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Abstract

A cell is dying when there is no repair after damage. Indeed, the etiology of cancers associates with damaged or unrepaired cells. Cancer results from imbalance between cell’s oxidant and antioxidant defenses. This study aimed to review formation of cancer associated to oxidative stress. Tumorgenesis is caused by deregulation of the redox homeostasis by reactive oxygen species that stimulate the formation of tumor by starting an abnormal introduction of signaling nets. Proliferation accompanied by uncontrolled growth could lead to development of mass cancer cells. Kinases/phosphatases, transcription factors, reactive oxygen–nitrogen species and signal transduction are the most important cascades. The biology of tumor is affected by: 1) redox control through growth factor receptor signal, 2) superoxide production due to small amount of oxygen, 3) infiltrating cytotoxic immune cells, 4) anti-cancer treatments, 5) repetitive ischemia–reperfusion cycles due to irregular blood supply and 6) inflammation.

Keywords: Oxidant; Anti–oxidant; Cancer; Bladder

Introduction

As a concept, oxidative stress has been introduced in the redox biology and medicine in 1985. Oxidative stress is an imbalance between the production of free radicals and reactive metabolites or reactive oxygen species (ROS) and reactive nitrogen species (RNS) as shown in Figure 1.

In fact, uncontrolled cell growth and mutations in DNA due to oxidative stress cause cancer. There is a conversion of pro–oncogenes into oncogene that lead to increase in proliferation of cell and transforming normal cell into malignant neoplastic cells. In cancer cells there are loss of contact inhibition, resistance to apoptosis, and insensitivity to cell growth arrest signals. The key characteristic of cancer cells is angiogenesis. In any type of cancer, oxidation exceeds the control mechanism, and as a result oxidative stress arises. There are deleterious modifications to a variety of macromolecular components such as DNA, lipids and proteins associated to chronic and cumulative oxidative stress. Free radical production occurs constantly in all cells as part of normal cellular function. However, excess free radical production originating from endogenous or exogenous sources might play a role in many diseases. Free radical can be defined as any molecular species capable of independent existence that contains an unpaired electron in an atomic orbital. The presence of an unpaired electron results in certain common properties that are shared by most radicals. Radicals are weakly attracted to a magnetic field and are said to be paramagnetic. Many radicals are highly reactive and can either donate an electron to or extract an electron from other molecules, therefore behaving as oxidants or reductants. As a result of this high reactivity, most radicals have a very short half–life (10^-6 seconds

Figure 1: The sources of Intracellular ROS/RNS
or less) in biological systems, although some species may survive for much longer. The most important free radicals in many disease states are oxygen derivatives, particularly superoxide and the hydroxyl radical. Radical formation in the body occurs by several mechanisms, involving a both endogenous and environmental factor. Free radicals are strongly associated in the pathogenesis of many diseases.3-8.

The aim of this review was to focus on the association between redox states with cancer through special extrapolation of initiating to bladder cancer (BC).

**How Inflammation could affect Redox States?**

In the presence of pathogens, chemicals or radiation, cystitis, bronchitis, otitis media, dermatitis, and many others inflammation, defensive response associated with immune system activates. An important key that associates to progression of many inflammatory diseases are deleterious concentrations of ROS as partially reduced metabolites of oxygen in addition to increased capabilities of oxidation. Glutathione depletors and diethyl maleate enhance the generation of ROS in any cancer including BC.9. Through enzymatic catalysis by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase (XO) or during electron transfer reactions in the electron transport chain of mitochondria, O2•− is generated by one-electron reduction of O2. In the presence of transitional metal iron, the highly sensitive OH− and OH produce. In the next step, in order to form Fe2+ and O2, Fe3+ reacts with O2•− in addition to reaction of Fe2+ with H2O2 to form both OH• (as the most potent oxidizing species of biological membrane proteins and lipids) and OH−. H2O2 and chloride generate HOCl by the enzyme myeloperoxidase. As a result, the major RO could be summarized as: hydroxyl radicals (OH•), hydrogen peroxide (H2O2), superoxide (O2•−), hydrogen anions (OH−), and hypochlorous acid (HOCl).

**Antioxidants**

In order to remove functions of ROS, antioxidants (AO) evolved in preventing the damage related to oxidants. The AO substance even in low concentration could able to delay or inhibit the oxidation of endogenous or exogenous stimuli. The main role of antioxidants is to liquidate the uncontrolled production of ROS that is being linked to pathogenesis of malignancy in any types of cancer including BC. The physiological role of AO is to prevent damage to cellular components arising as a consequence of chemical reactions involving free radicals.

In fact antioxidant, stimulates nitric oxide production, protects endothelial cells from oxidative functional damage, lowers platelet aggregation and directly inhibits cyclic adenosine monophosphate-specific phosphodiesterases. Therefore commencement, elevation and development the three different phases could be proceeded by carcinogenesis that could be influenced by AO. In fact, the AO enzymes superoxide dismutase (SOD; dismutates O2•− to H2O2), catalase, glutathione peroxidase (GPx; converts H2O2 to H2O), peroxiredoxins (Prx), and thioredoxin (Trx) to detoxify H2O2 are classified as ROS scavengers.

**Antioxidants in Bladder Cancer**

Related to urinary system, bladder has been issued as a target organ for many carcinogenesis. Smoking, metalloids such as arsenic or other environmental toxins metabolize in the human body, and then carcinogenic by-products reach the urinary bladder via urinary excretion. In fact the trivalent inorganic arsenic inhibits the production of glutathione that protects cells against ROS. In such conditions, binding to the sulfhydryl groups of dihydrolipoamide, result to decreased production of cellular ATP. Polycyclic aromatic hydrocarbons and nitrosamines associated to tobacco smoke increases the formation of ROS that results in oxidation of plasma proteins in BC.1,11,12. Associated to metabolism of toxins in liver or extrahepatic tissues, oxidation reactions could be catalyzed by CYP450 leads to electrophilic compounds in addition to act as a reducing system that leads to radical intermediates which may react on oxygen to produce many ROS leading to oxidative stress. Another enzyme that contributes to metabolic bioactivation is prostaglandin H synthase (PHS) that employs a part in prostaglandin producing substrate—derived free radical intermediates which can oxidize toxins to biologically sensitive intermediates changing them to oncogenic structures. High levels of PHS and low levels of cytochrome P−450 in bladder epithelium was reported previously. This metabolism is due to two enzymatic activities, a cyclooxygenase and a peroxidase.

Acting to protect the organism against these harmful pro—oxidants is a complex system of enzymatic antioxidants [e.g., superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase, and catalase] and nonenzymatic antioxidants [e.g., glutathione (GSH), vitamins C and D]. There are conflicting publications associated to the correlation between total antioxidant capacity (T−AOC) and its effect in early stage of carcinogenesis. There are some reports that stated AO could inhibit initiation and promotion associated to carcinogenesis. Others found that vitamin and antioxidant supplements have no preventive effect against BC. Regarding the beneficial effect in the prevention of BC in those who are deficient in vitamins or antioxidants, research are in progress toward the role of natural vitamins or antioxidants in fruits and vegetables or vitamin and antioxidant supplements.
Discussion

As a result of physiological process, oxidants are generated continuously in biological system by organelles that can generate ROS are mitochondria, endoplasmic reticulum and peroxisomes. In addition, oxygenase and intracellular oxidase can also generate ROS/RNS. It is well-known that in the presence of imbalance between oxidants and antioxidants the production of superoxide, lipid hydroperoxides, hydrogen peroxide, nitric oxide and peroxynitrite increase. In addition nicotinamide adenine dinucleotide phosphate (NADPH) oxidases known as NOX have been identified as major sources of oxidants in cancer. Natural compounds as inducers of oxidative stress are able to modulate the physiological functions of cancer cells leading to cell death or survival. Alteration of mitochondrial metabolism and bioenergetics might be as a result of unrepaired lesions that may cause oxidative phosphorylation of genes in patients with cancers. Smoking acts as a carcinogen by activating oxidative pathways. Publication confirmed that in the development of breast, prostate, pancreatic and colon cancer oxidative stress and gene—environment interactions play a significant role. In addition extended exposure to estrogen is associated with several kinds of DNA damage.

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References


