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Commentary

Antioxidants for prostate cancer chemoprevention: Challenges and opportunities

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ABSTRACT

Extensive research has led to the firm conclusion that antioxidants protect cells from damage caused by oxidative stress and its associated pathological conditions including inflammation. It has also been established that inflammation is a precursor in neoplastic transformation of the prostate. Although, a vast body of experimental and clinical evidence shows efficacy of antioxidants as preventive strategies for prostate cancer, there is a lack of consistent agreement in outcomes especially from recent large-scale randomized clinical trials. Despite these concerns, our understanding of the preventive mechanisms as well as clinical efficacy and safety data indicate that novel antioxidant therapeutics still hold great promise for prostate cancer chemoprevention. We propose that for effective use of antioxidants for prostate cancer prevention, further high impact translational research is needed with special attention on selecting those patients who will benefit from such intervention. Therefore, it is important to validate predictive biomarkers from successful trials and combine this with knowledge of preclinical characterization of antioxidants (and combinations) that will eventually facilitate the development of 'personalized prostate cancer chemoprevention'. In this review, we briefly describe some common and emerging antioxidants that have shown benefits in preclinical and clinical settings. Above all, we focus on summarizing the progress we made thus far in prostate cancer chemoprevention using antioxidants, the heightened interest and challenges in the future.

1. Introduction

Prostate cancer is the most commonly diagnosed cancer among men in the United States. Approximately 240,890 new cases and about 33,270 deaths are expected to occur in 2011 [1]. Until recently prostate cancer had been considered to be a major health problem in Western countries, however it is now reported as an emerging threat to the health of aging men in Asia [2]. In addition to aging, other factors such as genetic, epigenetic and environmental risk factors also increase the probability of developing prostate cancer. Recent studies have identified inherited variants (single nucleotide polymorphisms) as potential early markers for the risk of prostate cancer, particularly in disease aggressiveness [3–5]. Further, epidemiological and clinical studies suggest that several possible environmental factors such as carcinogens, hormone profile with age and inflammation are strongly associated with prostate carcinogenesis [6–8]. Diet is considered as a modifiable environmental factor that can influence prostate cancer incidence and clinical outcome [9,10].

Although little is known regarding etiology and factors that influence clinical outcome, 'elevated oxidative stress' in the cellular microenvironment is a common denominator in prostate cancer and aging. Oxidative stress causes damage to multiple cellular components such as DNA, proteins, and lipids, and is clearly implicated in prostate cancer. Cells have developed a robust antioxidant defense system to maintain cellular redox homeostasis and to protect from damage under conditions of oxidant attack. However, increased reactive species from inflammation or inhibition of defense mechanisms can easily overcome the capacity of the antioxidant system leading to perturbation of cellular redox balance. Knowledge of prostate cancer pathobiology gave rise to

Abbreviations: 8-oxo-dG, 8-oxo-2′-deoxyguanosine; ADT, androgen-deprivation therapy; AR, androgen receptor; ARE, antioxidant response element; ATBC, Alpha-Tocopherol, Beta-Carotene; BPH, benign prostatic hyperplasia; CARET, Carotene and Retinol Efficacy Trial; CRPC, castration-resistant prostate cancer; DRE, digital rectal exam; GPx, glutathione peroxidase; GSR, glutathione reductase; HGPIN, high-grade prostatic intraepithelial neoplasia; JPHC, Japan Public Health Center; NPC, Nutritional Prevention of Cancer; NQO, NADPH: quinone oxidoreductase; PCNA, proliferating cell nuclear antigen; PHS, Physicians' Health Study; PIA, proliferative inflammatory atrophy; PIN, prostatic intraepithelial neoplasia; PKC, protein kinase C; PSA, prostate-specific antigen; RNS, reactive nitrogen species; ROS, reactive oxygen species; SELECT, Selenium and Vitamin E Cancer Prevention Trial; SOD, superoxide dismutase; SU.VI.MAX, supplementation en vitamines et mineraux antioxydants; SWOG, Southwest Oncology Group; TRAMP, transgenic adenocarcinoma of the mouse prostate; TrxR, thioredoxin reductase.

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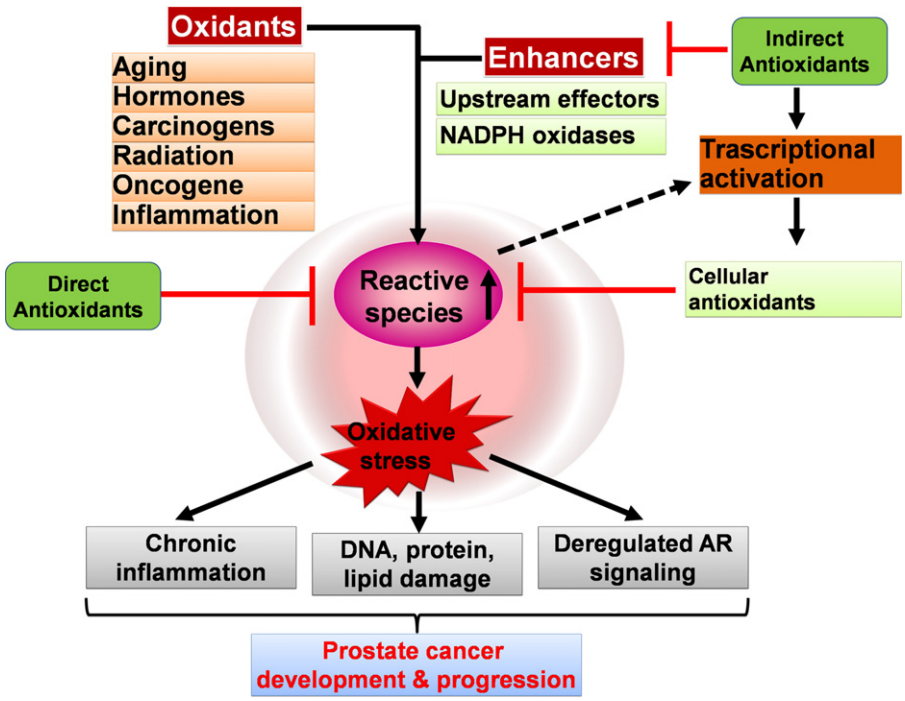

Fig. 1. Oxidative stress plays a central role in prostate cancer initiation and progression. Elevated oxidative stress is one of the hallmarks of prostate cancer. Although sources and nature of oxidants are heterogeneous, the most common sources include aging, genetic alterations, environmental insults, fluctuation in hormone and cellular metabolism. These changes in the prostatic microenvironment lead to recurrent and chronic inflammation, induction of DNA damage leading to genomic instability, induction of lipid and protein damage, and deregulation of cellular redox homeostasis via various important cellular pathways, which together lead to cancer progression. The modulation of increased oxidative stress by antioxidants may serve as novel biomarkers and chemopreventive targets for prostate cancer. (Solid arrow and broken arrow represent direct activation and redox balance in oxidative stress pathway, respectively. Red blunt arrow indicates inhibition of elevated oxidative stress by direct or indirect antioxidants.). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

the novel concept of antioxidants for its chemoprevention. Supplementation with antioxidants (direct antioxidants) or stimulation of cellular antioxidant systems (indirect antioxidants) can reduce oxidative injuries and thus prevent prostate cancer (Fig. 1). In this review, we briefly describe the role of antioxidants in prostate cancer prevention, the observed discrepancies between preclinical and clinical data regarding the use of antioxidants for prostate cancer chemoprevention and discuss challenges and opportunities that this system offers for its use as a prostate cancer chemoprevention strategy.

2. Antioxidants for prostate cancer chemoprevention

2.1. Significance of prostate cancer chemoprevention

Although surgery, radiation, chemo-, or hormonal-therapy, are used in the general management of prostate cancer; personalized treatment for prostate cancer still remains challenging. Many patients are either not cured by available therapeutic regimens and their cancer recurs, or cancers are diagnosed after it has metastasized. Long latency in the development of clinically significant prostate cancer combined with the indolent nature of its progression makes it a prime candidate for chemoprevention strategies. Therefore it is widely accepted that chemopreventive strategies not only reduce the risk of prostate cancer progression and mortality but can also reduce the need for invasive interventions.

The term chemoprevention was coined by Michael B. Sporn and is defined as the use of pharmacologic or natural agents to disrupt cancer [11]. The original term has since grown to include *primary* prevention in which the initiating DNA damage is blocked; *secondary* prevention whereby there is an arrest or reversal of the progression of initiated premalignant cells; and finally *tertiary* prevention in which metastatic progression of the primary tumor is blocked. Current chemopreventive strategies have empirically focused on two approaches: suppression of androgenic stimulation of the prostate and treatment with antioxidants to reduce damage to DNA [12]. The first strategy, androgen-deprivation therapy (ADT) is principally based on the pathological role of aberrant androgen receptor (AR) signaling which is clearly implicated in prostate carcinogenesis and prostate cancer progression [13]. The prostate and early-stage prostate cancers depend on androgens for growth and survival, therefore ADT causes tumor regression [14]. Recent chemoprevention attempts based on ADT, specifically using 5α-reductase inhibitors (finasteride and dutasteride), have shown significant benefits with an overall relative reduction of 23–25% in prostate cancer risk [15,16]. Benefit with the drugs was limited to low-grade prostate tumors with modified Gleason score of 6 or lower. In fact, in both trials, there was an absolute increase in the incidence of high-grade prostate cancers in the chemoprevention arm. It has been proposed that finasteride significantly enhances the ability of prostate specific antigen (PSA) to detect prostate cancer and high-grade prostate cancer [17]. However PSA has limited use and change in PSA is associated with other genitourinary conditions not related to prostate cancer. There are other concerns regarding the limitation and adverse effects of ADT including but not limited to the development of castration-resistant prostate cancer (CRPC), osteoporosis, neurodegenerative, and cardiovascular diseases [14,18–20]. Further finasteride is associated with hormonal and genitourinary side effects [21]. In addition there is no data available regarding the long-term effects of inhibiting 5α-reductase in otherwise healthy men. A combination of these reasons limits the use of finasteride as a primary chemoprevention agent for prostate cancer.

The second strategy using antioxidants holds abundant prospect for primary prevention of prostate cancer but still