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Review Article

REACTIVE OXYGEN SPECIES: A COMPREHENSIVE REVIEW

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ABSTRACT

Reactive oxygen species (ROS) has been well recognized for playing a dual role as both deleterious and beneficial species. Generation of ROS occurs by tightly regulated enzymes like nitric oxide (NO) synthase (NOS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. The overproduction of ROS arises from mitochondrial electron transport chain or excessive stimulation of NADPH, resulting in enhanced oxidative stress, a deleterious process which is an important mediator of cell damage including lipids, membranes, proteins and DNA. Moreover, ROS can be divided into many types, i.e., superoxide (O_2^-) ion, hydroxyl (OH^-) ion, hydrogen peroxide (H_2O_2) and peroxinitrite ($ONOO^-$) ions. Moreover, ROS play modulatory role in the pathogenesis of various neurological and cardiovascular disorders alongwith diabetes and cancer. This review article aims to discuss about the involvement of ROS in the pathogenesis of various diseased states.

Keywords: Reactive oxygen species, Superoxide, Hydroxyl, Pathogenesis.

INTRODUCTION

Reactive Oxygen Species (ROS) are the chemical molecules derived from oxygen which possess modulatory roles on the physiology of body cells.[1, 2] ROS have been reported to act as second messengers causing signal transduction in many systems. Moreover, ROS have been regarded as mammalian host protective instruments causing release of neutrophills from the respiratory system and release of NADPH oxidase complex which is regarded as the key signaling molecule.[3-5] Cellular sources of ROS include mitochondria, neutrophills, monocytes, cardiomyocytes, endothelial cells, xanthine oxidase, cytochrome P-450, lipoxygenase and nitric oxide synthase.[6, 7] ROS contains a number of reactive molecules released from the oxygen like O_2^- ion, OH^- ion, NO, H_2O_2 and $ONOO^-$ ion. ROS are more active than the normal oxygen molecules causing harm to the cells, as the oxygen molecules in ROS are reduced molecules with varying degree of complications.[8-10] ROS is characterized as O_2^- ions and is produced by electronic reductions of molecular oxygen, the reaction being catalyzed by NADPH oxidase. ROS has been further reduced to produce H_2O_2, the process of which occurs due to dismutation of O_2^- ions, usually at reduced ph. Hence, it has been suggested that once the O_2^- ions are formed, the H_2O_2 ions are also produced.[9] Further reduction of H_2O_2 ions has been noted to result in the formation of OH^- ions, which occurs in the presence of metal ions via Fenton reaction (Babior, 1999). OH^- ions have been considered as highly reactive ions having short half-life, reacting highly with the first molecules which come in its pathway.[8] Moreover, O_2^- ions react with NO resulting in the formation of highly reactive molecules called $OONO^-$ ions.[8-10] In addtion, ROS have been found to be involved in the pathogenesis of various diseases like rheumatoid arthritis, diabetes and cancer alongwith various neurological and cardiovascular disorders.[11-15] The review article critically highlights about the structure and regulation of ROS. Moreover, involvement of ROS in the pathogenesis of various diseased states has been vitally discussed involved in the present review.

ROS-INDUCED OXIDATIVE STRESS

Oxidative stress refers to an imbalance between the systemic manifestation of ROS and the ability of biological system to readily detoxify the reactive intermediates or to repair the resulting damage.[16] It has been documented that any kind of abnormal reaction in tissue may lead to the toxic effects which enable the production of peroxidase and free radicals, causing the harm to cells and its components like proteins, lipids and DNA.[17] Moreover, oxidative stress means increased production of oxidizing species that lead to the reduction of antioxidizing species, causing invariably harm to the biological cells. It has been comprehensively suggested that ROS-induced enhanced oxidative stress to minor extent results in cell death; the medium oxidation has been reported to cause apoptosis; whereas, intense oxidative stress leads to necrosis.[18] In addition, the ROS-mediated oxidative stress has been found to be responsible for the progression and development of various neurodegenerative diseases like Lou Gerhig, Parkinson, Alzheimer and Huntington disease.[19] Furthermore, ROS-induced oxidative stresses leads to the ischemic cascade, strokes and heart attacks. Oxidative stress has also been noted to contribute to tissue injury following irradiation and hyperoxia, alongwith diabetes.[20]. Moreover, ROS-induced oxidative stress is involved in age-related development of cancer, which is confirmed by the fact that ROS produced in oxidative stress cause direct damage to the DNA ultimately proving to be mutagenic that suppress apoptosis and promote proliferation, invasiveness and metastasis.[17, 20]

CHEMISTRY OF ROS

In the chemistry of ROS, the microenvironment of various species release specific cellular substrates to which the different species have been noted to react. ROS have been regarded as free radicals having unpaired electrons in their outermost orbit, and hence, are able to exist as single free molecules.[21] Oxygen (O_2) molecules act as strong oxidizing agents as they are capable of accepting the electrons in its antibonding orbital. The reductions in O_2 molecules when acquiring electrons, gets converted in O_2^- atoms by enzymatic reactions. The chemistry of O_2^- in organic solvent and aqueous medium is invariably different with the fact that the O_2^- is stable in organic medium and unstable in the aqueous medium. In support, O_2^- is unstable in aqueous medium because it has the characteristics of rapid dismutation to H_2O_2.[22] Further, H_2O_2 are produced by the eukaryotic cells by direct two-electron reduction process of O_2, the reaction being carried out by number of flavoprotien oxidases.[21] Moreover, H_2O_2 diffuse through cell membranes whereas O_2^- ions remains outside, and thus, H_2O_2 have been considered to be the weaker oxidizing agents as compared to that of O_2^-. But in the presence of metal ions such as iron and copper, H_2O_2 behave as the most toxic molecules because of its conversion into toxic OH^- ions.[23]

REGULATION OF ROS

It has been vitally studied that enzymatic and non enzymatic reactions are responsible for the synthesis of cellular ROS. Moreover, ROS are produced as by-products of electron transferring protein due to transfer of electrons. During reduced conditions, total O_2 consumption in mitochondria is 1-2% of total oxygen utilized.[24, 25] The larger concentration of superoxide dysmutase (SOD) in mitochondria leads to low and steady state levels of intramitochondrial concentration of O_2^-. However, H_2O_2 is capable of diffusing into the cytoplasm through the mitochondrial membrane, whereas, the mitochondria producing O_2^- are not able to

get into the cytoplasm.[26] The characteristics of mitochondrial ROS in order to carry out cell signaling mechanisms lead to the regulation of apoptotic process.[24, 27] Moreover, tumor necrosis factors (TNF-α) and interleukin (IL)-1 mediated apoptosis carries out mitochondrial derived ROS. In addition, the release of electrons in various enzymatic systems leads to the cellular damage of molecular DNA by causing release of ROS. Furthermore, in the process of peroxidative reactions, the peroxisomes utilize number of H_2O_2 in order to produce various oxidative reactions.[28] These oxidative reactions are important as they neutralize various toxic molecules in liver and kidney and are responsible for the oxidation of fatty acids in the cellular components like peroxisomes and mitochondria.[25] During catalytic cycling, enzymes like tryptophan dioxygenase, xanthine oxidase, aldehyde oxidase, flavoprotein dehydrogenase, dihydro-orotate dehydrogenase have been found to be responsible for the generation of ROS.[28, 29]

TYPES OF ROS

ROS contains numbers of reactive molecules which are released from oxygen that include O_2^-, OH^-, NO, H_2O_2 and peroxinitrite $ONOO^-$ ions.[8-10]

O_2^-: They are reduced state of oxygen produced by electrons transport chain in several autoxidation reactions. O_2^- is responsible for the dismutation and release of H_2O_2, which acts as precursors for OH^- formation by the catalysis of metal atoms.[30] O_2^- ions are produced from the molecular oxygen by the involvement of an electron. The ions do not have the capacity to enter the membranes composed of lipids and is stored in the place where it is produced. The release of O_2^- ions occur spontaneously in the aerobic environment with the activity of respirator chain enzymes like flavoenzymes, lipoxyginase and cycloxygenase.[31]

H_2O_2: They are able to penetrate the lipid membranes and are produced by the dismutation of O_2^- or by the direct reduction of O_2^- with two electrons reduced state.[32] H_2O_2 are not the free radicals but have been considered as important as they penetrate the lipid membranes easily. In the phagsomes of neutrophills, the enzyme myeloperoxidase is present which leads to the formation of highly reactive ROS and Hypochlorous (HOCl) acid alongwith OH^- which is highly reactive by the oxidation of transcription metals. H_2O_2 also acts as the signaling molecules for various intracellular reactions.[33, 34]

OH^-: They are very highly reactive molecules formed by the decomposition of $ONOO^-$ with the help of Fenton reaction with three electrons reduced state. Of all ROS present, OH hydroxyl radicals seriously damage the biological cells because of its strong deleterious activity.[35] They are produced by Fenton reaction which involves reaction of metal ions like $Fe_2^+$and Cu_2^+ with H_2O_2, the reaction takes place in the combination with different protein molecules.[35]

NO: It is characteristically similar to the free radicals family O_2^- and is able to react with various free radicals. However, it has been regarded as an odd member of the free radicals as it contains unpaired electrons and it is not reactive with various biocellular molecules.[36] NO is responsible for the generation of less reactive molecules, and hence, functions as free radicals scavengers in order to inhibit cellular oxidation of lipids in the cell membranes.[37] The reaction of O_2^- and NO causes the release of $OONO^-$ which is severely cytotoxic to the biological cell membranes.

$ONOO^-$: They are produced when the O_2^- molecules reacts with NO molecules. With the addition of protons, it leads to the hemolytic cleavage and releases OH radicals and nitrogen dioxide.[38]

Alkoxy (RO) and Peroxy (ROO) Radicals: They are released by the addition to the double bonds in the presence of oxygen.[39]

Hypochlorous acid (HOCl): They are formed by myeloperoxidase that have been produced from H_2O_2 having the characteristic features of solublizing the lipid molecules with highly reactive nature. Moreover, they have the inherent ability to oxidize the protein molecules such as thiol and amino groups.[39, 40]

MECHANISM OF ACTION OF ROS

The mechanism of action of ROS can be divided into two stages; first being the changes in redox state intracellulary and second being the oxidation alteration in the protein molecules.[41, 42] However, the changes in the redox state of intracellular cystol of the cells occur under reduced conditions, but this occurs only because of the presences of redox buffering ability of intracellular thiols groups like glutathione (GSH) and thioredoxin (TRX).[42] The oxidized form of GSH and TRX are maintained in their appropriate ratio only by the GSH reductase and TRX reductase activity. Both of these are responsible for the reduction of H_2O_2 and lipid peroxidase, which are carried out by the peroxidase enzymes. GSH and TRX have the ability to act as the antioxidant and are responsible for the cell signaling mechanism.[43] In addition, GSH invariably carries out the redox signaling process by carrying out the differenation in both of the total level of GSH and also in the ratio of its oxidized (GSSG) to reduced forms of GSH.[44] The reduced cellular proliferation in vascular endothelial cells and increased proliferation of fibroblast occurs due to cellular GSH depletion. Further, during the second stage of oxidase alteration in protein molecules, the ROS have been responsible for the alteration in the structure of protein molecules by causing protein dimerization and also by changing the amino acid residue molecule structure.[42] The modification in protein molecules oxidatively occur in many ways such as the cysteine residue. The sulfhydryl group (-SH) gets oxidized to produce the sulfenic (-SOH), sulfinic (-SO2H), sulfonic (SO_3H) moities. These modifications lead to alteration in the biological function of enzymes, when cysteine is located inside the catalytic domain.[45] Furthermore, reversible oxidation produced by ROS is responsible for the inactivation of PTP-1B by its catalytic site, Cys215, which is regarded as the mechanism of mitogenic signaling.[46] This proposed that both H_2O_2 and O_2^- possess the property of neutralizing the activity of PTP-1B with O_2^- to act more specific du to its higher specificity in its activity.

ROLE OF ROS IN PHYSIOLOGICAL FUNCTIONS

ROS have been comprehensively suggested to be the chemical molecules which possessing modulatory roles on the physiology of body cells. In addtion, ROS have been well reported to be involved in the pathogenesis of various pathological conditions like rheumatoid arthritis, diabetes, neurological and cardiovascular complications (Fig. 1).[11-15] The production of ROS by phagocytic NADPH oxidase is an inflammatory condition during which the oxidative burst occurs that causes the release of ROS. This ROS release has been noted to play the important role in the body's defense against microbial environment. Moreover, the release of activated neutrophills and macrophages in the inflammatory environment causes the large production of O_2^- radicals and ROS with the help of NADPH oxidase.[17] These activated neutrophils and macrophages causes the production of single oxygen with help of NADPH oxidase. Moreover, it has been reported that ROS plays an important functions in the regulation of the functions of the vascular and cardiac cells.[47] In addition, studies showed that ROS is responsible for carrying out the process of apoptosis in the living organisms. The process of programmed cell death occurs only because of the balance between the removal of positive signals and the deposition of negative signals.[48] It has been widely accepted that the cell adhesion is required by the living organism for the purpose of embryogenesis, cell growth, cell differentiation and wound repair.[49, 50] It has been noted that T-lymphocytes are activated by the ROS which is responsible for the activation of the immune system during the attacks of pathogen.

Ageing is defined as the continuous loss of physiological functions by humans after the reproductive stage of life. The concept of free radicals mediated ageing was given in the year 1956 by Denham Harman due to which the role of free radicals in the process of ageing acquired attention.[51] The free radicals have been noted to cause damage to the cells DNA. Moreover, the lipids and proteins accumulate during the process of ageing as the time passes away. The process of ageing starts with the action of oxygen in the electrons transport chain.[52] These electrons leak out from the electrons transport chain during the process of ageing and react with the oxygen molecules in the mitochondria to produce O_2^- ions having deleterious effects on the cells by damaging mitochondrial

DNA.[53] Moreover, modulatory role of ROS in the pathogenesis of various neurological disorders have been vitally studied. It has been suggested that human brain needs lots of oxygen for its proper functions are thus, is more prone to the oxidative stress caused by the oxygen due to the oxidation of polyunsaturated fatty acids. This contention has been supported by the fact that ROS-induced oxidative stress is related to most of the disease caused to brain like Alzheimer's disease (AD) and Parkinson's disease (PD).[54, 55] The patients presented with AD posess accumulated content of amyloid β-peptide (Aβ), causing the oxidative damage to the brain, which is responsible for the formation of neurofibrillary tangles and neutrophil threads.[54] Moreover, the Aβ acts through biphasic system and induces the neurotropic mechanism in order to produce the oxidative stress which ultimately causes neurotoxic action.[56] Furthermore, PD has been considered as a neurodegenerative disease in which the damage of neurons occurs present in the region of midbrain called as the substantia nigra.[55] In this situation substania nigra utilizes dopamine which acts as the neurotransmitter to communicate to the other region of the brain which is known as stratium. Due to this the level of dopamine gets reduced in the brain and also decreases in the straial dopamine levels and causes the PD.[57] It has been revealed that the oxidative stress causes the reduced level of dopamine which is the neurotransmitter leading to the PD disease.[58] Further confirmation of the role of ROS-induced oxidative stress in the pathogenesis of PD comes from the studies which showed that when the oxidative stress occurs in the brain, it causes the nigral cell damages and causes the PD.[59]

Rheumatoid arthritis (RA) is considered to be an autoimmune disease resulting in the inflammation in region of joints in the bone and tissues surrounding it alongwith infiltration of macrophages and involvement of activated T cells.[13] The generation of free radicals occurs at the site of joints which causes the inflammation in the nearby area.[60] The confirmation about the role of ROS in RA can be obtained from the studies showing that T cells present in the synovial fluid shows the presence of decreased intracellular GSH level.[61] In addition, the role of ROS in the pathogeneis and development of diabetes has been reported.[11] It has been well reported that hyperglycemia is caused by the increased level of oxidative stress during diabetic conditions.[62] ROS formation occurs from various sources during the hyperglycemia which include oxidative phosphorylation, cytochrome p450, monooxygenase and NOS. However, during the normal condition, the formation of O_2^- ions results from the mitochondrial membranes, whereas, during diabetic conditions, the O_2^- ions are generated from the complex II and becomes the source of electron production under the situation of diabetes.[63] In addition, in type II diabetes, oxidative stress defects leads to the oxidative phosphyraltion machinery and mitochondrial β-oxidation which causes the accumulation of these triglycerides in muscles and liver and making it unresponsive to the insulin produced.[64] Due to oxidative stress skeletal muscles also becomes resistance to the insulin produced and β-cells function is retarded due to long time exposure to the high level of glucose.[65] β cells are highly reactive to ROS as they are reduced during free radical quenching of enzymes like peroxidase superoxide and dismutase catalase. Hence, the mitochondrial cells are damaged by the oxidative stress in the diabetes leading to various other complications.[65, 66]

Furthermore, the role of ROS in the pathogenesis of various cardiovascular diseases has also been suggested.[14, 15] ROS have been noted to cause oxidative stress in the cardiac muscles and vascular myocytes due to which various cardiovascular complications occurs like ischemic heart disease, cardiac hypertrophy, hypertension and congestive heart failure.[67-69] The oxidative stress in the cardiovascular diseases have been documented to be produced due to various enzymes like xanthene oxidoreductase, NADPH oxidase and mitochondrial cytochromes.[70-71] Due to oxidative stress, the production of ROS has been noted to increase which further leads to the modification of phospholipids and proteins ultimately causing oxidation of thiol group and its peroxidation. Moreover, ROS has been found to cause alterations in the cellular function and membrane permeability. ROS at subcellular organelles level causes increased oxidative stress and abnormalities in the myocytes.[72] O_2^- ions cause proliferation of cardiac cells, whereas, H_2O_2 leads to the apoptosis and causes the activation of protein kinase in the case of ROS-induced vascular disease. Modulatory role of ROS in hypertensive patients has been confirmed by the fact that ROS-induced oxidative stress leads to the reductions in the level of antioxidants such as vitamin E, GSH and SOD.[73] Moreover, the cardiac injury is produced by ROS by oxidizing the proteins required for the excitation-contraction activity. The I/R injury is a condition in which damage occurs to the cardiac muscles.[74] It has been shown that enhanced generation of ROS occurs during ischemia due to various cellular sources. In addition, huge productions of ROS in I/R causes severe damage to the myocardial tissues.[75-76]

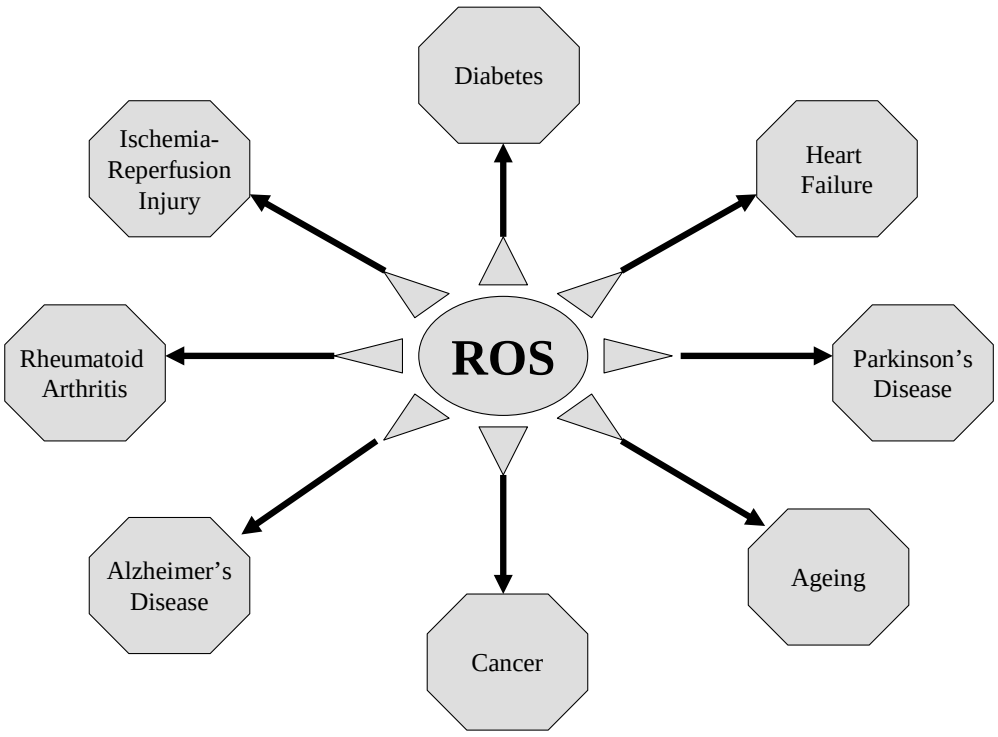

Fig. 1: Pathological role of ROS

CONCLUSION

ROS are the products of normal cellular metabolism, which are known to act as secondary messengers controlling various normal physiological functions of the body. Moreover, ROS participate in various redox-regulatory mechanisms of cells for the maintenance of cellular homeostasis. The overproduction of ROS has been noted to result in oxidative stress which is regarded as a deleterious process and is involved in damage of cell structures in order to cause various diseased states. However, the role of ROS in the pathogenesis of various cardiovascular and neurological complications have been reported but novel studies are still demanded in order to completely explicate the mechanisms of induction of cell damage by ROS in order to reduce further complications in the body due to them.

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