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Review

Oxidative and antioxidative mechanisms in oral cancer and precancer: A review

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SUMMARY

Development of cancer in humans is a multistep process. Complex series of cellular and molecular changes participating in cancer development are mediated by a diversity of endogenous and exogenous stimuli and important amongst this is generation of reactive oxygen species (ROS). Reactive radicals and non-radicals are collectively known as ROS. These can produce oxidative damage to the tissues and hence are known as oxidants in biological system. Many researchers have documented the role of ROS in both initiation and promotion of multistep carcinogenesis. To mitigate the harmful effects of free radicals, all aerobic cells are endowed with extensive antioxidant defence mechanisms. Lowered antioxidant capacity or the oxidant-antioxidant imbalance can lead to oxidative damage to cellular macromolecules leading to cancer. Oral cavity cancer is an important cancer globally and tobacco is the primary etiological factor in its development. Tobacco consumption exposes the oral epithelium to toxic oxygen and nitrogen free radicals that can affect host antioxidant defence mechanisms. Elevated levels of ROS and Reactive Nitrogen Species (RNS) and lowered antioxidants are found in oral precancer and cancer. Protection can be provided by various antioxidants against deleterious action of these free radicals. Treatment with antioxidants has the potential to prevent, inhibit and reverse the multiple steps involved in oral carcinogenesis. This review is an attempt to understand the interesting correlation between ROS and RNS mediated cell damage and enzymatic and non-enzymatic defence mechanisms involved in oral cancer development and its progression and the use of antioxidants in oral cancer prevention and treatment.

Introduction

The paradox of aerobic life is that higher eukaryotic aerobic organisms cannot exist without oxygen, yet oxygen is inherently dangerous to their existence [1]. It was towards the end of eighteenth century that oxygen emerged as the paragon among the elements which sustained life, promoted physical health and stimulated mental vigour. But too much of even the best is bad as was shown by Paul Bert in 1878 that oxygen in high concentrations could damage brain, lungs and other organs [2]. Today's concept of oxygen toxicity is not restricted only to hyperbaric oxygen but primarily focuses on the stress caused by oxygen metabolites (oxygen free radicals or reactive oxygen species) generated as an integral part of our daily life. At present number of researchers have documented role of free radicals and reactive oxygen species (ROS) in number of pathophysiological states including cancer. These intermediates of oxygen reduction attack DNA and other cellular components such as lipids, proteins, leaving behind reactive species that in turn can couple to DNA bases [3]. The accumulation of DNA damage through disrepair or incomplete repair may lead to mutagenesis and consequently cancerous transform cation.

Harmful effects of ROS are balanced by non-enzymatic and enzymatic antioxidants [4]. Depleted antioxidant defence mechanisms leads to oxidative damage to normal cells and tissues. Disruption of the delicate balance between oxidants/antioxidants in body plays a causative role in carcinogenesis. Enhanced ROS or reactive notrosative species (RNS) or both along with concomitant decrease in antioxidants is seen in various cancers including head

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and neck cancer [5–10]. To examine the involvement of oxidative stress and depleted antioxidant defence mechanisms in oral carcinogenesis, a literature search using online databases (Pubmed, MEDLINE, Scopus) was done using the search terms such as oxidative stress and cancer, role of oxidative stress in cancer, oxidative stress and oral cancer, antioxidants, antioxidants in oral cancer, and antioxidants in cancer prevention, and all relevant articles were reviewed and included. Role of oxidants in oral precancer and cancer as well as preventive and therapeutic importance of antioxidants, an outlook on modulation of oxidants and antioxidants in cancer therapeutics along with their utility as cancer biomarkers is discussed in this review.

Introduction to oxidative stress, ROS and RNS

In 1954, Gerschman and colleagues for the first time proposed that damaging effects of oxygen could be attributed to formation of oxygen free radicals [11]. Free radical is a molecule or molecular fragment containing an unpaired electron in the valence shell (i.e. radical) and capable of existing independently (i.e. free) [12]. ROS include both free radicals as well as non-radical derivatives of oxygen [13]. The relation between free radicals and disease can be explained by the concept of 'oxidative stress' elaborated by Sies [14]. He defined oxidative stress as an imbalance between oxidants and antioxidants in favour of oxidants, potentially leading to damage [15]. Products of biological damage are referred as biomarkers of oxidative stress [16].

Nitrosative stress

Nitric Oxide(NO) is an important biologic signalling molecule. Several different forms of NO synthase(NOS) enzymes generate nitrogen based radicals. Nitrosative stress (NS) is defined as the ratio of nitrosants to antioxidants as >1 similar to oxidative stress, but with involvement of RNS. This process involves a variety of oxygen–nitrogen species causing excessive oxidation and/or nitrosylation compared to antioxidation or reduction [17]. Nitrosative stress has been implicated in cellular damage or alterations in normal cell signalling pathways.

Chemistry and sources of ROS/RNS

Free radical contains an odd number of electron, which makes it unstable, short lived and highly reactive. Generally, it reacts with the nearest stable molecule, "stealing" its electron to gain stability. The attacked molecule looses its electron, it becomes a free radical itself, beginning a chain reaction cascade resulting in disruption of a living cell [12]. Most ROS are generated as by-products during mitochondrial electron transport. In addition they are formed as necessary intermediates of metal catalyzed oxidation reactions. RNS are formed from interactions of NO with O_2 or O_2^- resulting in formation of dinitrogen trioxide (N_2O_3) and peroxynitrite ($ONOO^-$).

Free radicals are formed by [12]:

A. Covalent bond cleavage of normal molecule or atom: Homolytic cleavage of molecule leads to formation of free radicals. Such type of cleavage requires high energy input. Whereas, in hetrolytic cleavage, one of the atom retains both the bonding electrons and another takes none resulting in formation of ionic species.
B. Electron transfer: is a common important source of free radical generation in biological system. (i) Oxidation reaction: By loss of single electron from a normal molecule. (ii) Reduction reaction: By addition of single electron to a normal molecule.

Sources of oxidative stress

ROS can be produced from endogenous and exogenous substances. Potential endogenous sources include mitochondria, cytochrome P450 metabolism, peroxisomes, and inflammatory cell activation [18]. Exogenous sources include environmental agents such as non-genotoxic carcinogens, various xenobiotics, ultrasound and microwave radiation [19,20].

Various ROS and RNS are given in Table 1. They have dual nature, on one hand they are necessary for normal cellular functions but when in excess they can cause cellular damage and can lead to cancer.

Mechanism of action of ROS in cancer

Cancer development is characterised by cumulative action of multiple events occurring in single cell and can be described by three stages: initiation, promotion and progression. ROS is involved in all these stages. The effect of oxidative stress at a certain stage of carcinogenesis is directly proportionate to the type and the reactivity of radicals involved. Initiation results when a normal cell sustains a DNA mutation that, when proceeded by a round of DNA synthesis, results in fixation of the mutation, producing an initiated cell. Initiation of cancer by ROS is supported by presence of oxidative DNA modifications in cancer tissues [22]. The promotion stage is characterized by clonal expansion of initiated cells, by induction of cell proliferation and/or inhibition of apoptosis [19]. Oxidative stress is strongly involved in this stage. ROS can stimulate expansion of mutated cell clones by temporarily modulating the genes which are related to proliferation or cell death [23] and by regulating activity of certain transcription factors such as NFκB, Nrf2, HIF, and p53 [24] which control cell growth and oncogenesis [23,25]. It can lead to NFκB activation, with subsequent induction of genes encoding for proteins that inhibit apoptosis [26]. It can also act at signal-transduction level to exert pro-survival functions. Oxidative stress can activate ERK/MEK and PI3K/AKT pathways. This could result in inactivation of proapoptotic proteins and upregulation of antiapoptotic genes [27]. A low level of oxidative stress can stimulate cell division in promotion stage and thus promotes tumour growth [28]. This implies that ROS production during this stage is the main mechanism of ROS-related tumour promotion. ROS also contributes to the last stage of carcinogenesis, Progression. In this stage, generation of large amounts of ROS may contribute to mutate, inhibit antiproteisases, upregulate matrix metalloproteinases (MMPs) [29,30] and injure local tissues [31]. Increased levels of oxidatively modified DNA bases may contribute to genetic instability and metastatic potential of tumor cells in fully developed cancer [32]. ROS is reported to be crucial for triggering angiogenic response, which is important in cancer metastasis [33]. This suggests that ROS is involved in all these stages of carcinogenesis. ROS, which are formed through various events and pathways, react with and damage cellular components and contribute to neoplastic transformation [34,35]. Here is an overview of this (Fig. 1).

ROS mediated damage to biomolecules (Table 2) and its role in carcinogenesis

Oxidative nuclear and mitochondrial DNA damage

DNA is highly sensitive to ROS attacks. Permanent modification of genetic material resulting from this represents first step involved in mutagenesis and carcinogenesis. Elevated levels of oxidative DNA lesions have been noted in many tumors, strongly