ScienceDirect

Cancer Letters

Volume 282, Issue 2, 18 September 2009, Pages 125-136

Mini-review

Oxidative stress in prostate cancer

Lakshmipathi Khandrika [a 1], Binod Kumar [a 1], Sweaty Koul [a], Paul Maroni [a b], Hari K. Koul [a b]

Show more

https://doi.org/10.1016/j.canlet.2008.12.011

Get rights and content

Abstract

As prostate cancer and aberrant changes in reactive oxygen species (ROS) become more common with aging, ROS signaling may play an important role in the development and progression of this malignancy. Increased ROS, otherwise known as oxidative stress, is a result of either increased ROS generation or a loss of antioxidant defense mechanisms. Oxidative stress is associated with several pathological conditions including inflammation and infection. ROS are products of normal cellular metabolism and play vital roles in stimulation of signaling pathways in response to changing intra- and extracellular environmental conditions. Chronic increases in ROS over time are known to induce somatic mutations and neoplastic transformation. In this review we summarize the causes for increased ROS generation and its potential role in etiology and progression of prostate cancer.

Introduction

Prostate cancer is the most frequently diagnosed non-cutaneous malignancy in males, statistics from the American Cancer Society project 186,000 new cases and 28,000 deaths in US for the year 2008 [1]. This is a multi-focal, field-type disease which forms solid tumors of glandular origin. Androgens play an important role in the differentiation, development and normal functioning of the prostate and therefore likely have a role in developing prostate carcinogenesis. Conventional therapies produce a high rate of cure for patients with localized prostate cancer, but there is no cure once the disease has spread beyond the prostate. Traditionally, treatment of prostate cancer was based on the deprivation of androgens to the developing tumor [2]. Though initially successful, this form of therapy fails in advanced stages of the disease, as the cells develop the ability to sustain growth and proliferation even in the absence of androgens, thus

acquiring androgen independence [3]. Although several molecular alterations are known to be involved in the acquisition of androgen independence, the precise mechanism of this phenomenon is poorly understood. Molecular genetic changes in androgen independent prostate cancer cells result in a shift from paracrine to autocrine regulation driven by growth factor and cytokines [4], [5], [6].

Prostate cancer cells that proliferate in the absence of androgens typically have an aggressive phenotype. Though multiple factors and signaling pathways have been implicated in the development of aggressive prostate cancer [7], [8], the trigger for initiation of malignancy is still a topic of debate. Prostate cancer is mainly a disease of aging, with most cases occurring in men over the age of 55. Therefore, progressive inherent or acquired changes in cellular metabolism occurring over the years may play a very important role in the development of this disease. Many factors like diet, environmental carcinogens, and other inflammatory diseases have been linked to an increased risk of prostate cancer.

Hydroxyl radicals, peroxides and superoxides are ROS that are generated during everyday metabolic processes in a normal cell. ROS, generated either endogenously (mitochondria, metabolic process, inflammation etc.) or from external sources [9], play a vital role in regulating several biologic phenomena. While increased ROS generation has traditionally been associated with tissue injury or DNA damage which are general manifestations of pathological conditions associated with infection, aging, mitochondrial DNA mutations and cellular proliferation; new and exciting information points to an essential role for increased ROS generation in several cellular processes associated with neoplastic transformation and aberrant growth and proliferation [10], [11]. Processes associated with proliferation, apoptosis, and senescence may be a result of the activation of signaling pathways in response to intracellular changes in ROS levels [12]. Thus, excessive production of ROS or inadequacy in a normal cell's antioxidant defense system (or both) can cause the cell to experience oxidative stress and the increased ROS may play a broader role in cellular processes associated with initiation and development of many cancers including prostate cancer.

Over the last decade association between prostate cancer risk and oxidative stress has been recognized, and epidemiological, experimental and clinical studies have unequivocally proven a role for oxidative stress in the development and progression of this disease. Differences in prostate cancer incidence among various races, environment, diet, life style, genetic constitution and hormone of an individual/community are some of the contributing risk factors for occurrence of prostate cancer [13], [14], [15]. Though recent studies have indicated that oxidative stress is higher in the epithelium of prostate cancer patients than men without the disease, the association of ROS-mediated oxidative stress and prostate cancer risk remains to be elucidated. Theories abound regarding their role in initiation of prostate cancer, and include but are not limited to, failure of antioxidant defense mechanism (due to persistent oxidative stress that leads to inherited and acquired defects in the defense system), mtDNA mutations, chronic inflammation, defective DNA repair mechanism and apoptosis etc., finally leading to the development of prostate cancer. Thus, many of the factors that are associated with prostate cancer like aging, imbalance of androgens, antioxidant system, dietary fat, and pre malignant conditions like high grade prostate intraepithelial neoplasia etc. may be linked to oxidative stress. In recent years several antioxidant trails have been conducted against prostate cancer, but the usefulness of such therapies needs extensive research before put into practice [16].

In this article, we reviewed literature pertaining to the role of ROS generation in prostate cancer, and the cellular effects of oxidative stress (Fig. 1). In addition, we will also discuss the relationship between prostate cancer susceptibility and oxidative stress in relation to antioxidant defense system, metabolic switch,

mtDNA mutation, inflammation and regulation of androgens. This review is aimed at providing an overview about the role of ROS in promoting prostate cancer.

Section snippets

Antioxidant therapy in prostate cancer: where are we?

In 1981, a landmark study by Doll and Peto estimated that a higher percentage of cancer deaths in USA could be attributed to dietary factors, and proposed that antioxidant present in diet could deactivate formation of free radicals inside the cell [17]. After this discovery, a set of projects on cancer prevention were funded by NCI on a large scale, including clinical trials to test the role of dietary antioxidants in cancer prevention. Among the available antioxidant vitamins, vitamin E was of …

Role of antioxidants in prostate cancer

Prostate cancer is commonly associated with a shift in the antioxidant–prooxidant balance towards increased oxidative stress. Previous studies highlighted the altered prooxidant–antioxidant status in prostatic tissue of man, rat and also in cell lines, where the imbalance between these antagonist played a major role in the initiation of prostate carcinogenesis [23]. However, there is very little idea about the cause of this imbalance. Androgens are considered to be the most powerful candidates…

Metabolic switch and mitochondrial DNA mutations in prostate cancer

Mitochondrial DNA mutations are very frequent in cancer, and the accompanying mitochondrial dysfunction and altered metabolism may contribute to tumor pathogenesis and metastasis [30], [31], [32]. In the case of a normal prostate, higher concentration of zinc present in the tissue causes a block in Krebs cycle and accumulation of citrate in the prostatic fluid. Thus, normal prostate glandular epithelial cells have low respiration causing low terminal oxidation, are energy inefficient and…

NADPH oxidase: an emerging candidate in prostate cancer

The NAD(P)H dependent reduction of molecular oxygen is responsible for the generation of ROS in a cell, in the form of superoxide anion (O_2^-), which is then dismutaed to form peroxide (H_2O_2) [42]. Phagocytic cells generate higher amount of ROS using NADPH oxidases (Nox, Fig. 3) as part of their armory of microbicidal mechanisms. Recent reports also indicate their presence in some of the non-phagocytic tissue like fetal kidney, thyroid, prostate, colon etc. [43], [44]. NAD(P)H oxidase is…

Aging, oxidative stress and prostate cancer

Aging is associated with many metabolic disorders and also with increased incidence of various cancers [50], [51]. Prostate cancer is a major age related malignancy with most incidences occurring between 54 and 75 years and rapid onset after 45 years [52], [53]. Many theories have been formulated to explain the

molecular and biochemical aspect of aging, but Harman proposed “free radical theory of aging” in which he suggested that accumulation of damage to biomolecules caused by free radicals…

Hypoxia and ROS

Extensive cell proliferation coupled with unorganized vasculature present in a tumor result in a low oxygen environment (hypoxia) forcing the cells to shift to anaerobic glycolysis for their energy requirements [81], [82]. Tumor cells have the ability to overcome low oxygen tension due to concomitant activation and stabilization of hypoxia inducible factor (HIF-1). Studies in many systems have shown an increase in intracellular ROS production when exposed to hypoxic environment [83] and mostly…

Bacterial and non-bacterial prostatitis

Prostatitis is a manifestation characterized by painful inflammation of the prostate. Even though the reason for the occurrence of prostatitis is much in debate, two classes of prostatitis have been recognized, Bacterial and non-bacterial prostatitis [90]. Prostatitis is often associated with symptoms that range from voiding discomfort to adverse sexual function [91]. Epidemiological studies suggest that on an average about 11–16% of men in the United States have been or are diagnosed with…

Summary and future directions

Evidence from epidemiological, experimental and clinical studies suggest that prostate cancer cells are exposed to increased oxidative stress. Environmental factors like diet, inflammation, and changes in cellular functions pertaining to NAD(P)H oxidase, androgen signaling, mtDNA mutations, aging, and redox imbalance are possible mechanisms that contribute to increased ROS generation (Fig. 1). This increased ROS may further stimulate cell proliferation, cause somatic DNA mutations and promote…

Conflicts of interest statement

None declared.…

Acknowledgements

Supported in part by NIH/NCI-P20 CA103680-Schwartz/Byers Program PI’s (H Koul, Pilot-Project PI), University of Colorado Cancer Center and Department of Surgery-School of Medicine Academic Enrichment Funds (H Koul).…

Special issue articles Recommended articles

References (113)

J.T. Isaacs