



Mini-Review

REACTIVE OXYGEN SPECIES AND THEIR RELATION TO CARCINOGENESIS

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ABSTRACT

Oxygen reactive free radicals, more known as reactive oxygen species (ROS) have dual nature. On the one hand, they necessary for normal function of the cell, but on the other side when ROS is in excess can be mediators of damage to cell structures and this harmful effect is termed oxidative stress. The organism counteracts to ROS by the action of enzymatic and non-enzymatic antioxidants systems, such as trying to maintain redox balance. Although the effect of antioxidant protection, oxidative damage accumulates during the life cycle and is common for many types of cancer cell that are linked with altered redox regulation of cellular signaling pathways. Also and radical-related damage to DNA, to proteins and to lipids are suggested to play a main role in the progress of age-dependent diseases such as cancer, arteriosclerosis, neurodegenerative disorders and other conditions. This review examines the evidence for involvement of the oxidative stress in the carcinogenesis process. Attention is focused on chemical and biochemical aspects of free radicals, the endogenous and exogenous sources of their generation, the DNA damage, the damage to lipids and proteins by free radicals and the mechanisms of carcinogenesis.

Key words: Free radicals, oxidative stress, carcinogenesis.

INTRODUCTION

In the last few years, there has been a serious interest in the role of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in clinical medicine (1). Free radicals can be defined as reactive chemical compounds having a single unpaired electron in an outer orbit (2). This unpaired electron usually generates highly reactive free radicals through reactions with adjacent molecules, such as proteins, lipids, carbohydrates, and nucleic acids (3). ROS/RNS are known to play a dual role in biological systems, because they can be either harmful or useful to living systems (4). The harmful effects and biological damage consequence by the action of ROS and RNS is termed oxidative stress and nitrosative stress (5). These effects of ROS are balanced by the

antioxidant enzymes and supported by antioxidant action of non-enzymatic antioxidants (6). Although the presence of the antioxidant defense system to act against oxidative damage from ROS, oxidative damage accumulates during the life cycle, and radical-related damage to DNA, to proteins and to lipids has been proposed to play a main role in the progress of age-dependent diseases such as cancer, arteriosclerosis, arthritis, neurodegenerative disorders and other conditions (1). Useful effects of ROS involve physiological roles in cellular responses to noxia such as defense against infectious agents, and in the function of a number of cellular signaling systems. In contrast, at high concentrations, ROS can be basic mediators of damage to cell structures, including lipids and membranes, proteins and nucleic acids; this damage is known as “oxidative stress”(7). This review aims to examine the cellular effects of oxidants and their impact on cellular components, as well as possible association with carcinogenesis.

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SOURCES OF ROS AND RNS

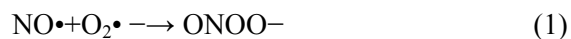
ROS formation depends on many factors, mainly they are divided into exogenous and endogenous (8). Endogenous sources include mitochondria, cytochrome P450, peroxisomes, and inflammatory cells activation (9). Hydrogen peroxide (H_2O_2), though not a radical species is formed in the mitochondria and as its ROS precursor is superoxide ($O_2^{\cdot-}$). Ubisemiquinone has been suggested as the main reductant of oxygen in mitochondrial membranes (9). Mitochondria produces approximately 2–3 nmol of superoxide/min per mg of protein, the general presence of which demonstrate it to be the most important physiological source of this radical in living organisms (9). Superoxide radicals generated on both sides of mitochondrial inner membranes are undergo detoxification to hydrogen peroxide and then to water by Cu, Zn-SOD (SOD1, localized in the intermembrane space) and Mn-SOD (SOD2, localized in the matrix) (10).

Other cellular source of superoxide radical is enzyme known as xanthine oxidase (XO). It is widely distributed and catalyses the hydroxylation of purines (11). XO catalyzes the reaction in which hypoxanthine is converted to xanthine and xanthine to uric acid. In both steps, molecular oxygen is reduced, forming the superoxide anion in the first and hydrogen peroxide in the second (4).

Cytochrome P450 enzymes are others, who have also been proposed as sources of reactive oxygen species. Cytochrome P-450 act as detoxify of foreign compounds into less toxic products (4). Via the induction of cytochrome P450 enzymes, the possibility to produce reactive oxygen species, especially superoxide anion and hydrogen peroxide, emerges following the breakdown or uncoupling of the P450 catalytic cycle (12). Also such endogenous sources of cellular ROS are neutrophils, esinophils and macrophages. Active, macrophages initiate an increase in oxygen uptake as a result of which, rise to a variety of reactive oxygen species, including $O_2^{\cdot-}$, nitric oxide ($NO\cdot$) and hydrogen peroxide H_2O_2 (13). In addition, microsomes and peroxisomes are sources of ROS, and microsomes are responsible for the most of hydrogen peroxide generated in vivo at hyperoxia sites (14).

Hydrogen peroxide is the main precursor of hydroxyl radical $\cdot OH$. Hydroxyl radical is formed by the Fenton reaction from hydrogen peroxide in the presence of ferrous ions ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^-$) or by the Heber-Weiss reaction from hydrogen peroxide and superoxide radical ($O_2^{\cdot-} + H_2O_2 \rightarrow O_2 + \cdot OH + OH^-$) (1). The hydroxyl radical is highly reactive with a half-life in aqueous solution of less than 1 ns. Thus when produced in vivo it reacts close to its site of formation (10).

Nitric oxide is generated in biological tissues by specific nitric oxide synthases (NOSs), which metabolise arginine to citrulline with the formation of $NO\cdot$ via a five-electron oxidative reaction (15). Cells of the immune system produce both the superoxide anion and nitric oxide during the oxidative burst triggered during inflammatory processes. Under these conditions, nitric oxide and the superoxide anion may react together to produce significant amounts of a much more oxidatively active molecule, peroxyxynitrite anion ($ONOO^-$), which is an oxidizing free radical that can cause DNA fragmentation and lipid oxidation (16):



$NO\cdot$ has effects on neuronal transmission as well as on synaptic plasticity in the central nervous system. Nitrosative stress may lead to nitrosylation reactions that can alter the structure of proteins and so inhibit their normal function (10).

In addition, reactive oxygen species can be produced by a host of exogenous processes (10). Environmental sources including: ultraviolet light, ionizing radiation, and pollutants such as paraquat and ozone. All of these sources of free radicals, both enzymatic and non-enzymatic, have the potential to cause oxidative damage on a wide range of biological macromolecules (17).

ANTIOXIDANT DEFENSE SYSTEM

The effect of reactive oxygen species is balanced by the help of antioxidant enzymes, as well as by non-enzymatic antioxidants (10). An ideal antioxidant should be easily absorbed and counteract free radicals, and chelate redox metals at physiologically relevant levels. It should also work in both aqueous and/or membrane domains and have a positive effect on gene expression. Endogenous antioxidants play a crucial role in maintaining optimal

cellular functions (3). The most important enzymatic antioxidants involve superoxide dismutase, catalase and glutathione peroxidase (18). Non-enzymatic antioxidants involve Vitamin C, Vitamin E, carotenoids, thiol antioxidants (glutathione, thioredoxin and lipoic acid), natural flavonoids, melatonin and other compounds (19).

Enzymatic antioxidants

Superoxide dismutase

One of the most efficient intracellular enzymatic antioxidants is superoxide dismutase (SOD) (EC 1.15.1.1). Superoxide dismutase is the antioxidant enzyme that catalyzes the dismutation of $O_2^{\cdot-}$ to O_2 and to the less-reactive species H_2O (10). Superoxide dismutase exists in some isoforms, in humans there are three forms of SOD: cytosolic Cu, Zn-SOD, mitochondrial Mn-SOD, and extracellular SOD (20). SOD destroys $O_2^{\cdot-}$ with high reaction rates by successive oxidation and reduction of the transition metal ion at the active site in a "Ping-Pong" type mechanism (18).

Catalase

Catalase (EC1.11.1.) is present in the peroxisome of aerobic cells and plays a major role in the conversion of hydrogen peroxide to water and molecular oxygen. Catalase has one of the highest turnover rates for all enzymes: one molecule of catalase can convert approximately 6 million molecules of hydrogen peroxide to water and oxygen each minute (3).

Glutathione peroxidase

Glutathione peroxidase has two forms, one of which is selenium-independent (glutathione-S-transferase, GST, EC 2.5.1.18) while the other is selenium-dependent (GPx, EC 1.11.1.19) (18). Humans have four different Se-dependent glutathione peroxidases (18). All GPx enzymes are known to add two electrons to reduce peroxides by forming selenoles (Se-OH). The antioxidant properties of these selenoenzymes allow them to eliminate peroxides as potential substrates for the Fenton reaction (21). Selenium-dependent glutathione peroxidase acts in association with the tripeptide glutathione (GSH), which is present in cells in high concentrations and catalyzes the conversion of H_2O_2 or organic peroxide ROOH to water or alcohol while simultaneously oxidizing GSH. It also competes with catalase for H_2O_2 as a substrate and is the major source

of protection against low levels of oxidative stress (21).

Non-enzymatic antioxidants

Vitamin E

This is a fat-soluble vitamin that exists in eight different forms. In humans, α -tocopherol is the most active form, and is the main powerful membrane bound antioxidant hired by the cell (22). The basic function of Vitamin E is to protect against lipid peroxidation (23). During the antioxidant reaction, α -tocopherol is converted to an α -tocopherol radical by the donation of a labile hydrogen to a lipid or lipid peroxy radical. The α -tocopherol radical can therefore be reduced to the primary α -tocopherol form by ascorbic acid (24).

Vitamin C

Vitamin C (ascorbic acid) is a very important and powerful water-soluble antioxidant and thus works in aqueous environments of the body. Its main antioxidant partners are Vitamin E and the carotenoids as well as working along with the antioxidant enzymes. Vitamin C cooperates with Vitamin E to regenerate α -tocopherol from α -tocopherol radicals in membranes and lipoproteins (24, 25). In addition supports intracellular glutathione levels thus playing an important role in protein thiol group protection against oxidation (3).

Thiol antioxidants

One of the main thiol antioxidants is the tripeptide glutathione (GSH), which is an intracellular antioxidant and is considered to be the major thiol-disulphide redox buffer GSH/GSSG of the cell (26). It is located in cytosol, nuclei, and mitochondria, and is the major soluble antioxidant in these cell compartments (26). The antioxidant activity of thiols is due to the sulphur atom, which can easily accommodate the loss of a single electron (3). The basic protective function of glutathione against oxidative stress are that it can act as a co-factor for several detoxifying enzymes, involved in amino acid transport through plasma membrane, scavenge hydroxyl radical and singlet oxygen directly, and regenerate Vitamins C and E back to their active forms (26). The accumulated oxidized glutathione (GSSG) inside the cells and the ratio of GSH/GSSG is a good measure of oxidative stress of an organism (27).

Carotenoids and Flavonoids

The other non-enzymatic antioxidants that participate in oxidative stress defense are

carotenoids and flavonoids. Carotenoids are pigments that are present in plants and microorganisms. Carotenoids contain conjugated double bonds and their antioxidant activity arises primarily as a consequence of the ability to delocalize unpaired electrons (28). Various studies have shown that carotenoids may protect or inhibit certain types of cancer, atherosclerosis, age-related muscular degeneration, and other diseases (10).

Flavonoids are a large class of low molecular ubiquitous groups of plant metabolites and are an inseparable part of the human diet (29). They are benzo- γ -pyrone derivatives containing phenolic and pyran rings (3). The phenolic compounds acting as antioxidants may operate as inhibitors of free radical chains and as chelators of redox-active metal ions which are capable of catalyzing lipid peroxidation (10). Recent interest in flavonoids due to their antioxidant capacity, chelating properties and their possible role in the prevention of chronic and age-related diseases (3).

OXIDATIVE DAMAGE TO BIOMOLECULES AND CARCINOGENESIS

Lipid peroxidation

Cell membranes are very sensitive to ROS damage and have been found to be frequent targets of radical-induced damage. The majority of polyunsaturated fatty acids in membrane contain a methylene group between two double bonds that makes the fatty acids more sensitive to oxidation (4). ROS can react with fatty acids in membranes and form lipid peroxides. Formation of lipid peroxides can lead to production of carcinogenesis compounds like malondialdehyde (30). Other toxic final products of lipid peroxidation are alkanes, aldehydes (n-aldehydes, 2, 4-alkadienal, 4-hydroxy alkenal and MDA), conjugated dienes etc. (31). Some of them with short chains (ethane, pentane) are used for *in vivo* indicators of lipid peroxidation (31). In addition, it has been established that in diseases conditions in humans is activated lipid peroxidation, but not always clear, whether it triggers pathological processes or their effect (31).

One of the major aldehyde products of lipid peroxidation MDA (32) is mutagenic in bacterial and mammalian cells and carcinogenic in rats (10). MDA can react with

DNA bases dG, dA, and dC to form adducts M₁G, M₁A and M₁C respectively (10). M₁G has been found in human liver, white blood cells, pancreas, and breast tissue (33). Several studies concluded that M₁G is a reactive electrophile in the genome (4). The product of fast and quantitative ring-opening of M₁G is N²-Oxo-propenyl-dG that also electrophilic, but targets regions of DNA different from M₁G (4). While the functionality of M₁G is present in the major groove, the functionality of N²-oxo-propenyl-dG is present in the minor groove of DNA (10). Thus the interconversion of M₁G and N²-oxo-propenal-dG within the DNA may lead to the formation of DNA–DNA interstrand crosslinks or DNA–protein crosslinks (10).

Proteins

Other main targets for ROS are the proteins. Protein damage is a consequence of overproduced ROS generation *in vivo* (34). The oxidative damage of proteins involves loss of histidine residues, oxidative scission, the introduction of carbonyl groups, and the formation of protein-centered alkyl, R•, alkoxyl, RO•, and alkylperoxyl, ROO•, radicals (10). Thus the protein oxidation by ROS is connected with the formation of many different types of inter- and intra-protein crosslinkages, including those formed, by the oxidation of sulphhydryl groups of cysteine residues to form –S–S– cross-links; by the oxidation of tyrosine residues to form –tyr–tyr– cross-links; by interaction of two carbon-centered radicals produced by the hydroxyl radical-driven abstraction of hydrogen from the polypeptide backbone; by addition of lysine amino groups to the carbonyl group of an oxidized protein (10). The amino acid residue side chains that are very susceptible to attack by ROS and RNS lead to the formation of the following derivatives: glutamate→4-hydroxy-glutamate; arginine→glutamic semialdehyde; histidine→2-oxo-histidine; tyrosine→3,4-dihydroxy phenylalanine, Tyr–tyr cross-linked proteins, 3-nitro-tyrosine; proline→glutamic semialdehyde, 2-pyrrolidone-4-hydroxy-proline; cysteine→cys–S–S–cys, cys–S–S–R disulphided; valine→3,4-hydroxy valine; methionine→methionine sulphone and sulphoxide [35]. As a result of radical-protein interaction can damage the function of important extracellular and cellular proteins as an example DNA repair enzymes, which can lead to increase the frequency of mutations in DNA. The fact that protein

carbonyl groups are formed by many different pathways and have been developed a number of highly sensitive methods for the assay of protein carbonyl groups, shows that quantity of protein carbonyl groups is a significant indicator of ROS mediated protein oxidation (10).

Oxidative DNA damage and carcinogenesis

DNA is also highly sensitive to ROS attacks. It is well established that in different cancer tissues free radical-mediated DNA damage was found (36). It has been estimated that one human cell is exposed to approximately 1.5×10^5 oxidative hits a day from hydroxyl radicals and other such reactive species (37). The hydroxyl radical is known to react with all components of the DNA molecule: damaging both the purine and pyrimidine bases and also the deoxyribose backbone (38). ROS-induced DNA damage includes the following: modification of all bases, production of base-free sites, deletions, frame shifts, strand breaks, DNA-protein cross-links, and chromosomal rearrangements (4). Permanent modification of genetic material resulting from these "oxidative damage" incidents represents the first step involved in mutagenesis, carcinogenesis and ageing (10). DNA damage can result either in arrest or induction of transcription, induction of signal transduction pathways, replication errors and genomic instability, all of which are associated with carcinogenesis (39, 40).

In terms of oxidative DNA damage, major interest has focused on modifications to DNA bases (4). Main oxidative DNA damage products include 8-oxo-7,8-dihydroadenine (8-oxo-A), 8-oxo-7,8-dihydroguanine (8-oxo-G), 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG), and 5,6-dihydroxy-5,6-dihydrothymine as well as the ring-open lesions of 4,6-diamino-5-formamido-pyrimidine and 2,6-diamino-4-hydroxy-5-formamido-pyrimidine (41). One of the most frequent base modifications is 8-OH-G. This base modification occurs in approximately one in 10^5 guanidine residues in a normal human cell (10) but its rate of formation increases by 35–50% in individuals using tobacco smoke – a well known carcinogenic source of ROS (10). In addition, almost 50% higher rates of 8-oxo-G levels have been monitored in lung, prostate or breast cancer patients when compared to healthy individuals (41). This oxidised DNA product is considered important because it is both

relatively easily formed and is mutagenic and carcinogenic, and also is a good biomarker of oxidative stress of an organism and a potential biomarker of carcinogenesis (10). In addition, high levels of 8-oxo-G and possibly other DNA lesions are suggested as reliable risk factors associated with the transformation of benign to malignant tumors (10). Furthermore, 8-oxo-G lesions are known to induce abnormal modifications in adjacent DNA a hypothesized mechanism that significantly contributes to the genetic instability and metastatic potential of tumor cells (41). Mutations that may arise due to formation of 8-oxo-dG involve GC → TA transversions (42).

The cancer development is characterized by cumulative action of multiple events occurring in a single cell and can be described by three stages: initiation, promotion and progression, which is one of theories for cancer development. ROS can act in all these stages of carcinogenesis (13).

Initiation involves a non-lethal mutation in DNA that produces changes in cell followed by at least one round of DNA synthesis to fix the damage (e.g. 8-OH-G) formed during the initiation (43). Oxidative DNA damage can occur by the following processes: Through hydroxyl radical ($\cdot\text{OH}$), which is produced from H_2O_2 in the presence of metal ions (Fe^{2+}) or (Cu^{2+}), present or in close proximity to DNA, or released from their normal sequestration sites (44). If dividing cells are damaged for whatever reason, they can interrupt temporarily their cell cycle at stage G1, S, or G2, repair the damage, and resume division (43).

The promotion stage is characterized by the clonal expansion of initiated cells by the induction of cell proliferation and/or inhibition of programmed cell death (apoptosis) (10). The result of this process is the formation of an identifiable focal lesion (10). This stage dose-dependently requires the continuous presence of the tumor promotion stimulus and therefore it is a reversible process (43). The oxidative stress is strongly involved in this stage of carcinogenesis. Moreover, many tumor promoters have a strong and immediate inhibitory effect on cellular antioxidant defense systems such as SOD, CAT and GSH-Px activities (45). ROS can stimulate the expansion of mutated cell clones by temporarily modulating gene related to

proliferation or cell death (44). While a high level of oxidative stress is cytotoxic to the cell and stops proliferation by inducing apoptosis or even necrosis, a low level of oxidative stress can in fact stimulate the cell division in the promotion stage and thus stimulate the promotion of tumor growth (46). This suggests that production of ROS during this stage of carcinogenesis is the base line of ROS-related tumor promotion (10). In addition, direct effects of ROS have been shown to regulate the activity of the transcription factor NF-kappa B (44). This factor controls cell growth and oncogenesis, taking part in the induction of gene products that controls proliferative responses and suppress apoptotic cascades, such as those induced by tumor necrosis factor (TNF-alpha), expression of oncoproteins and genotoxic stress (47,48). NF-kappa B activation also potentiates proliferation by blocking differentiation in certain settings, and this phenomenon may also promote oncogenesis (48). In summary, a number of tumor promoter classes have been proposed to act either by stimulating endogenous oxygen radical production or by altering cellular metabolic processes (44).

Progression is the third and last stage of the carcinogenic process (13). It consists of the acquisition of malignant properties by the tumor. Progression is irreversible and is described by accelerate cell growth, escape from immune system, tissue invasion, metastasis (49), accumulation of additional genetic damage, leading to the transition of the cell from benign to malignant (10). This stage involves cellular and molecular changes that occur from the preneoplastic to the neoplastic state (10). Since the generation of large amounts of ROS may contribute to the ability of some tumors to mutate, inhibit antiproteases and injure local tissues, it has together with the increases in the level of oxidatively modified DNA bases (50). Conversely, the increased levels of modified DNA bases may contribute to the genetic instability and metastatic potential of tumor cells in fully developed cancer (51). In addition other authors report that on the one hand an intense oxidative stress may kill cells being less effective in introducing DNA modifications in a cell population (46), by the other hand there may be cases in which oxidative DNA damage levels are increased, but cancer development does not ensue (52-54). It has been proposed that oxidative DNA base damage can not alone

cause cancer development, or damage over only a certain range is effective, excessive damage can cause an anti-cancer effect by promoting apoptosis (55).

DNA alterations such as strand breaks, base modifications and DNA-protein cross linkages, are all strongly implicated in the initiation stage of carcinogenesis (56). The importance of $\cdot\text{OH}$ 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 (8). 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 (57). In addition, nitric oxide can induce oxidative DNA damage by formed of ONOO \cdot . Furthermore, ONOO \cdot involved to the formation of 8-oxo-7, 8-dihydro-2'-deoxyguanosine and 8-nitroguanine, which are biomarkers for inflammation induced carcinogenesis (58-60). It has been accepted that 8-nitroguanine is a highly mutagenic molecule and can give rise to G>T transversions (61,62). In lung and liver cancer, G>T transversions have been observed *in vivo* in the *ras* oncogene and the *p53* tumor suppressor gene (63). These findings point that ROS and RNS may participate in carcinogenesis, by both activation of proto-oncogenes and inactivation of tumor suppressor genes.

Many studies 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 after translation is modified at crucial residues after exposure to NO and its derivatives (64). Similarly, DNA repair and signal-transduction molecules such as DNA protein kinases are activated by exposure to NO (64). Thus NO can participate in carcinogenesis by affecting the proteins that are essential to cell function including: cell-cycle checkpoints, apoptosis and DNA repair (65).

In addition, in the presence of cumulative oxidative stress, repair mechanisms often are ineffective and mutations accumulate in result

of failed repair mechanisms, such as have been found in the *ras* oncogene and the *p53* tumor suppressor gene (66). A recent study has showed a direct relationship between oxidative stress, DNA damage and increased frequency of *p53* mutations in human dysplastic colon and in colorectal carcinoma (67). This protein *p53* is known that regulate cell cycle entry and also act as a redox-active transcription factor whose function is linked in regulating ROS generation as well as mediating ROS-induced apoptotic cell death (66). During normal cell proliferation, *p53* triggers mechanisms that eliminate oxidative DNA damage in comparison to the presence of oxidative damage where *p53* triggers apoptotic cell death. However, during the carcinogenic process an imbalance between cell proliferation and cell death exists that shifts towards uncontrolled cell proliferation (10). In addition, *p53*-depleted cells showed significant disruption of cellular ROS homeostasis characterized by reduced mitochondrial and cellular superoxide and increased cellular hydrogen peroxide levels (68).

ROS-mediated mutations in mitochondrial DNA (mtDNA) have been shown as an important contributor to human carcinogenesis (69). Hydrogen peroxide and other ROS activate nuclear genes that regulate the biogenesis, transcription and replication of the mitochondrial genome. Moreover, mutations in mitochondrial genes encoding complexes I, III, IV and V and in the hypervariable regions of mtDNA, have been detected in various human cancers (66). Furthermore, mtDNA is more vulnerable to oxidative damage than nuclear DNA because; mitochondrial DNA repair capacity is limited, mitochondrial DNA is not protected by histones, and under physiological conditions, the mitochondria converts approximately 3–5% of oxygen consumed into superoxide anion and subsequently hydrogen peroxide (66). As noted previously, mtDNA is vulnerable to free radical damage because of the lack of histone proteins as well as its location in close proximity to the respiratory chain and thus is frequently exposed to ROS-induced oxidative damage. As a result, mtDNA has more than two orders of magnitude higher frequency of oxidative damage than that of nuclear DNA and significantly correlates with the development of cancer (70).

CONCLUSION

Overproduction of ROS by endogenous or exogenous source is harmful to living organisms and is termed oxidative stress. ROS attack DNA, proteins and lipids producing other reactive species that can react in turn with DNA bases. The most extensively studied DNA lesion is the formation of 8-OH-G. DNA mutation is a critical step in carcinogenesis and elevated levels of oxidative DNA lesions have been noted in various tumors, strongly implicating such damage in the etiology of cancer (10). The harmful effect of ROS is compensated by the action of the enzyme as well as non-enzymatic antioxidant system. Mn-SOD is considered as one of the most effective antioxidant enzymes with anti-tumor activity. Generally, antioxidants are involved directly in the conversion of ROS to less-reactive species. However, antioxidant protection therapy against free radicals should be used only with caution since its effects depend on the stage at which it is introduced. When used during the progression stage of cancer, it might actually stimulate growth of tumors through the enhanced survival of tumor cells. The level to which oxidative DNA damage contributes to the process of carcinogenesis is not yet clear, but there is evidence that the DNA damage is predominantly linked with the initiation process (10).

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