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Review

Oxidative stress and cancer: An overview

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ABSTRACT

Reactive species, which mainly include reactive oxygen species (ROS), are products generated as a consequence of metabolic reactions in the mitochondria of eukaryotic cells. In normal cells, low-level concentrations of these compounds are required for signal transduction before their elimination. However, cancer cells, which exhibit an accelerated metabolism, demand high ROS concentrations to maintain their high proliferation rate. Different ways of developing ROS resistance include the execution of alternative pathways, which can avoid large amounts of ROS accumulation without compromising the energy demand required by cancer cells. Examples of these processes include the guidance of the glycolytic pathway into the pentose phosphate pathway (PPP) and/or the generation of lactate instead of employing aerobic respiration in the mitochondria. Importantly, ROS levels can be used as a thermostat to monitor the damage that cells can bear. The implications for ROS regulation are highly significant for cancer therapy because commonly used radio- and chemotherapeutic drugs influence tumor outcome through ROS modulation. Moreover, the discovery of novel biomarkers that are able to predict the clinical response to pro-oxidant therapies is a crucial challenge to overcome to allow for the personalization of cancer therapies.

1. Introduction

Aerobic respiration generates energy in the mitochondria of eukaryotic cells, and as a result of this oxidative metabolism, several compounds are produced. Most of these compounds are beneficial; however, less than 5% of them can be toxic for the cell if their concentration increases. These normally low-concentration compounds that are derived from oxidative metabolism are necessary for certain subcellular events, including signal transduction, enzyme activation, gene expression, disulfide bond formation during the folding of new proteins in the endoplasmic reticulum, and the control of the caspase activity that is activated during the apoptotic mechanism.

Sources of internal oxidative stress include peroxisomes and enzymes, particularly the detoxifying enzymes from the P450 complex, xanthine oxidase, and the nicotinamide adenine dinucleotide (NADPH) oxidase complexes, which include the Nox family. Most of these enzymes act in the mitochondria, which is the main source of oxidative stress. External sources of oxidative stress include UV radiation, chemical compounds (e.g., environmental pollutants, smoking and alcohol), and exercise. Reactive species can be classified into four groups based on the main atom involved: ROS, reactive nitrogen species (RNS), reactive sulfur species (RSS) and reactive chloride species (RCS) (Bannister, 2007). Of all the compounds derived from oxidative metabolism, ROS are the most abundantly produced. Their half-lives range from a few nanoseconds to hours, depending on the stability of the molecule. ROS include superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^-), singlet oxygen ($^1O_2$) and ozone (O_3) (Simic et al., 1989). ROS and RNS are produced during intracellular metabolic processes, such as the electron transport chain. The most abundant RNS is nitric oxide (NO^-), which is able to react with certain ROS, including the peroxynitrite anion and $ONOO^-$, which is produced by the interaction between the superoxide anion and nitric oxide; nitric oxide is later converted into peroxynitrous acid and ultimately into a hydroxyl radical and nitrite anion (NO_2^-).

The damage that these ROS can cause to the cell not only depends on their intracellular concentration but also on the equilibrium between the ROS and the endogenous antioxidant species. When the pro-oxidant/anti-oxidant equilibrium is lost, oxidative stress is generated, altering and damaging many intracellular molecules, including DNA, RNA, lipids and proteins (Veskoukis et al., 2012). These reactive species cause nicks in the DNA and malfunctions in the DNA repair mechanism. DNA oxidation by these reactive species generates 8-hydroxy-2′-deoxyguanosine, which is

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a product that is able to generate mutations in DNA in a process that enhances aging and carcinogenesis (Matsui et al., 2000). Moreover, the cell membrane is rich in polyunsaturated lipids that are susceptible to oxidation by reactive species. Reactive species liberate lipid peroxidation reactions and consequently increase the permeability of the cell membrane, which could lead to cell death (Halliwell and Chirico, 1993). Proteins are the most affected by a cellular environment with a high concentration of reactive species. Proteins suffer from the generation and accumulation of carbonyl groups (i.e., aldehydes and ketones) and thiol groups (–SH) that may be converted into sulfur reactive radicals (Levine, 2002). Due to this oxidation-induced modification, there is an alteration in the protein structure and, consequently, changes or loss of protein function.

Natural antioxidants are the cell's defense mechanisms that scavenge reactive species, and they can be classified into different groups according to their properties: endogenous antioxidants, natural antioxidants and synthetic antioxidants. Endogenous antioxidants include glutathione, alpha-lipoic acid, coenzyme Q, ferritin, uric acid, bilirubin, metallothionein, L-carnitine, melatonin, enzymatic superoxide dismutase (SOD), catalase (CAT), glutathione peroxidases (GPXs), thioredoxins (TRX) and peroxiredoxins (PRXs). PRXs are a ubiquitous family of antioxidant enzymes (PRX I-VI) that also control cytokine-induced peroxide levels and mediate signal transduction in mammalian cells. For example, PRX III scavenges up to 90% of H_2O_2, and PRX V behaves more effectively as a scavenger of peroxynitrite. Natural antioxidants coexist in a delicate balance with oxidative inputs. Other antioxidants can be obtained from the diet, such as ascorbic acid (Vitamin C), tocopherol (Vitamin E), β-carotene (Vitamin A), lipoic acid, uric acid, glutathione and polyphenol metabolites. Examples of synthetic antioxidants include N-acetyl cysteine (NAC), tiron, pyruvate, selenium, butylated hydroxytoluene, butylated hydroxyanisole, and propyl gallate (Yoshida et al., 2003).

Oxidative stress is important from a biomedical point of view because it is related to a wide variety of human diseases, such as neurodegenerative disease (e.g., Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis), inflammatory disease (e.g., rheumatoid arthritis), cardiovascular disease (e.g., muscular dystrophy), allergies, immune system dysfunctions, diabetes, aging and cancer. For example, inflammatory cells release chemical mediators of inflammation, particularly ROS, in swollen tissue, which also affects normal cells. When this is a chronic process, the extremely high ROS levels saturate the cell defense mechanisms (i.e., antioxidants), and intracellular molecules become seriously damaged, affecting surrounding neighboring cells.

The mechanisms and pathways involved in oxidative stress are conserved in mammalian cells. ROS can promote many aspects of tumor development and progression, which can be classified into the following biological processes: (a) cellular proliferation (e.g., extracellular-regulated kinase 1/2 (ERK1/2) activation and ligand-independent RTK activation), (b) evasion of apoptosis or anoikis (e.g., Src, NF-κB and phosphatidylinositol-3 kinase (PI3K)/Akt activation), (c) tissue invasion and metastasis (e.g., metalloproteinase (MMP) secretion into the extracellular matrix (ECM), Met overexpression, and Rho-Rac interaction), and (d) angiogenesis (e.g., the release of vascular endothelial growth factor (VEGF) and angiopoietin).

Regarding cellular proliferation, oxidative stress affects several biochemical pathways (from epidermal growth factor receptor (EGFR) to mTOR) that involve key signaling proteins, such as nuclear factor erythroid 2-related factor 2 (Nrf2), kelch-like protein 19 (Keap1), Ras, Raf, mitogen activated protein kinases (MAPK) such as ERK1/2, MEK, p38α, c-Jun N-terminal kinase (JNK), c-myc, p53 and PKC (Matsuzawa and Ichijo, 2008; Nguyen et al., 2009; Wiemer, 2011). Among them, Nrf2 is considered to be the master regulator of the antioxidant response, but others are also important. For example, p38α acts as a key sensor of oxidative stress, and its redox-sensing function is essential in the control of tumor development (Luo et al., 2011). In contrast to other MAPKs, p38α suppresses tumorigenesis by blocking proliferation or promoting apoptosis.

This review is focused on the relationship between oxidative stress and cancer from both the molecular and clinical point of views.

2. Metastasis-related processes that influence oxidative stress

2.1. Epithelial-mesenchymal transition (EMT)

An important event that leads to metastasis is EMT, which is a biological process by which epithelial cells undergo biological and chemical alterations that permit the development of a more aggressive mesenchymal phenotype (Mani et al., 2008). These changes are associated with an increase in ECM proteins, which provide the cells with migratory properties and allow them to move to other regions of the body via the bloodstream. There are various ROS-associated signaling pathways that are implicated in the EMT process. Among these pathways, the proteins Smad (activated by tumor growth factor β (TGF-β)), Snail, E-cadherin, β-catenin, integrin, matrix metalloproteinases (MMPs), hepatocyte growth factor receptor (HGFR/c-Met), AP1 (activated by PKC activator), v-ets erythroblastosis virus E26 oncogene homolog 1 (Ets-1) and transforming growth factor β-activated kinase 1 (TAK1) are mostly activated in a ROS-dependent manner (Haorah et al., 2007; Ni et al., 2007; Omori et al., 2012). One of the first studies that established a direct connection between ROS and EMT is related to TGF-β signaling. TGF-β activation provokes an increase in intracellular ROS in a process that is associated with the phosphorylation of Smad2, p38α and ERK1/2 (Rhyu et al., 2005). Moreover, intracellular ROS may regulate EMT through a mechanism involving NF-κB in strict collaboration with hypoxia-inducible factor 1 (HIF-1α) and cyclooxygenase-2 (COX-2). The role of ROS as a crucial EMT mediator is further corroborated by MMP-3 (matrix metalloproteinase 3), which is also known as Stromelysin-1. MMP-3 is an enzyme that is involved in the breakdown of the extracellular matrix, which plays a key role in tumor metastases by degrading collagen, fibronectin, and laminin. MMP-3 has been reported to be upregulated in certain tumors, such as breast cancer, and is an EMT inducer in transgenic mice. In mice, MMP-3 secretion is associated with Snail upregulation, E-cadherin loss and β-catenin nuclear translocation events, which, in turn, are dependent on the small GTP-binding protein Rac 1 (Rac1b) (Radisky et al., 2005; Rhyu et al., 2005). In addition to MMP-3, other metalloproteinases, including MMP-2 and MMP-9, play important roles in Rac1b stimulation to influence ROS. Most of these proteins are oncogenic in mouse models, and their overexpression contributes to human tumorigenesis.

Other cellular pathways involved in metastasis are also targeted by ROS, such as Wnt/TCF (T cell factor), integrin-mediated MAPK signaling, protein kinase C (PKC), protein tyrosine phosphatases, and p21-activated kinase 1 (PAK-1) signaling pathways (Almeida et al., 2007; Lee and Esselman, 2002). For example, ROS oxidize cysteine residues in the PKC protein and inactivate protein tyrosine phosphatases, which are important molecules in tumor cell invasion. ROS also regulate PAK-1, which is involved in Rac-associated cytoskeleton remodeling, which is directly linked to metastasis and angiogenesis (Diebold et al., 2010). Proteins such as Snail, TGF-β, Twist, Wnt/β-catenin and Zinc finger E-box-binding homeobox 1 (Zeb), which induce EMT, also modulate the tumor microenvironment. Rac1b enhances the expression of Zinc finger protein SNAI1 (Slug), a transcriptional inhibitor of E-cadherin that can ease