhibitory protein (IκBα) which can down regulate the inflammatory response.

The main chemical effectors in inflammatory response are free radical species derived from oxygen. Free radicals may act as direct or indirect damaging agents through their reaction with other chemical or structural components in target cells. ROS can also recruit other inflammatory cells leading to additional ROS production and amplify the damage [32].

INFLAMMATION AND ANGIOGENESIS

Chronic inflammation is also associated with angiogenesis [44]. Macrophages, platelets, fibroblasts, and tumor cells are a major source of angiogenic factors such as: basic fibroblast growth factor, vascular endothelial growth factor, prostaglandins-E_1 and E_2 [37]. These inflammatory angiogenic mediators augment the production of ROS/RNS and subsequently, increase the risk of cancer [45]. Prostaglandins are derived from the metabolism of arachidonic acid in inflammatory cells, and have been shown to contribute to cancer development by many researches [46, 47]. It has been suggested that Prostaglandins can increase the risk of cancer by inducing the expression of inflammatory cytokines, which in turn enhance ROS and RNS production.

Cyclooxygenase (COX) is a key enzyme responsible for the biosynthesis of prostaglandins from arachidonic acid. COX exists in two isoforms commonly referred to as COX-1 and COX-2. During inflammation COX-2 is the main enzyme that is unregulated in the macrophages. This enzyme is also expressed in noninflammatory cells such as fibroblasts, epithelial and endothelial cells. Bacterial infections and inflammatory cytokines increase COX-2 expression [48, 49]. Many research and investigations revealed that COX-2 production is increased in many cancers such as colon, breast, lung, esophagus, and head and neck cancer. Studies from COX-2 transgenic mice and knockout mice confirm that COX-2 plays a role in colon cancer development, both through angiogenesis and through the activation of different oncogenes, including *v-src*, *v-ha-ras*, *her-2/neu* and *wnt* [50].

Free radicals react with membrane phospholipids generating hydroperoxides, lipoperoxides and toxic aldehydes such as MDA, which in turn may alter membrane permeability and microcirculation.

It is now known that many oncogenes act by inhibiting apoptosis, thereby conferring a survival advantage to preneoplastic and malignant cells. On the other hand, several chemotherapeutic drugs exert their action by promoting cell death via increasing ROS production [51]. Carcinogenesis may be mediated by ROS and RNS directly by chronic inflammation (oxidation, nitration of nuclear DNA/RNA or lipids), or may be mediated indirectly by the products of ROS/RNS, proteins, lipids, and carbohydrates that are capable of forming DNA adducts [52]. ROS can also increase the expression of transcriptional factors such as *c-fos* and *c-jun* involved in neoplastic transformation and enhancement of tumor angiogenesis [32].

DIRECT EFFECT OF FREE RADICALS ON DNA DAMAGE AND CARCINOGENESIS

To date, more than 100 oxidized DNA products have been identified. ROS-induced DNA damage involves single or double stranded DNA breaks; purine, pyrimidine or deoxyribose modifications; DNA intrastrand adducts; and DNA-protein crosslinks [53]. DNA damage can result in either transcriptional arrest or induction/replication errors, or genomic instability, which all these processes are associated with carcinogenesis [54].

The importance of OH in DNA damage process is not completely understood because it has a very short half-life and must be produced directly adjacent to DNA to induce damage. However, peroxynitrite ($ONOO^-$) can diffuse within cells, and cause damage during chronic inflammation [55]. The less reactive molecules such as nitric oxide (NO) can be released from innate immune cells specially macrophages and act on neighboring cells, leading to somatic mutations and cancer [56]. Nitric oxide can react with superoxide and form $ONOO^-$. This reactive intermediate can induces oxidative DNA damage. Moreover, $ONOO^-$ participates to the formation of 8-oxo-7, 8-dihydro-20-deoxyguanosine and 8-nitroguanine, which are biomarkers for inflammation-induced carcinogenesis [57-59]. It has been recognized that 8-nitroguanosine is a highly mutagenic molecule and can give rise to G>T transversions [60,61]. In lung and liver cancer, G>T transversions have been observed *in vivo* in the *ras* gene and the *p53* tumor suppressor gene [62]. These findings indicate that ROS and RNS may participate in carcinogenesis, by both activation of proto-oncogenes and inactivation of tumor suppressor genes.

Oxidative damage to mitochondria is also implicated in carcinogenesis. Hydrogen peroxide and other ROS activate nuclear genes that regulate the biogenesis, transcription and replication of the mitochondrial genome. Recently, a large amount of evidence supports mitochondria involvement in carcinogenesis [5]. MtDNA fragments have been found inserted into nuclear DNA, suggesting a possible mechanism of oncogene activation. As noted previously, MtDNA is vulnerable to free radical damage because of the lack of histone proteins [63-65]. Free radical induced MtDNA damage reflects as mitochondrial respiratory chain dysfunction, which in turn increases the production of hydroxyl radicals and further DNA damage [66, 67]. Mutations and altered expression in mitochondrial genes encoding for complexes III, IV, V, and I and in the hypervariable regions of mitochondrial DNA have been identified in various human cancers [68-70].

Free radicals can alter cell growth and tumor promotion by activating signaling pathways, which result in the induction of growth stimulatory proto oncogenes, like *c-fos*, *c-jun*, and *c-myc* [71]. It has been shown that that phosphorylation and poly-ADP-ribosylation of chromosomal proteins are involved in the transcription of c-fos by oxidants, and that a pro-oxidant state can promote neoplastic growth [72, 73]. Cancer promotion can be explained by a consequence of extensive and continued free-radical related damage [74].

Many investigations have shown that DNA is not the only molecule at risk of oxidative damage. In addition to DNA damage, free radicals interfere with cellular mutation repair systems in parallel. These interference include: function of proteins such as DNA repair enzymes, apoptotic modulators, and the p53 protein which may be modified during exposure to free radicals. It has been shown that p53 is post-translationally modified at crucial residues after exposure to NO and its derivatives [75]. Moreover, DNA-repair and signal-transduction molecules such as DNA-protein kinases are activated by exposure to NO [75]. NO can participate in carcinogenesis by influencing the proteins that are crucial to cell function, including cell-cycle checkpoints, apoptosis and DNA repair [76].

FREE RADICALS IN AGING

Generally, there are two types of theories describing the aging processes: damage-accumulation theories [77] and genetic theories [78]. Damage accumulation theories include the “free radical theory”, the “glycation theory”, the “error catastrophe theory”, the “membrane theory”, the “entropy theory” and others, among which the “free radical theory” is probably the most complex approach to explain the aging processes. The “free radical theory” is based on the fact that the random deleterious effects of free radicals produced during O_2 metabolism accumulate over time, causing damage to DNA, lipids, and proteins [79]. The genesis of aging starts with oxygen, occupying the final position in the electron transport chain [6]. Even under ideal conditions,

some electrons leak from the electron transport chain. These leaking electrons interact with oxygen to produce superoxide radicals. Under physiological conditions about 3% of the oxygen molecules in the mitochondria are converted into superoxide. As noted above, the primary site of radical oxygen damage from superoxide radicals is mtDNA. Therefore, extensive MtDNA damage accumulates over time and eventually shuts down mitochondria, causing cells to die and the organism to age. Many correlations between oxygen consumption and aging have been observed [80]. Lowered oxygen consumption explains why queen bees live 50 times longer than actively flying worker bees, and houseflies that are prevented from flying (by removing their wings) lived much longer than flying insects. Larger animals consume less oxygen per unit of body mass than smaller ones, and live longer. Different rates of ROS generation also influence the life span of animals. For example, rats and pigeons have similar metabolic rates but different life spans (rat: 3 years, pigeon: 30 years). *in vitro* Experiments show that pigeon tissues generate ROS more slowly than rat mitochondria. Caloric restriction in rodents plays an important role in the aging process and is associated with increased DNA repair capacity, decreased production of superoxide, and decreased levels of DNA, lipids, and proteins damage. Longer-lived species have more efficient antioxidant protective mechanisms (SOD, carotenoids, GSH, glutathione peroxidase, and Vitamin E) in relation to oxygen uptake rates than do the short-lived species. Koya disclosed methods of treating a proliferative disease, such as cancer, with bis (thio-hydrazide amides) or a tautomer, pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, in combination with hyperthermia treatment. Also disclosed are methods of treating a proliferative disease, such as cancer, with bis (thio-hydrazide amides) or a tautomer, pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, in combination with radiotherapy [81].

In humans, the level of oxidative DNA damage as measured by urinary biomarkers can be modulated by caloric restriction and dietary composition [82]. Consequently, longevity may depend not only on the basal metabolic rate but also on dietary caloric intake. The accumulation of free radical-induced damage to biomolecules is illustrated by an age-related increase in the serum 8-hydroxydeoxyguanosine (8-OH-dG) level in disease-free individuals over a range of 15-91 years [5]. Several studies have reported the *in vivo* and *in vitro* accumulation of 8-OH-dG as well as other lesions with advancing age, both in nuclear and mitochondrial DNA [83]. DNA repair capacity correlates with species-specific life span, and this repair activity appears to decline with advancing age. However, several animal studies reported that age-related increase in 8-OH-dG in nuclear and mitochondrial DNA is due to a tissue's increased sensitivity to oxidative damage rather than age-related decreased repair capacity. However, antioxidant level does not change significantly with advancing age. Human studies have shown that the level of SOD, GSH, catalase, and ceruloplasmin were not altered among a wide-range of age groups [84]. Studies in many different animals show that aging is frequently associated with the accumulation of oxidized proteins. The role of protein modification in aging is illustrated by different enzymes isolated from younger animals that are catalytically more active and more heat stable than the same enzymes isolated from older animals [85]. Enzymes derived from young animals exposed to metal-catalyzed oxidation led to changes in activity and heat stability similar to those observed during aging. Thus, it was proposed that ROS-mediated protein damage is involved in the aging processes.

AGE-ASSOCIATED CHANGES IN LIPID OXIDATION

A number of studies have examined the effects of aging on lipid peroxidation in mammalian tissues by measuring thiobarbituric acid-reactive (TBARS) content as a marker of endogenous lipid peroxidation [86]. It has been reported that aging is associated with a 50% increase in TBARS in male rat's liver, but the effect of aging in female rats was a 50% decrease in hepatic TBARS. Curiously, the age-dependent differences in TBARS concentration were not related to changes in antioxidant molecules [87]. It has been reported that, age-associated changes are observed in some organs but are not evident in others. The data for male Wistar rats, for instance, indicate that TBARS may increase with age in liver and brain, but not in heart or lung [88]. Myhill *et al*. Disclosed a method for reducing the undesirable side effects of free radicals in a subject by administering to a subject in need of such antioxidants an effective amount of antioxidant-promoting composition of the invention [89].

Although fewer similar studies have been carried out in mice, these studies also have produced conflicting results. For example, hepatic TBARS concentrations were elevated in old female C57BL mice but were unaffected by aging in males [90,91]. The effects of age and gender differ from those reported for rat liver, where elevated TBARS are observed in old males, but not in old females [86]. Altogether, the findings suggest that age-associated changes are species-, strain-, sex-, and tissue-specific, and that increased lipid peroxidation is not an inevitable consequence of aging in any organ.

AGE-ASSOCIATED CHANGES IN ANTIOXIDANT

Review of the published data indicates that age-related changes in antioxidant defenses are quite varied. Many studies have shown that one or more antioxidant enzymes or molecules decrease as a consequence of aging. This has led to the belief that aging is associated with a decrease in antioxidant status and that age-dependent increases in lipid peroxidation are consequences of diminished antioxidant protection [86].

Changes in mitochondrial enzymes differ from those found in cytosolic enzymes. Significant differences between young adult and old rats were demonstrated for GSH peroxidase, superoxide dismutase, and GSSG reductase activities. These differences included age-related increases as well as decreases and were different for males than for females [88]. Heaney *et al.* utilized fructose and other monosaccharides for the treatment of cancer. They used these compounds to mimic or corrupt metabolic pathways of fructose and/or signal transduction pathways related to cancer cells for the treatment of cancer [92].

CURRENT & FUTURE DEVELOPMENTS

In one half century ago, Harman proposed free radical theory of aging based on his observation that irradiation of living things will increase free radicals in the body inducing changes similar to aging processes and shortening their lifespan [91].

A free radical is any chemical species like: molecule, ion or atom that contains an unpaired or odd electron in its outer orbit of its molecule. Most common source of these chemicals in biological system is oxygen and to a lesser extends nitrogen molecules. The most abundant source of free radical formation is mitochondria which use more than 90% of oxygen intake to burn proteins, lipids, and hydrocarbons and convert them to energy and water (cellular metabolism and energy production). This is the link between the high calory theory of aging and free radical theory of aging. The second source of free radicals is the byproducts of oxidative burst in activated neutrophils and monocyte/ macrophages in response to inflammation and microbial infections or even tissue injuries leading to release of pro-inflammatory cytokines. This is the basis of "inflammation theory of aging".

In addition to generation of free radicals, as byproducts of cellular metabolism and immune response to infection, intracellular induction of this molecule from environmental sources such as ultraviolet and ionizing radiation, ozone, etc. contribute to consumption of free radical scavenging mechanism (antioxidants) resulting to excessive level of free radical in the body and leading to oxidative stress.

Many important molecules including proteins, lipids, and nucleic acid chains are very susceptible to oxidizing reactions; thus, it is not unexpected to see many deteriorating events following oxidative stress leading to decrease longevity of the cells as well as living organisms. In fact, certain strains of fruit flays that have greater resistance to oxidative stress, exhibit longer lifespan. Free radical attacks to macromolecule especially highly susceptible molecules such as DNA and RNA can knock out bases or cause a strand breakage with potential to cellular transformation or even cell apoptosis. It has been estimated more than 10000 oxidative hits to DNA occur in an average human cell per day [3]. This would describe how oxidative stress can increase rate of cell transformation (malignancy).

It has been shown that nonsteroidal anti-inflammatory drugs (NSAID) can prevent incidence of several cancers in families with history of high cancer risk. It has also been shown that indomethacine blocks carcinogenesis by reducing the production certain cytokines called pro-inflammatory cytokines (IL-1, IL-6, IL-15 and TNF-α). Moreover, it has been demonstrated that those people who regularly take NSAID show a lower cancer risk [93].

On the basis of these considerations, pro-inflammatory cytokines are key elements in malignant transformation of the cells and pro-angiogenic activities leading to cancer; thus, chronic inflammation should be considered as a high risk factor for cancer causing especially in elderly people; since, increase of oxidizing reaction in one hand and immune senescence in the other hand will predispose the individual to harbor tumor and die from it. Based on these analogies, it should be recommended that elderly people should consume higher anti-oxidant compounds, and take NSAID regularly. It is also recommended that any chronic inflammatory disease and /or infection must be taken seriously and treated effectively as soon as possible by the practitioners.

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