Review Article

Free Radicals Have an Important Role in Cancer Initiation and Development

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Abstract

The present review deal with the role of free radicals in cancer initiation and development because of the importance of free radicals in signal cascade transition of the cells in addition to defense properties against inflammation, the negative function of free radicals when the cells unable to equilibrate the excessive production of free radical which lead to a harmful effect in cell components such as lipid peroxidation, protein structure alteration, and DNA mutation and structural modification of nucleic acid. This review deal with free radicals generation, function, and its role in different cancer stage starting with initiation, survival, development, proliferation, invasion, and angiogenesis, can be concluded the role of oxidative stress in our healthy life and use it as one of the cancer therapy strategies in the future.

Keywords: Cancer, DNA mutation, free radicals, oxidative stress, role

Introduction

The oxidative stress is unbalance between production of free radicals and ability of body to detoxification the harmful effect of them by antioxidant molecules in the biological systems; oxidative stress has a major role in biological processes. The effect of oxidative stress in the incidence, development, and treatment of cancer depends on the free radical production level and types, these free radicals found into two types such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), the most important ROS types are $^1O_2$, O2•−, H_2O_2, and •OH. O_2 is harmful at high concentration.[1] The RNS includes nitrosonium cation, nitroxyl anion, higher oxides of nitrogen, and S-.[2]

The Free Radicals Generation

The ROS types such as hydrogen peroxide (H_2O_2), superoxide anions (O_2-), and hydroxyl radicals (OH·) produced in different cell organelles naturally, for example, the O_2- are produced as a byproduct by cellular respiration in electron transport chain naturally in mitochondria, the oxygen molecules are reduced by accepting electron. The ROS generation associated with nicotinamide adenine dinucleotide phosphate (NADPH) oxidases Nox family which catalyzes the electron transferred from NADPH to oxygen, and subsequent H_2O_2 and OH · are formed.[3] In addition of production OH · by Fenton reaction, an electron acquired from iron to H_2O_2; later it splits into two OH·. The exogenous factor also produced ROS by radiolysis. Oxidize water by ionizing radiation causes reactivity and convert to OH·.[4]

The Free Radical Function

The moderate production of free radicals has a major role in the biological systems such as the immune response against pathogens. In fact, phagocytes produced and store free radicals, for excreting it when invading pathogenic microbes have to be killed.[5,6] It has be found that the deficiency in ROS synthesis causes persistent infections as in granulomatous disease, the patients suffered from unable to $O_2^{\bullet-}$ synthesis because of defect in the defective NADPH oxidase system.[6,7] The free radicals also contributed in cell signaling pathways which produced through isoforms of nonphagocytic NADPH oxidase, these free radicals involved in the cascades of intracellular signaling

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regulation, and this was observed in several cell kinds such as vascular smooth muscle, cardiac myocytes, fibroblast, and endothelial cells.[8-10] The nitric oxide NO has been found that it is an important molecules in the messengers among cells for flew modulation of blood contributed in thrombosis, and for the normal neural activity, in addition to use in nonspecific host defense to decreased pathogens and eliminate tumor cells and mitogenic response induction.[8,9] The contribution of ROS in cell signal transduction was notable in oxidize cysteine residues for enzyme activity regulation, thus it is involved in several signal transduction pathways, as in the cell's response to growth factors.[11]

Moreover, ROS was observed that it is an effect in the cell cycle. ROS may be contributed in return cell to the G0 phase, when the levels of ROS are normally peak at the G2/M phase.[12] The ROS also shared in the memory formation mysterious process during the DNA demethylation.[13] Thus, ROS production is a necessary for biological function in the cells at moderate levels in any organisms.

Deleterious Activities of Free Radicals

In addition of an important role of free radicals in cellular function, there were several harmful effects of in its over expression; investigations found that the un balanced between free radicals and the systems that trapped it generated a phenomenon known as oxidative stress; this phenomenon has deleterious effects in the cellular organelles such as cell membrane proteins, lipids, lipoproteins, and nucleic acid if cells do not have ability to equilibrium the excess of free radicals formed,[6,8,9,14] and this excessive formation causes damage in cell components such as lipid peroxidation caused by OH · and peroxynitrite resulted to the production of malondialdehyde considered as cytotoxic and mutagenic to cells.[15] The ROS and NOS also effect in proteins structures lead to loss enzyme activity.[10,15] Different lesions were observed in DNA that can cause mutation. The accumulation of deleterious effect in DNA induced a variety of chronic and degenerative diseases.[10,14]

Reactive Oxygen Species and DNA Damage

The free radicals caused different lesions in DNA structures, which lead to mutation induction which strong linked with carcinogenesis. The effects of free radicals in DNA included single purine base lesions single pyrimidine bases, intrastrand cross-links, purine 5′,8-cyclonucleosides, adduct between DNA and protein, finally interstrand cross-links formed by the reactions of either the nucleobases or the 2-deoxyribose moiety with the OH·, one-electron oxidants, singlet oxygen, and hypochlorous acid.[16] These mutations become most dangerous if they locate in oncogenes such as inactivate tumor suppressant genes such as p53; investigations found that mutations associated with ROS tend to unclose the transversion guanine to thymine.[6] This occurs because of the 8-oxoguanine mutation is mispaired with adenine, and then it is repaired by the DNA glycosylase OGG1 enzyme. These types was happen frequently in the p53 gene.[14] Furthermore, ROS causes other carcinogenesis mutation types such as nucleotides bases oxidation, alkali mutation lead to form breaking strand, and DNA instability. In addition of the deletions, translocations and substitutions are much more likely.[8]

The 8-hydroxyguanosine induced by OH · found that unstable because of its unstable arrangement of electron make it more active to react with cellular components. The OH · able to entrance to nucleus and damage DNA but its rarely comparative to H_2O_2.[17] Meanwhile, H_2O_2 observed at low levels than other types of ROS that involved in the DNA damage according to its low reactive than other ROS and can be diffused through cell membranes and damage DNA directly.[18]

The ROS can block expression of the mismatch repair genes as a mutS homolog 2 and mutS homolog 6, resulted to low repair efficiency in cell then lead to carcinogenesis.[17] Furthermore, ROS can stimulate methyltransferases expression for some genes methylation that necessary in different biological process such as DNA repair (hMLH1), cell cycle regulation (CDKN-2), and tumor suppressants (BRCA1).[19] Moreover, the forming of 8-OH-G by OH · in binding site of transcription factor which riches GC sequences that targeted by free radicals lead to altered or inhibited causes impaired expression.[20]

To now, different cancer types were found that association with ROS and RNS damage such as lung, breast, brain, prostate cancer, leukemia, lymphoma, sarcoma, and other types.[17]

The Genotoxicity and DNA Damage

The OH · is able to rises to twofold bonds of DNA bases at second-order rate constants, provided OH-adduct radicals of DNA bases during additional reactions, and the abstraction reaction formed carbon-centered sugar radicals and allyl radical of thymine. Hence, the peroxyl radicals are formed in the full oxygen environment during oxygen addition to OH-adduct radicals and also to carbon-centered radicals at diffusion-controlled rates.[21]

The OH · interaction with pyrimidines (C, T) at the C5 and C6 site to formed C5-OH- and C6-OH-adduct radicals later the proton released and OH or water addition resulted to from oxidative reactions of the C5-OH-adduct radicals of thymine and cytosine that generation of glycols of thymine and cytocin.[22] The purins also attached by OH · to generate C4-OH-, C5-OH-, and C8-OH-adducts. In C8-OH-adduct radicals, single-electron oxidation and single-electron reduction produced formamidopyrimidines and 8-hydroxypurines (7,8-dihydro-8-oxopurines).[23]

The important types of DNA oxidation are 8-oxo-deoxyguanosine (8-oxo-dG), its most detectable as DNA oxidation production; the healthy genome cells include this base at about one in 10^5 guanidine residues. The main indicator of DNA oxidation is detected 8-oxoG damage due to it is relatively because of simply generated and ability to mutagenesis.[24] The studies proved the potential mutagenic

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of 8-oxo-dG is insertion adenine during polymerization that lead to base pairing specificity missed, misreading of adjacent pyrimidines. The transversions GC → TA mutation may be happened according to the generation of 8-oxo-dG. The 2-oxy-dA forming in the nucleotide unite considers another mutation mechanism.[25]

Cancer and Oxidative Stress

There are different complex factors contributed in cancer development in human including exogenous and endogenous induction; the oxidative stress has been established the relation with cancer initiation and development.[8,26,27] The initiation and promotion of cancer correlated with the genetic alteration that activation oncogene by free radicals. The formation of hydroxyled bases of DNA is an important phenomenon in chemical carcinogenesis that interference with cell growth regulation and changes the normal transcription of.[10,26] On the other hand, other changes were observed that resulted from DNA oxidative damage like modification in DNA structure or lesions in nitrogen base and ribose sugar, strand breaks, cross-links between DNA and protein, and finally deletion or base free site.[28]

Reactive Oxygen Species in Cellular Transformation

The oxidative stress was found to be subscribed in different steps of carcinogenesis from initiation to the final steps, which included the transformation of cells, promotion, proliferation, survival, angiogenesis, invasion, and in addition of metastasis.[29,30] In the initiation steps, ROS causes damage in DNA such as mutation and structural alteration; during the second stage of cancer or promotion stage, the free radicals involved in changes gene expression and stopped cells' communication resulted to modified the systems of gene expression and increased cell proliferation with eliminated apoptosis, and finally in third stage, other DNA mutation can be addition to the cell's modifications that contributed in the progression of cancer.[31,32] Study proved that there was association among cancer, inflammation, and oxidative stress by recruit inflammatory cells to generate ROS.[33] The inflammatory cells capable to elevated DNA destroyed by activating pro-carcinogens to DNA-damaging species, as an aromatic amines, toxins such as aflatoxins, hormones such as estrogens, some chemical compounds such as phenols, polycyclic aromatic hydrocarbons that generated by neutrophils through ROS-dependent mechanisms.[33,34] On the other hand, both neutrophils and macrophages have themselves been shown to release large quantities of superoxide, H_2O_2, and OH · following the activation of their redox metabolism.[35]

Tumor Cell Survival Related with Reactive Oxygen Species

The ROS has been found to impact tumor cell survival. Several studies reported ROS tumorigenicity due to modification in cell proliferation, survival, as well as the cellular migration ability to initiate the tumor and progression.[36] However, ROS may trigger cellular senescence, and cell death; thus its consider anti-tumorigenic agents. Although of the two opposite functions of ROS in survival cells, the type of cell and tissue, ROS concentration and types, function, and sources of production were detection the function of ROS in cells.[34,37] The cellular information was transition among cells by signaling pathways in order to provide the cell survival and establishing cell fate of tumor. One of the ROS source production is NADPH oxidase (Nox) which proved to enhance tumor cell survival and growth, as well as in Nox4 and Nox5 which prefer cancer cell survival in lung and pancreatic cancers.[37,38] Another types of promote tumor cell survival factors activate by ROS is serine-threonine kinase Akt that downregulate antioxidant defenses.[39] Akt may cause tumorigenesis by multiple such as apoptosis blocking and elevated oxidative metabolism, Akt locate at the hub of complex signaling networks that integrate a multitude of potentially oncogenic signals ways.[40,41]

Reactive Oxygen Species Contributed in Cancer Cell Proliferation

The cancer cell proliferation required multiple signals pathways and the important oxidant effect on signaling pathways is mitogen-activated protein kinase/AP-1 and nuclear factor-kappa B (NF-κB) pathways.[42] The redox-sensitive pathways trigger during tumor cell proliferation is important for cell division and provided high energy requirements in addition of metabolites production from energy-generating reactions, which must be buffered to prevent oxidative damage and ultimately cell death.[43] The NF-κB regulation found that its affected by Redox status. It was found that it regulates some genes contributed in cell transformation, proliferation, and angiogenesis the high expression of NF-κB enhances cell proliferation and block expression inhibits cell proliferation,[44,45] also it is activated by an external factor such as ultraviolet (UV) radiation, alcohol, asbestos, and benzo (a) pyrene.[46]

The association between NF-κB activation and ROS is complicated, but studies pointed that the mild oxidative stress causes simple NF-κB activation, while the excessive oxidative stress can blocked NF-κB.[47] Study supported the relation of ROS in activation NF-κB that all inducers can be inhibited by antioxidants such as L-cysteine, N-acetylcysteine, polyphenols of green tea, and Vitamin E.[48] H_2O_2 also involved in kinases proteins activation[49] such as B/Akt (PKB/Akt), related with several proteins such as heat shock protein 27 (Hsp27).[50]

Reactive Oxygen Species Involved in Tumor Cell Invasion

Studies found that the free radicals have an impact in invasion and metastasis of tumor by enhancing cell migration rates. Through epithelial cell transformation to invasive carcinoma,

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the morphology and adhesive mode were alteration and loosing polarization and differentiation resulting more motile and invasive cells, a study found that the treatment mice with H_2O_2 enhancing lung metastasis formation.[37] The subscribe of free radicals in cancer metastasis may be eliminated the tumor cell attachment to the basal lamina, or due to the elevated activity or proteins expression regulated cellular motility such as intercellular adhesion protein-1 (ICAM-1).[17]

Investigation observed that the matrix metalloproteinases (MMPs) members family were upregulated by free radicals,[50] and the gelatinases (MMP-2 and -9) were posttranscriptionally activated by prolonged oxidative treatment. The MMPs are able of cleaving some compounds of the extracellular matrix and basement membrane.[51] The activation of MMPs happened due to the ROS interaction with thiol groups in the domain of protease catalytic.[52] Other free radicals elevated iNOS expression and induced some MMPs members such as H_2O_2 and nitric oxide.[53]

Studies proved that the metastatic cascade regulated by redox signaling[54] that can affect during critical cysteine residues posttranslational modification in proteins such as actin, vimentin, and tubulin.[55,56] Researchers exhibited that ROS promotes the migration of transendothelial of melanoma cells through intravasation, which induced by UV radiation during the elevated thioredoxin interacting protein expression (Txnip) and thioredoxin (Trx) inhibition.[57]

Reactive Oxygen Species Role in Tumor Cell Angiogenesis

The angiogenesis is the process that tumor cells are employed some factors for forming network of blood vessels to supply it by nutrients and oxygen for tumor growth and metastatic.[58] Study found that ROS has a role in induced angiogenic signaling.[59] Furthermore, the excessive expression of Ras has been related to vascularization of tumors.[60] Its stabilized HIF-1α protein which has an impact in angiogenesis and stimulate the generating of angiogenic factors by cancer cells.[61] Moreover, the angiogenic factors such as vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor are secreted into the cancer cell microenvironment in response to ROS.[62]

All stages of cancers proved that the ROS has been contributed in these stages such as colon cancer developed from colitis after inflammatory infiltration, lead to elevated ROS production.[63] In addition of esophagitis and pancreatic, both induced by tobacco and alcohol stimulate ROS productions.[64,65]

The present review concluded that free radicals have a role in all cancer stages. Furthermore, individuals should be applied healthy lifestyle to ensure capability of body cell to equilibrate excessive free radical production.

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Conflicts of interest

There are no conflicts of interest.

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