Zinc: An effective agent in dietary chemoprevention of early stage of prostate cancer

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Prostate cancer is one of the frequently diagnosed cancers in men. Dietary intake of nutrients is considered crucial for preventing the initiation of events leading to the development of carcinoma. Many dietary compounds have been considered to contribute in cancer prevention including zinc, which plays a pivotal role in host defense against the initiation and promotion of several malignancies. Zinc is an essential trace element for human health and is a critical component of many proteins and transcription factors involved in DNA damage response and repair. The prostate is known to accumulate high levels of zinc, but levels are markedly decreased with cancer development. Zinc plays a critical role in maintaining DNA integrity in the prostate and zinc deficiency would lead to increased DNA damage and altered DNA damage response mechanisms. Zinc has been ascribed roles in the metabolism and interaction of malignant prostate cells, particularly in apoptosis. Zinc is involved in structural stabilization and activation of the p53 that appears to be an important component of the apoptotic process and also in activation of certain members of the caspase family of proteases. Zinc exerts a positive beneficial effect against chemically induced preneoplastic progression in rats and provides an effective dietary chemopreventive approach to disease in vulnerable section of population with family history of carcinoma. The present review provides an insight into the research conducted on cell line, animals as well as on human subjects for providing the concept that zinc deficiency is an important factor in the development and progression of malignancy and that zinc could be efficacious in the prevention and treatment of prostate cancer. However, it needs further exploration with regard to other definitive bioassays including protein expression and documentation of specific molecular markers to establish the exact mechanism for zinc-mediated prostate cancer chemoprevention. Preclinical trials need to investigate the genetic and epigenetic pathways of chemoprevention by zinc.

Keywords: Apoptosis; Cancer; Chemoprevention; Prostate Cancer; Zinc; Zn deficiency

INTRODUCTION

Zinc (Zn) is an essential mineral that is integral to many proteins and transcription factors that regulate key cellular functions such as the response to oxidative stress, DNA replication, DNA damage repair, cell cycle progression, and apoptosis. In particular, several proteins involved in DNA damage signaling and repair, replicative enzymes, such as DNA and RNA polymerases, and transcription factors, such as tumor protein p53 (p53), require zinc for proper function (Pavletich et al., 1993; Dong et al., 1999; Witkiewicz-Kucharczyk and Bal, 2006). The notable selection and frequent utilization of Zn as the predominant functional element of so many biological molecules have been understood in terms of its chemical properties and its use in biochemical systems. Two properties of Zn need to be highlighted. First, unlike other metals, including those of IIB series, Zn is virtually nontoxic even at higher doses (Berholf, 1988). The homeostatic mechanisms that regulate its entry into, distribution in and excretion from cells and tissues are so efficient that no disorders are known to be associated with its excessive accumulation in contrast to iron, copper, mercury and other metals (Vallee and Falchuk, 1993). Second, its physical and
chemical properties, including its generally stable association with macromolecules and its co-ordination flexibility, makes it highly adaptable to meet the needs of proteins and enzymes that carry out diverse biological functions (Vallee and Auld, 1989; 1990). These chemical properties form the basis for the extensive participation of Zn in protein, nucleic acid, carbohydrates and lipid metabolism as well as in the control of gene transcription and other fundamental biological processes.

Zinc is required in the diet of human beings in trace quantities, which is approximately 15 mg Zn/day (Tapiero and Tew, 2003). It is found in all body tissues and fluids in relatively high concentrations, with 85 per cent of the whole body Zn in muscle and bone, 11 per cent in the skin and the liver and the remaining in all the other tissues. The average amount of Zn in the adult body is about 1.4–2.3 g (Calesnick and Dinan, 1988). Zn is present at higher concentrations in liver followed by pancreas, kidney, heart, pituitary, adrenal, and prostate. There are many reports that clearly emphasize that Zn is a principal limiting factor in the nutrition of children and adolescents and that its deficiency probably accounted for the growth retardation so commonly seen in such age groups. Zn is virtually nontoxic to living organisms. It is the only pre-, post-, and transitional element that is neither cytotoxic nor systematically toxic, nor is it carcinogenic, mutagenic, or teratogenic. Zn is not stored in the body and excess intakes result in reduced absorption and increased excretion. However, there are reports on a few cases of acute Zn poisoning (Stepanidou et al., 2006). Although Zn is an essential element and is nontoxic at lower doses (Berholt, 1988), yet its metabolic role is not clearly known (Yang et al., 1995). It has been considered a trace metal of prime concern as it is essential for carrying out function of various DNA and RNA synthesizing enzymes (Robinson et al., 1991). It is a part of most cellular aspects of body and participates in all major metabolic pathways and is involved in the development and maintenance of competent immune system.

Zn deficiency, after prolonged reduction of intake or excessive uncompensated losses, has been described both in animals and humans. Long-term deprivation of Zn renders an organism more susceptible to injury induced by oxidative stress. More specifically, Zn deficiency increases the levels of lipid peroxidation in mitochondrial and microsomal membranes and the osmotic fragility of erythrocyte membranes, while the presence of Zn prevents lipid peroxidation and thus plays an important role in protecting the cells from oxidative stress (Vallee and Falchuk, 1993; Tapiero and Tew, 2003). Studies have also demonstrated the protective efficacy of Zn in regulating the activities of various antioxidant enzymes, thyroid hormones, liver marker enzymes as well as histological alterations under toxic conditions induced by various xenobiotics (Goel et al., 2005; 2006; Bandhu et al., 2006; Dani and Dhawan, 2006; Dhawan et al., 2006; Chadha et al., 2008).

**Zinc and the prostate gland**

Zn exists in very high concentrations in the healthy prostate, which is important for male fertility. First described in detail by Mawson and Fischer (1952) in the 1950s, the prostate contains more Zn than any other soft tissue. In addition, the prostate secretes high Zn levels into seminal fluid, playing an important role in sperm release and motility (Sorenson et al., 1999; Yoshida et al., 2008). The prostate is organized into distinct lobes and each lobe varies in Zn content (Fig. 1 & 2). The dorsolateral lobe in rodent prostate and the peripheral lobe in human prostate have the greatest Zn concentrations and these 2 lobes are primarily involved in the secretion of prostatic fluid (Costello and Franklin, 1998). In its entirety, the human prostate contains >3 times more Zn than other soft tissues (~150 mg Zn/g (1 g Zn = 0.015 mol Zn) prostate compared with ~20–50 mg Zn/g for other organs). Similarly, prostatic fluid contains ~500 mg Zn/mL fluid compared with 1–2 mg Zn/mL of plasma (Costello and Franklin, 1998). In addition to influencing sperm motility, Zn is attributed with antimicrobial functions in prostatic fluid (Fair et al., 1976) and within the prostate itself (Cho et al., 2002). Interestingly, the major function of Zn in the prostate may be to facilitate the secretion of citrate. Unlike most cells in which Zn is sequestered into vesicles and organelles, Zn in cytoplasm of the prostate cell comprises almost 35% of the total intracellular Zn content. This Zn is loosely bound to small molecular weight molecules such as citrate and is considered biologically active (Costello and Franklin, 1998). The current dogma suggests that this bioactive Zn pool is essential for inhibiting m-acitnase, sparing citrate oxidation in the Krebs cycle, and providing high amounts of citrate for secretion into prostatic fluid [reviewed in (Costello et al., 2005)]. To maintain high cellular Zn concentration and secretion, Zn homeostasis in the prostate must be tightly regulated and only recently have possible modes of regulation for Zn homeostasis been elucidated [reviewed in (Dhawan and Chadha, 2010)]. Figure 1.

Such substantial Zn accumulation for optimal function likely requires integration of multiple Zn importing processes. To date, 3 Zip proteins (Zip1, Zip2, and Zip3) have been described in the prostate (Franklin et al., 2005; Iguchi et al., 2006). Zip1 is primarily found on the basolateral membrane of epithelial cells of the peripheral zone, (although some Zip1 is detected on the apical membrane) (Franklin et al., 2005) and is thought to be responsible for Zn uptake from circulation. Iguchi et al. (2006) documented Zip2 expression in the lateral prostate of the rat, which positively correlates with Zn concentration in this lobe and is positively regulated by testosterone. Zip2 and Zip3 are localized to the apical
membrane of prostate epithelium in humans (Desouki et al., 2007) and are implicated in maintaining cellular Zn status by importing Zn from prostatic secretions. Figure 2.

These three Zn transporters offer us candidate regulatory molecules responsible for Zn accumulation, although the contribution of further Zip proteins has not been ruled out. Once acquired by the prostate cell, Zn is compartmentalized for numerous functions. Expression of 6 ZnT proteins has been described in the prostate, and their expression and cellular localization are lobe dependent, likely reflecting the differential need for lobe-specific functions. Evidence suggests that changes in Zn requirements occur in the prostate during sexual development. Expression of ZnT1 is greatly reduced at sexual maturity (Kirschke and Huang, 2008), potentially reflecting a role for Zn accumulation in the prostate for optimal cellular proliferation. In addition, ZnT2 expression increases in the anterior lobe but remains constant in the other lobes during sexual maturation (Kirschke and Huang, 2008). Although the dorsolateral prostate is the primary site of Zn secretion, the anterior and ventral prostate produce secretions of their own; the anterior prostate produces many of the same proteins as the dorsolateral prostate such as probasin, experimental auto-immune prostatitis antigen
2, and IgG-binding protein-like protein (Fujimoto et al., 2006).

In all lobes, ZnT2 staining pattern is consistent with endoplasmic reticulum (ER) localization (Kirschke and Huang, 2008), suggesting that while ZnT2 imports Zn into the ER, there may be lobe specific Zn requirements for optimal function. In addition, several other Zn transporters known to import Zn into the secretory compartment have been detected in the prostate. ZnT4, ZnT5, ZnT6, and ZnT7 are expressed throughout the prostate and localization is consistent with a role for Zn import into the ER and/or Golgi apparatus (Kirschke and Huang, 2008), presumably to provide Zn directly for secretion (Ellis et al., 2005; Ishihara et al., 2006; Fukunaka et al., 2009) or for Zn specific proteins that function within the secretory pathway as has been proposed for the mammary gland (McCormick et al., 2010). Surprisingly little is known regarding the mechanism(s) responsible for Zn secretion from the prostate considering the high Zn required to provide for optimal sperm viability. Prostate mitochondria also accumulate a large amount of Zn and do so in a lobe specific manner (~1 mg Zn/mg protein in lateral prostate compared with ~0.1 mg Zn/mg protein in the ventral or dorsal lobe) (Liu et al., 1997). Additionally, prostate mitochondria have a higher Zn content compared with other cell types such as hepatocytes (~0.05 mg Zn/mg protein).

A specific role for Zn in prostate mitochondria may be to prevent citrate oxidation through the inhibition of m-aconitase activity, thus expanding the citrate pool. Similarly, we hypothesize that modulation of mitochondria Zn pools may serve to regulate cell metabolism in other secretory tissues such as the mammary gland (McCormick et al., 2010). A distinct gap in our knowledge is understanding how Zn is accumulated by prostate mitochondria, because there are currently no known Zn transporters localized to this organelle. Understanding the role, regulation, and consequences of subsequent dysregulation of Zn metabolism in the prostate may offer insight into the cause and treatment of prostate disease. Future studies need to determine the role and regulation of Zip proteins expressed in prostate epithelial cells to help understand how and why this unique cell type accumulates and utilizes Zn.

The ability of Zinc to retard oxidative process has been recognized for many years. The antioxidant role of Zinc on ventral prostate of PCB exposed rats has been studied in our laboratory (Venkataraman et al., 2004). Decreased levels of serum testosterone in PCB exposed rats yields decreased level of prostatic zinc content and serum zinc concentration. PCB exposure induced hypothyroidism which leads to decreased ventral prostatic zinc content along with serum testosterone and estradiol. After the administration of Zinc, decreased levels of testosterone and estradiol were reversed and stimulate the ventral prostatic zinc content and serum zinc concentration (Venkataraman et al., 2004)

**Zinc and Aging**

Aging is associated with low Zn levels in the prostate and prostate fluid, which is associated with decreased fertility in humans (Elzanaty, 2007). Iguchi et al. (2010) also showed similar age related differences in prostate Zn concentration in the ventral prostate of aged rats. Somewhat counterintuitively, this is associated with increased expression of ZnT2, a Zn responsive (Guo et al., 2010), key Zn transporter in the prostate, suggesting Zn independent mechanisms of transcriptional control as has been observed in the mammary gland (Qian et al., 2009). Curiously, little is known regarding changes in Zn transporter expression in the prostate of aged animals and whether this tissue may experience a diminished capacity to accumulate or secrete Zn or modulate specific Zn responsive functions. In light of our lack of understanding of the relationship among age, low prostate Zn content, and dysregulated function, it is important to explore what may be causing this dysregulation in Zn homeostasis and evaluate its specific role in age-related decreased fertility.

**Prostate Disease**

Low prostate Zn content is also associated with prostatic disease. The major prostate diseases that affect older men are benign prostatic hyperplasia and prostate carcinoma. Some studies have documented reduced Zn content in prostate (Zaichick et al., 1997) and prostatic secretions (Zaichick et al., 1996) in men with prostate disease compared with healthy men. It is not fully understood whether low Zn content is a cause or consequence of prostate cancer, but recent data suggest it may in fact be a critical factor in malignancy (Costello et al., 1997; Franklin and Costello, 2007; Feng et al., 2008). Understanding the exact role Zn plays in the transformation of prostate cells will help to identify mechanisms of dysregulation, and understanding these mechanisms in relation to aging may help to develop therapeutic tools or perhaps preventative measures. Zn may play a key role in the prevention of prostatic disease by ameliorating oxidative stress, which can subsequently result in DNA damage, increasing the risk of mutation and malignant transformation.

As discussed above, there is a relationship among advanced age, decreased prostate Zn content, and increased oxidative stress (Bianchi-Frias et al., 2010). In fact, dietary Zn deficiency has been associated with increased DNA damage in the prostate during oxidative stress (Song et al., 2010). Specifically, Zn deficient
prostate cells have greater DNA damage and altered expression of genes associated with this damage, indicating that marginal Zn intake may sensitize the prostate to oxidative damage (Yan et al., 2003; Dani et al., 2010). As oxidative stress increases, so does the cellular Zn requirement for protective mechanisms, thus perpetuating the harmful effects of Zn deficiency.

In addition, Zn inhibits citrate oxidation in the mitochondria of prostate cells (Costello et al., 1997). Low Zn accumulation in the prostate will therefore allow excessive citrate oxidation and ATP production, which will in turn increase oxidative stress in the mitochondria and may in turn exacerbate DNA damage. Increased ATP production coupled with increased risk of DNA damage creates the perfect opportunity for malignant transformation. Many associations between low prostate Zn and prostatic disease exist, but direct evidence of the function of Zn in preventing oxidative stress and DNA damage in the prostate is still needed. Franklin and Costello (Franklin and Costello, 2007) examined the relationship between Zn and prostate malignancy and implicated Zn dysregulation in malignant transformation of prostate cells. In normal tissues, high mitochondria Zn levels inhibit m-aconitase activity, sparing citrate from oxidation in the Krebs cycle, thus making it available for secretion into prostatic fluid (Franklin and Costello, 2007).

Cancerous prostate tissue accumulates and secretes less citrate than normal tissue, which is associated with low prostate Zn levels. It is thought that the low Zn levels permit citrate oxidation, producing more ATP and providing an energy source for excess proliferation and transformation. Zn also imparts antitumorigenic effects by inducing apoptosis; Zn induces Bax expression, which initiates mitochondrial apoptosis by allowing the release of cytochrome c to initiate the caspase cascade (Feng et al., 2008). Suppressed expression of Zn importers such as Zip1, Zip2, and Zip3 (Franklin et al., 2005; Desouki et al., 2007) is associated with prostate cancer and suggests a possible reason for low Zn levels seen in the malignant prostate. The cause, however, of reduced Zip expression in malignant prostate cells is yet to be determined. Great strides have been made in understanding the interplay of Zn and malignant transformation in the prostate, but more information is needed to fully understand Zn homeostasis in normal tissue and the dysregulation that may lead to malignancy. If we consider this information along with the decreased expression of key Zn importers and cell Zn content in cancerous prostate tissue, we see the highlighted importance of Zn in maintaining DNA integrity and overall prostate health.

**Zinc and Cancer**

A large body of evidence suggests that a significant percentage of deaths resulting from cancer could be avoided through greater attention to proper and adequate nutrition. Although many dietary compounds have been suggested to contribute in the prevention of cancer, yet there is a strong evidence to support the fact that Zn, a key constituent or cofactor of over 300 mammalian enzymes, may be of particular importance in host defense against the initiation and progression of cancer. Remarkably, 10 per cent of the U.S. population consumes less than half the recommended dietary allowance for Zn and is at increased risk for Zn deficiency (Ho, 2004). Zn is known to be an essential component of DNA-binding proteins with Zn fingers, as well as copper/Zn superoxide dismutase and several proteins involved in DNA repair. Thus, Zn plays an important role in the functions of transcription factor, antioxidant defense system and DNA repair. Dietary deficiencies in the intake of Zn can contribute to single and double-strand DNA breaks and oxidative modifications to DNA that increase risk for cancer development (Ho, 2004). Zinc is an essential mineral that is integral to many enzymes and transcription factors that regulate key cellular functions such as the response to oxidative stress, DNA replication, DNA damage repair, cell cycle progression, and apoptosis. In particular, several proteins involved in DNA damage signaling and repair, replicative enzymes such as DNA and RNA polymerases and transcription factors such as tumour protein p53 (Ho et al., 2003), require Zn for proper functions (Pavlletich et al., 1993; Dong et al., 1999; Witkiewicz-Kucharczyk and Bal, 2006). Consequently, Zn deficiency could disrupt the function of both signaling molecules and proteins directly involved in DNA replication and repair. Limited availability of cellular Zn due to Zn deficiency could result in a loss of activity of these Zn-dependent proteins involved in the maintenance of DNA integrity and may contribute to the development of cancer. Zn deficiency has also been shown to upregulate expression of the tumour suppressor protein, p53, but impair the DNA binding abilities of p53, nuclear factor kB (NFkB), and AP-1 transcription factors in rat glioma C6 cells (Ho and Ames, 2002). These studies suggest that a decrease in cellular Zn alone causes DNA damage and impairs DNA damage response mechanisms, resulting in a loss of DNA integrity and potential for increased cancer risk.

There is evidence to suggest an intriguing link between Zn and cancer. In *in vivo* studies, it has been shown that Zn treatment increases resistance against tumor challenge in mice (Singh and Zaidi, 1992) and decrease the incidence of spontaneous lung tumors arising in mice (Satoh et al., 1993). Studies from our laboratory have also advocated the inhibitory effects of Zn on the histological changes and antioxidant status in the colon of the rats during the initiation and promotion phase of experimentally induced colon carcinogenesis (Dani et al., 2007a; 2007b). The studies clearly indicated that the administration of Zn in the presence of procarcinogen 1, 2 dimethylhydrazine (DMH) brings about decrease in tumour incidence and tumour burden.
as well as profound alterations in the antioxidant status with restoration of normal colonic histoarchitecture. Another study by our group has demonstrated the regulatory role of Zn on the membrane fluidity parameters and surface abnormalities following colon specific carcinogen treatment to rats (Dani and Dhawan, 2009).

Zn has been ascribed roles in the metabolic functions and interaction of malignant cells (Schrauzer, 1979). The Zn content of leukaemic leukocytes has been found to be reduced (Fong et al., 1978), and it has also been reported that Zn deficiency enhances the carcinogenic effects of nitrosomethylbenzylamine (Fong et al., 1978). Zowezak et al. (2001) found an increase in serum copper/Zn ratios in patients with cancers of the lung, breast, gastrointestinal tract and gynecological malignancy. Nutritional Zn deficiency in rats increases oesophageal cell proliferation and the incidence of N-nitrosomethylbenzylamine (NMBA) induced oesophageal tumours. Replenishing Zn with a Zn sufficient diet reduces these effects in Zn deficient rats. Zn replenishment rapidly induces apoptosis in oesophageal epithelial cells and thereby substantially reduces the development of oesophageal cancer (Fong et al., 2001). Using the Zn deficient rat model, Fong et al. (1998) have shown that after a single, otherwise non-tumourigenic dose of NMBA (Siglin et al., 1995), sustained, increased cell proliferation in the Zn deficient oesophageal epithelium was associated with a highly tumourigenic response and accompanying genetic events. In addition, they demonstrated (Fong et al., 1998) that, if a Zn-sufficient diet was administered to Zn deficient rats after the second of six NMBA doses, oesophageal cell proliferation was effectively reversed and tumour incidence was reduced from 100 per cent in Zn deficient rats to 14 per cent in pair-fed Zn-replenished rats (whose food consumption matched that of Zn deficient rats) and to 26 per cent in Zn-replenished rats fed a Zn-sufficient diet ad libitum (Fong et al., 1998). Zn deficiency in humans is associated with an increased risk of developing oesophageal squamous cell carcinoma (Abnet et al., 2005). Another mechanism by which Zn might prevent cancer is through its effect on angiogenesis and tumour progression. Endostatin is a potent angiogenesis inhibitor both in vitro and in vivo and has ability to bind Zn\(^{2+}\), essential for its antiangiogenic activity (Boehm et al., 1998). A report by Jaiswal and Narayan (2004) has also stated the mechanisms by which Zn causes growth arrest in colon cancer cells. The results suggest that Zn treatment stabilizes the levels of the wild-type adenomatous polyposis coli (APC) protein at the post-translational level since the APC mRNA levels and the promoter activity of the APC gene were decreased in HCT-116 cells (which express the wild-type APC gene) after treatment with Zn chloride (Jaiswal and Narayan, 2004). Therefore, this relationship provides a rational basis for the concept that restoration of high Zn levels in malignant cells could be efficacious in the treatment and prevention of cancer.

Though the results from these studies have suggested the anticancer role of Zn, little is known about the mechanisms by which Zn exerts its action on cancer cells. In particular, it is not known whether Zn directly acts on tumour cells or its in vivo action is related to a modulation of the immune effectiveness or to the Zn dependent regulation of the production of other anticancer substances. Some recent fragmentary evidence has indirectly supported the possible modulation of apoptosis by Zn (Kane et al., 1993; Sandstrom et al., 1994). In fact, a Zn dependent modulation of reactive oxygen species (ROS), which has been implicated as modulators of apoptosis (Kane et al., 1993; Sandstrom et al., 1994; Lindahl et al., 1998; Noh and Koh, 2000), suggests a possible influence of Zn on apoptosis through the modulation of the intracellular redox state.

**Zinc and human epidemiological/clinical studies**

The role of Zn in cancer has received increasing attention as a link between Zn deficiency and cancer has now been established in human studies. It is now reported that Zn status is compromised in cancer patients compared to healthy people. Abnet et al. (2005) observed an initial connection between Zn and oesophageal squamous cell carcinoma in humans and their findings clearly demonstrated significantly lower average tissue Zn concentration in subjects who developed oesophageal cancer than in control subjects. Lee et al. (2004) also reported that intake of dietary Zn is associated with a decreased risk of both proximal and distal colon cancer in postmenopausal women. Further, a report by Prasad et al. (1998) also provides evidence based on Zn deficiency and cell mediated immune disorders, and the effects of Zn status on clinical morbidities in patients with head and neck cancer. Zn deficiency and cell mediated immune dysfunctions were frequently present in patients with head and neck cancer and Zn deficiency was associated with an increased tumor size and the overall stage of the cancer (Prasad et al., 1998). Abdulla et al. (1979) observed that plasma Zn was decreased and the copper: Zn ratio in the plasma was significantly higher in patients with squamous cell carcinoma of the head and neck in comparison to healthy controls. Also, the role of Zn in the development and progression of prostate malignancy and its potential application in the prevention and treatment of prostate cancer are known (Costello et al., 2005). The overwhelming clinical evidence provides a compelling rational basis for the concept that prostate Zn accumulation is an important factor in the development and progression of prostate malignancy; and that Zn could be efficacious in the prevention and treatment of prostate cancer (Costello et al., 2005).
Zinc and Prostate cancer

It has been seen that the most consistent and persistent biochemical characteristic of prostate cancer is the marked decrease in Zn levels in the malignant cells, thus providing compelling evidence that the lost ability of the malignant cells to accumulate Zn is an important factor in the development and progression of prostate malignancy (Costello et al., 2004). A report by Gallus et al. (2007) found a direct association between high Zn intake and prostate cancer risk, particularly for advanced cancers. To sum up, Ho and Song (2009) proposed the possible mechanisms of Zn chemoprevention which include the effects of Zn on the inhibition of terminal oxidation, induction of mitochondrial apoptosis and suppression of NF-kB activity. Zn may also play an important role in the maintenance of DNA integrity in normal prostate epithelial cells by modulating DNA repair and damage response proteins, especially p5339 cells. In addition, findings support the role of Zn transporters as tumor suppressors in the prostate (Franklin et al., 2005). Zinc has also been shown to inhibit the invasive capabilities of malignant prostate cells. Ishii et al. (2004) reported that the ability of LANcA cells to invade Matrigel was strongly suppressed by Zn++. In another study Ishii et al. (2001) found that aminopeptidase N purified from human prostate was irreversibly inhibited by low concentrations of zinc; which, they concluded, could be associated with invasive capability. Uzzo et al. (2006) reported that the suppressive effect of zinc on the angiogenic and metastatic potentials of cancer cells was also mediated through the inhibition of specific pathways that regulate progression of prostate cancer. Therefore, the decrease in cellular zinc levels in the malignant cells is necessary to permit these cells to invade the host tissue and to metastasize to other tissue sites. The inhibition of these activities by zinc imposes another tumor suppressor effect.

In rats, dietary zinc deficiency led to an increased susceptibility to tumor development when exposed to carcinogenic compounds (Fong et al., 1978; 1996; 1997; Fong and Magee, 1999; Fong et al., 2001). In animals fed a zinc-enriched diet, the zinc levels in tumor xenografts established from PC-3-hZIP1 cells were significantly higher compared with zinc levels in tumor tissue specimens obtained from animals with PC-3-CMV tumors. Notably, the increased zinc accumulation in PC-3-hZIP1 tumors was associated with inhibition of tumor growth, decreased levels of NF-kB activity and reduced VEGF and IL-8 contents (Golovine et al., 2008). In vitro studies showed that zinc deficiency led to an increased oxidative damage to testicular cell DNA (Oteiza et al., 1995). Zinc also plays an important role in maintaining proper functions of prostate. Several studies have implicated changes in zinc accumulation in the development and progression of prostate malignancy (Costello and Franklin, 1998; 2000). Moreover, an increase in dietary zinc was associated with a decrease in the incidence of PCa (Kristal et al., 1999). However the precise role of zinc in the prostate health is largely unknown.

Zinc content serves as one of the biochemical markers for the function of prostate gland. Costello and Franklin (2000) have proposed that zinc inhibits mitochondrial aconitase activity and citrate oxidation in prostate epithelial cells. It also induces mitochondrial apoptosis in prostate cell and has ability to increase resident Bcl-2 associated X protein (Bax)-mitochondrial interaction that is associated with Bax-induced pore formation (Feng et al., 2008). It has been evidenced that increasing zinc bioavailability through direct injection into tumors would impact PCa malignancies in prostatic carcinoma cell (PC-3) tumor xenograft into SCID mice model (Shah et al., 2009). This study showed that increased intraprostatic zinc, can effectively moderate prostate tumor growth (Shah et al., 2009). Prasad et al. (2010) have reported that the optimal zinc concentration has a protective role against prostate cancer in transgenic mice, TRAMP model. Our study showed that zinc inhibits initiation of the prostate cancer i.e Prostatic intraepithelial neoplasia and it was found to inhibit the growth and decrease prostatic PACP, zinc, citrate levels, phase I drug metabolizing enzymes activities, lipid peroxide, H2O2 levels, PCNA, Bcl-2, Bcl-XL expressions with concomitant increase in phase II enzymes activities, GSH level, p53, Bax, caspases-3 expressions in MNU testosterone-induced model of Sprague Dawley rat prostate carcinogenesis (Banudevi et al., 2011a; 2011b). Zinc may also be effective in inducing regression in PIN and that its utility as a chemopreventive agent during the long latency period of prostate cancer should be further explored.

Zinc and intracellular signaling in prostate cancer

Zinc plays an important role in the proliferation, differentiation and metabolic function of all mammalian cells. It does this through the many zinc binding motifs that are present in the primary structure of proteins that result in structural, catalytic and cocatalytic zinc sites (Auld, 2001). In addition, zinc should be considered an intracellular signaling molecule similar to calcium. As is true of intracellular calcium, intracellular zinc is homeostatically maintained at extremely low levels either by sequestration in intracellular vesicles or by binding to intracellular metalloproteins and low molecular weight ligands (see Franklin and Costello, 2007). Various extracellular signals e.g. redox stress, cytokines and growth factors stimulate the release of zinc from metallothionein or alter the transport of zinc which alters the intracellular level of mobile reactive zinc (Cousins et al., 2006). Zinc then binds to and activates metal-responsive transcription factors or interacts directly with intracellular signaling molecules to modulate the expression of zinc responsive genes and to regulate specific signal transduction pathways. Zinc has been
reported to inhibit Ras signaling (Bruinsma et al., 2002). This is a function of zinc that is conserved, since homologous mammalian and nonmammalian zinc export transporters activate Ras by decreasing the intracellular level of zinc.

The mechanism for zinc regulation of signaling pathways is not well understood; however, recent studies suggest that zinc stimulates the activity of kinases in specific signaling pathways. Physiological levels of zinc in the presence of the zinc ionophore pyrithione increased phosphorylation of Akt at threonine 308 and serine 473 which resulted in activation of Akt (Min et al., 2007). Zinc is reported to inhibit TNF-α induced activation of nuclear factor kB (NFkB) while activating AP1 in PC-3 and DU-145 prostate cancer cells (Uzzo et al., 2006). Zinc also increased the phosphorylation of ERK1/2, p38 and JNK. The mechanism of NFkB activation involved zinc induced activation of IkB kinase (IKK) which phosphorylates and inactivates the inhibitor protein IkB which allows activated NFkB to enter the nucleus. Insulin-like growth factors signaling plays a major role in prostate cancer development. One of our study showed that zinc downregulates IGF-IR signaling pathway by inhibiting the upregulation of PI-3K-Akt-cyclin D1 signaling molecules in PC-3 cells. It also decreased the activation of ERK1/2 signaling pathway in PC-3 cells (Banudevi et al., 2010). The inconsistent and variable effects reported for zinc are dependent on a number of factors, such as the cell type, the concentration of zinc, and other conditions employed in the studies. An important unresolved issue is the identification and characterization of the factors that determine if the response of a specific cell type to physiological levels of zinc will be inhibition or induction of apoptosis or no response. Obviously this is a complex issue. In prostate we propose that the high level of zinc contributes to the balance of cell survival, proliferation and apoptosis through its effects on intermediary metabolism and intracellular signaling pathways. Moreover, the loss of zinc accumulation by the prostate results in the loss of these effects and the development and progression of prostate cancer.

Future Perspectives

It is evident from the vast research studies that zinc exerts diverse importance in oncology. Despite of Zn's multiple role in cancer, still its research is relatively at a early stage of its evolution. Accelerated research is required to achieve a proper understanding of their definitive bioassays including protein expression and documentation of specific molecular markers as well as zinc homeostatic mechanism in immune system and signal transduction to establish the exact mechanism for zinc-mediated cancer chemoprevention. Only by understanding the basic mechanisms by which zinc can exert its chemopreventive properties we would be able to devise rational uses for this metal as an intervention in cancer management.

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