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Zinc and prostatic cancer

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Abstract

Purpose of review—Aim to understand the connection between zinc and prostatic cancer, and to summarize the recent findings about the functions of zinc in the maintenance of prostate health.

Recent findings—Contradictory findings have been reported by epidemiologic studies examining the association between zinc intake and the risk of prostate cancer. However, a growing body of experimental evidence support that high zinc levels are essential for prostate health. The possible mechanisms include the effects of zinc on the inhibition of terminal oxidation, induction of mitochondrial apoptogenesis, and suppression of NFκB activity. The most recent finding is the effects of zinc in the maintenance of DNA integrity in normal prostate epithelial cells (PrEC) by modulating the expression and activity of DNA repair and damage response proteins, especially p53. Zinc depletion in PrEC increased p53 expression but compromised p53 DNA binding activity resulting an impaired DNA repair function. Moreover, recent findings support the role of zinc transporters as tumor suppressors in the prostate.

Summary—Future studies need to discover sensitive and specific zinc biomarkers and perform more in vivo studies on the effects of zinc on prostate functions in normal animals or prostate cancer models.

Keywords

zinc; prostatic cancer; DNA damage; zinc transporter

Introduction

The prostate contains the highest concentration of zinc of any soft tissue and secretes high amounts of zinc in prostatic fluid [1]. Zinc concentrations in malignant prostate tissues are about 10-25% of in healthy prostates [2], suggesting that high zinc concentrations may be essential for the maintenance of prostate health [3-5]. Although results from epidemiologic studies have been mixed about the association between zinc intake and the risk of prostate cancer [6, 7], experimental evidence strongly suggests that zinc plays roles in prostate cell functions and survival [5, 8]. However, the specific functions of zinc in the prostate and the mechanisms by which zinc maintains prostate health are still unclear. The purpose of the current article is to review the main mechanisms have been proposed for the functions of zinc in the prostate, and summarize the recent epidemiologic and experimental findings in the field of zinc and prostatic cancer.

Zinc intake and the risk of prostate cancer

Several large observational cohort studies have found that plasma zinc concentrations or dietary zinc intakes are inversely associated with cancer or all cause mortality risks [9-11]. Specifically for prostate cancer, a case-control study done by Kristal AR et al. observed that the usage of individual zinc supplements was associated with reduced prostate cancer risk [7]. Recently the VITamins And Lifestyle (VITAL) cohort study found that although long-term usage of zinc supplements was not associated with reduced prostate cancer risk, it was associated with reduced risk of advance prostate cancer [12]. Moreover, a study done in South Carolina found that area with lower soil zinc content had higher prostate cancer rate [13]. However, there also have been some cohort and case-control studies observed that long-term and/or high dose usage of zinc supplements increased the risk of prostate cancer [14]. One reason for these mixed results from epidemiologic studies could be that none of these studies used zinc biomarker to evaluate ‘real’ zinc status, and the levels of dietary zinc and zinc supplements intake could not possibly accurately reflect zinc status in the observed populations. Although the commonly used zinc biomarkers such as plasma zinc have been criticized for lack of sensitivity and specificity, functional biomarkers such as IL-2 gene expression in mononuclear cells [15] have been proposed that to be good indicators for zinc status. Therefore, future studies using accurate biomarker to reflect zinc status would help clarify the real association between zinc status and risk of prostate cancer.

Several mechanisms by which zinc may protect prostate cells from malignancies have been proposed, including zinc as an inhibitor to m-aconitase activity, apoptogenic effects and as a protector for DNA integrity.

Zinc suppresses overall energy production in prostate cells

Prostate epithelial cells have characteristically high aerobic glycolysis, low respiration rates and high citrate secretion [16-18], and high zinc concentrations in the prostate may be required for these properties. Costello et al have found that zinc in the prostate epithelial cells reduces the activity of mitochondrial aconitase and inhibits the terminal oxidation in the electron transport chain. The inhibitory effect of zinc on m-aconitase may contribute to the properties of high citrate secretion and low respiration in the prostate [8, 19]. Zinc depletion in the prostate may remove the inhibitory effects on citrate oxidation and terminal oxidation, and increase cellular respiration. Thus, decreases in cellular zinc levels in the prostate epithelial cell and subsequent release of aconitase activity could result in an elevated cell respiration that favors cell growth and differentiation, and enables these cells to manifest their malignant properties [5].

Zinc imposes apoptogenic effects and suppresses tumor progression

Zinc depletion induces apoptosis in some mammalian cells. The possible mechanisms include defects in growth factor signaling pathways, activation of caspases and induction of the intrinsic pathway of apoptosis [20]. However, zinc has opposite effects on cell growth in the prostate; zinc in the prostate induces mitochondrial apoptogenesis and reduces cell growth. Costello et al evaluated the effects of exposure to the physiological levels of zinc on mitochondrial apoptogenesis in three human cancer cell lines, PC-3, BPH and HPR-1 [21].

They found that zinc only induced apoptosis in PC-3 and BPH which both maintained the capacity of accumulating high intracellular zinc, but not in HPR-1 which lost its zinc accumulation ability. The effects of zinc on apoptosis in the prostate cancer cells may be exerted through the modulation of the expression of Bax and its binding with mitochondria membrane [22] and the subsequent releasing of cytochrome c from mitochondria [21].

Studies done by Kolenko VM et al suggested that zinc may suppress prostatic tumor progression by decreasing NFκB activity and the subsequent expression of angiogenic and pro-metastatic cytokines VEGF, IL-6 and IL-8 [23].

Zinc protects DNA integrity in the prostate

The general functions of zinc in the maintenance of DNA integrity may be also very important for prostate health. Zinc depletion in cells including normal prostate epithelial cells (PrEC) increased DNA strand breaks [24-26], and dietary zinc depletion also elevated DNA damage in rat testes or monkey livers [27, 28]. Our lab have recently shown that dietary zinc depletion (4mg/d for 6wk) in health men significantly increased DNA damage in peripheral blood cells, and zinc repletion (11mg/d, 4 wk) reversed the DNA damage back to the baseline levels (Song Y, Ho E, in press). Since zinc is an essential component in numerous transcription factors, antioxidant defense enzymes and DNA repair proteins, zinc may protect DNA integrity through two different mechanisms: 1) zinc has antioxidant properties and suppresses the generation of oxidative damage; 2) zinc is essential for DNA damage responses and help repair DNA damage or remove damaged cells [29].

It has been established that zinc has antioxidant capacity, and that zinc depletion in rats generates carbon-centered free radicals in lung microsomes [30] and oxidatively modified proteins and lipids in various tissues [31-34]. Studies in our lab have shown that both severe [35] and marginal zinc depletion increases F_2-isoprostanes in rat plasma. The mechanisms for the antioxidant functions of zinc include: 1) zinc protects the sulfhydryl groups from oxidation, thereby maintains normal functions of proteins such as 5-aminolaevulinate dehydratase [36]; 2) zinc maintains the reductive intracellular environment though the modulation of thiol status [33, 37]; 3) zinc antagonizes the activity of bivalent transition metals including iron and copper, and prevents the deleterious free-radical reactions (e.g. Fenton reaction); 4) zinc regulates the expression of metallothionein [38, 39] and CuZn SOD activity.

Since zinc may inhibit terminal oxidation of prostate mitochondria, depletion of zinc in the prostate may not only remove the antioxidant effects of zinc, but may also remove the this inhibitory effects of zinc on terminal oxidation and increase the generation of free radicals. Therefore, the high zinc levels may protect the prostate from oxidative stress by both suppressing the generation of free radicals and promoting the removal of free radicals. However, no *in vivo* studies to date have been performed to evaluate the effects of zinc deficiency in the prostate on oxidative stress and DNA damage. The most recent findings from our lab showed that dietary zinc depletion in rats underwent exogenous stress, such as vigorous exercise, substantially increased oxidative DNA damage in the prostate (Song Y, Ho E, submitted paper).

Normally, the accumulation of DNA strand breaks and DNA adducts stimulates cellular responses to repair the DNA damage or to remove the damaged cells. These cellular responses to DNA damage are triggered by multiple pathways including DNA repair pathways, initiation of cell cycle arrest and apoptosis, and the induction of multiple genes. Zinc depletion may interfere with some of these cellular responses and potentiate the accumulation of DNA damage. First of all, zinc depletion may influence cell cycle arrest and apoptosis by regulating cell signaling pathways. For example, zinc deficiency decreases the circulating level of insulin-like growth factor-1 (IGF-1) [40] and disrupts intracellular receptor tyrosine kinases (RTKs) signaling transduction pathways [41], and thereby affecting cell proliferation and survival.

Secondly, zinc deficiency may impair DNA repair functions. Many proteins involved in DNA repair pathways are zinc-containing metalloproteins, such as tumor suppressor gene p53, Xeroderma pigmentosum A (XPA), Replication Protein A (RPA), and poly ADP ribose polymerase (PARP). These proteins are involved in DNA repair pathways of damage recognition, nuclear excision repair (NER) or base excision repair (BER). Since zinc is essential for the function of some DNA repair proteins, zinc depletion may impair the activity of these proteins and interfere with the DNA repair functions.

Our lab has shown that zinc depletion in PrEC cells altered the expression of genes involved in DNA damage repair and responses, such as TP73, MRE11A, XRCC4, BRCA2 and TP53 [26]. Among them, p53 is one of the zinc-containing tumor suppressors, and plays an essential role in regulating DNA repair, cell proliferation and cell death [42]. Mutations in the DNA binding domain of p53 protein are found in many tumor cells [42], and zinc is located in the DNA binding domain and is essential for the DNA binding activity of p53. Although p53 is consistently induced in zinc depleted cells, including normal prostate epithelial cells, the DNA binding activity of nuclear p53 is not increased with zinc deficiency [24-26]. One possible mechanism may be that decreased intracellular zinc interferes with the incorporation of zinc ion to the DNA binding domain of p53, so that p53 is deprived of DNA binding capacity and is unable to function normally in cellular activities such as DNA repair and cell apoptosis, resulting a void activation.

In summary, zinc may directly suppress the generation of oxidative DNA damage through its antioxidant properties. At the same time, zinc depletion may also affect the activities of both zinc-dependent and zinc-independent proteins that are involved in DNA damage repair or cell apoptosis. Altogether, the accumulation of DNA damage may be substantially increased in zinc deficient prostate cells, and thereby may predispose cells to the development of cancer.

Zinc transporter and prostate cancer

Zinc homeostasis is likely maintained by the activities of a group of zinc transporters in the cell plasma membrane and intracellular organelles. At least ten ZnT and fourteen Zip family members have been identified in mammals, and their tissue expression, cellular localization and regulation are very different (see [43] for detail review).

Since it has been recognized that high zinc levels are essential for prostate health, a loss of function or dysregulation of certain zinc transporters would result in the impairment of zinc homeostasis and predispose prostate cells to the development of cancer. Dysregulation of zinc transporters including ZnT1, ZnT3, Zip1, Zip2 and Zip3 have been found to be associated with the low intracellular zinc content in human prostate cancer tissues or prostate epithelial cancer cell lines. hZIP1, hZIP2 and hZIP3 gene and/or protein expressions were downregulated in human prostate adenocarcinomatous glands and malignant cell lines [44]. In addition, tumorigenic human prostate epithelial cell lines (RWPE2) had decreased ZIP1 protein expression and redistributed intracellular ZIP3 in comparison with the non-tumorigenic human prostate epithelial cell line RWPE1 [4]. Moreover, overexpression of hZIP1 in the tumorgenic RWPE2 prostate cells increased the intracellular zinc concentrations, induced cell apoptosis and suppressed cell growth [4]. A recent study done by Kolenko VM group also found that overexpression of hZip1 in PC-3 cells inhibit tumor growth in C.B17/lcr-scid mice inoculated s.c. in the flank region [45]. NFκB activity and NFκB-pathway dependent angiogenetic and pro-metastatic cytokines expression were also suppressed in these transfected PC-3 cells. In terms of the ZnT family members, lower levels of ZnT1 gene are expressed in human prostate cancer tissues [46] and in the androgen-independent subline of LNCaP cells[47]. ZnT4 gene expressions are also decreased in human prostate benign hyperplasia (BPH) and carcinoma tissues [48]. These studies provide important preliminary evidence for the potential role of specific zinc transporters in prostate cancer progression.

Conclusion

Although the connection between dietary zinc or zinc supplements intake and risk of prostate cancer are still unclear and inconclusive, a growing body of evidence support that high zinc levels in the prostate are essential for prostate health and protect prostate cells from malignancies. The possible mechanisms include the effects of zinc on the inhibition of terminal oxidation, induction of mitochondrial apoptogenesis, suppression of NFκB activity and maintenance of DNA integrity. Moreover, because of the importance of zinc homeostasis to prostate health, a number of zinc transporters have been identified as tumor suppressors in the prostate. Since experimental animal studies are inadequate compared to the in vitro studies, future studies on the effects of zinc status on prostate function in normal animals or prostate cancer models would be helpful. Moreover, searching for good zinc biomarker would significantly help performing in vivo studies.

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