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Zinc Supplementation and Prostate Cancer

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1. Introduction

Prostate cancer continues to be one of the most common fatal cancers in men (Jemal et al., 2010). The comprehensive understanding of the etiology of this disease is however, far from complete because of multitude of genetics and environmental factors involved in the development of this disease (Deutsch et al., 2004; Giovannucci, 2001). One characteristic feature of the prostate gland is its unique ability to accumulate high concentrations of zinc, which may otherwise be toxic to other tissues (Costello & Franklin, 1998). For reasons primarily still unknown, cancerous prostate cells somehow lose its ability to accumulate intracellular zinc concentrations. This is based on consistent observations of low zinc concentrations in malignant prostate tissues as compared to normal prostate and benign prostatic hyperplasia tissues (Feustel & Wennrich, 1984; Ho, 2004; Vartsky et al., 2003; Zaichick et al., 1997). These findings thereby, imply a potential importance of zinc in the pathogenesis of prostate cancer.

It is suggested that dietary zinc supplementation protects against oxidative damage, reduces cancer risk (Ho, 2004) and has therapeutic potentials against prostate cancer (Franklin & Costello, 2007). Epidemiologic studies, however, provided contradictory findings on the effectiveness of zinc in prevention against prostate cancer. While there are studies that showed zinc reduces the risk of developing prostate cancer (Key et al., 1997; Kristal et al., 1999), others showed that advanced prostate cancer is associated with high intake of zinc and potentiate the development of benign prostate hyperplasia (BPH) and progression towards cancer (Gallus et al., 2007; Lagiou et al., 1999; Lawson et al., 2007; Leitzmann et al., 2003; Moyad, 2004). Various mechanisms have been proposed to explain how high zinc regulates prostate health and indirectly, how its absence or low concentration could have contributed to the occurrence of prostate cancer. Restoration of high zinc to cancerous prostate tissues has been shown to inhibit prostate cancer cells proliferation (Feng et al., 2002; Feng et al., 2000; Iguchi et al., 1998; Liang et al., 1999) and invasion (Ishii et al., 2004; Ishii et al., 2001a; Ishii et al., 2001b; Uzzo et al., 2006). In contrast, there are studies which showed that zinc under non-physiological conditions could promote cancer cell growth and invasion (Boissier et al., 2000; Nemoto et al., 2000; Wong & Abubakar, 2008a; Wong & Abubakar, 2010).

Because of the diverse roles of zinc in cell signaling, the exact pathways and genes affected by the absence or presence of high zinc concentrations in prostate cancer cells remain unraveled. In an attempt to further understand the complexicity of the role of zinc in prostate cancer, this

chapter will discuss issues related to the regulatory roles of zinc in normal prostate, the consequences of losing this regulatory role in the malignant cells and the implications of zinc supplementation in the cancer cells.

2. Zinc and human health

Zinc is an essential trace element, critical for diverse biological functions in the human body. Its importance in humans was not discovered until 1961 where zinc deficiency was found to be the cause of growth retardation and hypogonadism in Iranian and Egyptian patients (Prasad et al., 1961; Prasad et al., 1963). Meat, poultry, oyster, dairy products, legumes and cereals are food rich in zinc. However, phytates, which are present in some cereals and legumes can reduce the bioavailability of zinc by inhibiting absorption of zinc in the intestines (Sandstrom, 1997; Wise, 1995). The recommended dietary allowance (RDA) for daily intake of zinc in 97-98% healthy individuals is 8 mg/d for women, 11 mg/d for men, 11-12 mg/ml for pregnant and lactating women. Children from 1-3 years old, 4-8 years and 9-13 years old require 3, 5 and 8 mg/d of zinc, respectively (Food and Nutritional Board of Medicine, 2010a). The tolerable upper intake level (UL), defined as the maximal daily intake unlikely to cause adverse health effects is 40 mg/d for adults. For children of 1-3, 4-8 and 9-13 years old, ULs are 7 mg/d, 12 and 23 mg/d, respectively, (Food and Nutritional Board of Medicine, 2010b).

Deficiency of zinc is associated with significant health problems. Early manifestations of zinc deficiency include decreased immunity resulting in increased susceptibility to infections such as diarrhea, common cold, acute lower respiratory infection and malaria. Zinc-deficient individuals also display dermatitis, delayed wound healing and alopecia. Prolonged deficiency leads to retardation of growth, genital development, hypogonadism and impaired neuropsychological functions (Prasad, 2008). Zinc deficiency in pregnancy retards fetal growth and postnatal development, causes neural tube defects and premature birth but the use of zinc supplementation in women still requires further studies (Osendarp et al., 2003; Uriu-Adams & Keen, 2010).

Zinc supplements are found in the forms of zinc gluconate, zinc sulfate, and zinc acetate, where the percentage of elemental zinc can varies (Haase et al., 2008). Studies have shown that supplementation with zinc corrects growth and gonadal development, improves immune functions and hastens recovery from diarrhea, common cold, acute lower respiratory infection and malaria (Black, 2003; Fischer Walker & Black, 2004). It is also used to treat genetic disorders such as acrodermatitis enteropathica (Maverakis et al., 2007) and Wilson's disease (Brewer, 2001). Zinc excess can induce copper deficiency and it is used in Wilson's disease to interfere with uptake of copper and subsequently reduce excessive copper accumulation. While zinc supplementation may be beneficial in certain conditions excessive zinc intake can pose serious health risks. Acute zinc toxicity causes gastrointestinal-related symptoms such nausea, vomiting, tenesmus and diarrhea (Brown et al., 1964). Chronic zinc toxicity can lead to copper deficiency and its related hematological and neurological manifestations (Maret & Sandstead, 2006). Chronic high intake of zinc can also cause abnormalities of genitourinary functions (Johnson et al., 2007).

3. Zinc homeostasis and transport

Total zinc in human body is about 2-3 g for a 70 kg adult (Wastney et al., 1986). Ninety percent is incorporated in the muscle, most of which are poorly exchangeable and tightly

bound to high molecular weight ligands such as metalloenzymes, metalloproteins, nucleoproteins and nucleic acids. The remaining 10% of zinc is readily exchangeable and loosely bound to amino acid and citrate (Frederickson, 1989; Outten & O'Halloran, 2001). This pool of zinc is found in plasma, liver and bone and is metabolically active, rapidly exchanged and sensitive to changes in the bioavailability of zinc in the diet. The prostate gland, pancreas, adrenal gland, certain areas of the brain, inner ear and eye, skin, nails, hair, red and white blood cells are known to accumulate high concentrations of zinc (Tapiero & Tew, 2003).

The concentrations of zinc are strictly regulated *in vivo* because dysregulation of zinc homeostasis can result in pathogenic consequences. Approximately 30-40% of intracellular zinc is localized in the nucleus, 50% in the cytosol and cytosolic organelles and the remainder are associated with cell membranes (Vallee & Falchuk, 1993). Zinc transporters play important roles in maintaining zinc homeostasis, as zinc ions are hydrophilic and do not cross cell membranes by passive diffusion (Cousins & McMahon, 2000). There are two known families of zinc transporters i.e. the ZIP (Zrt/Irt-like proteins (SLC39A)) family and the cation diffusion facilitator/Zinc transporter (CDF/ZnT (SLC30A)) family. At least 15 members of the ZIP family (Zn^{2+}-regulated metal transporter) (Cousins et al., 2006) and 10 members from the ZnT family (Eide, 2004) are found in mammalian cells. ZnT transporters regulate zinc efflux from cells or into intracellular vesicles, hence, reduce intracellular zinc availability, whereas ZIP members of the ZIP family participate in the transport of zinc, iron, and/or manganese. The human ZIP1, ZIP2, and ZIP4 proteins are involved in zinc uptake across the plasma membrane of various cell types (Eide, 2004).

4. Major functions of zinc

4.1 Structural and catalytic functions

Zinc has structural, catalytic and regulatory functions. It is a structural element found in many enzymes essential for DNA synthesis, transcription, aminoacyl-tRNA synthesis and ribosomal functions. It is found in zinc finger motifs of more than two thousands of transcription factors where these motifs provide a platform for interaction with DNA or other proteins (Vallee et al., 1991). Zincs are also found in LIM domains in proteins important for cytoskeletal organization, organ development and oncogenesis (Kadrmas & Beckerle, 2004). Zinc regulates cell proliferation and differentiation by modulating nucleic acid metabolisms and protein synthesis. It also controls cell growth by activating, transporting and modulating growth hormone, insulin-like growth factor-1, prolactin, testosterone and other steroid hormones (Costello et al., 1999; Ozturk et al., 2005; Prasad et al., 1996; Turgut et al., 2005). Zinc, unlike the highly reactive copper and iron, does not participate in redox reactions (Berg & Shi, 1996). The incorporation of zinc into proteins instead of these highly reactive elements helps prevent the generation of free radicals (Ho, 2004). Zinc, hence, has anti-oxidant activities. It maintains proper folding, stability and activity of zinc-dependent enzymes by protecting these enzymes from free radicals attacks (Coleman, 1992). Some of the zinc-dependent enzymes include superoxide dismutase, carbonic anhydrase, alkaline phosphatase, glutamic dehydrogenase, nucleotidase, carboxypeptidase A, retinal dehydrogenase and angiotensin-converting enzymes. Intracellular zinc also protects several compounds from oxidative damage and these include citrate in the prostate gland (Omu et al., 1998) and insulin in the secretory granules of the islet beta cells (Zalewski et al., 1994). In addition, zinc exerts its anti-oxidant abilities

indirectly by maintaining an adequate level of the free radical scavengers such as metallothioneins (MTs) (Prasad, 1993; Tapiero & Tew, 2003). It also stabilizes cell membrane structure such as that of the red blood cells (Hennig et al., 1996) and sperm cells (Omu et al., 1998). Zinc-bound melanin granules of the skin, choroids, iris, retina, photoreceptors of the eye also provide protection against oxidative damage and apoptosis (Borovansky, 1994).

4.2 Zinc and immunity

Zinc is critical for immune function and is involved in many aspects of the immune system (Shankar & Prasad, 1998). Deficiency of zinc causes dysfunction of cells involved in innate immunity such as macrophages, neutrophils and natural killer (NK) cells and affects phagocytosis, intracellular killing, cytokine production, complement activity and delayed-type hypersensitivity. Zinc is also important for gene regulation in T lymphocytes. It activates pituitary growth hormone and thymulin, the thymic hormone that stimulates division, differentiation and maturation of T-cells, lymphocyte proliferation and cytotoxic activity of natural killer cells (Baum et al., 2000; Prasad, 1998). It also modulates the function of T-helper cells by regulating lymphokines, interleukin-2 (IL-2), interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α) in response to invasion of pathogens (Baum et al., 2000). It is also known that zinc helps in tissue repair and wound healing by stimulating keratinocyte proliferation and migration to the injured area (Tenaud et al., 2000) and scavenges proinflammatory cytokines-produced nitric oxide to prevent tissue damage (Yamaoka et al., 2000).

4.3 Zinc in cell signaling

Zinc is involved in many aspects of cell signaling, ranging from signal recognition, second messenger metabolisms to the regulation of gene expressions. It regulates signaling processes by directly modulating the activities of kinases, phosphatases, and transcription factors (Beyersmann & Haase, 2001) or acting on its own as an intracellular secondary messenger (Fukada et al., 2011; Yamasaki et al., 2007). Zinc initiates the signaling cascades by stimulating the activation of several receptors and ion channels and these include epidermal growth factor receptor (EGF-R) (Wu et al., 1999); insulin growth factor-1 receptor (IGF-1-R) (Haase & Maret, 2005); Gamma-AminoButyric Acid (GABA) receptor (Parviz & Gross, 2007); N-methyl-D-aspartate (NMDA) channels of the neuronal cells (Smart et al., 2004); voltage-gated Ca^{2+} (Magistretti et al., 2003), the calcium permeable α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) channels (Blakemore & Trombley, 2004), transient receptor potential ankyrin (Hu et al., 2009) and ATP-sensitive K^+ channels (Prost et al., 2004). It also affects the activities of several second messengers. It is shown that zinc inhibits cyclic adenosine monophosphate (cAMP) signaling (Klein et al., 2002) and elevates cyclic guanosine monophosphate (cGMP) levels (Watjen et al., 2001).

Zinc regulates the transcription of genes important for cell proliferation and differentiation by modulating transcription factors such as metal response element-binding transcription factor-1, MTF-1 (Langmade et al., 2000); Egr-1 (Adamson et al., 2003); AP-1 and NF-κB (Herbein et al., 2006; Uzzo et al., 2006); Jun and ATF-2 (Samet et al., 1998). Among these, MTF-1 to date is the best-characterized zinc-activated transcription factors. MTF-1 responds acutely to changes in intracellular zinc concentrations by binding with zinc and translocates to nucleus. It then activates genes transcription by binding to promoters of other known zinc-responsive genes such as metallothioneins (MTs) and zinc transporter, ZnT-1 that

regulate intracellular zinc concentrations (Langmade et al., 2000). Other zinc finger transcription factors such as Egr-1, AP-1 and NF-κB are important for the regulation of genes that control cells proliferation. Deregulation of these transcription factors contributes to cancer cells proliferation, metastasis and angiogenesis. How zinc affects the regulation of these transcription factors and their outcomes, however, varies. It is shown in a number of studies, that zinc at different concentrations activate or suppress the activities of NF-κB in different cell lines resulting in different cellular responses (Kim et al., 2007; Uzzo et al., 2006; Uzzo et al., 2002).

Zinc modulates kinases and phosphatases of major cells signaling pathways. A number of studies showed that zinc stimulates EGF receptor phosphorylation and activates members of the MAPKs family such as ERK (Hansson, 1996; Klein et al., 2006; Samet et al., 1998; Uzzo et al., 2006) and p38 kinase (Huang et al., 1999; Wu et al., 1999; Wu et al., 2005) activities in prostate cancer cells, murine fibroblasts, human bronchial epithelial cells, human airway epithelial cells and mouse cortical cells. Zinc also induces the phosphorylation of p70S6 kinase in murine fibroblasts, c-jun N-terminal kinase (JNK) in mouse cortical cells through phosphatidylinositol 3-kinase (P13K) signaling pathway (Eom et al., 2001; Kim et al., 2000), protein kinase C (PKC) activation (Csermely et al., 1988), protein kinase B (PKB) and glycogen synthase kinase (GSK)-3β activities in neuroblastoma cells (An et al., 2005). A number of studies also described the role of zinc in the modulation of phosphatases. Treatment of the human airway epithelial cells and C6 rat glioma cells with zinc increased protein tyrosine phosphorylation by inhibiting phosphatases such as PTP1B and SHP-1 (Haase & Maret, 2005) and zinc also inhibits the dual-specificity phosphatase VHR (Kim et al., 2000). These findings illustrate the extensive involvement of zinc on cellular signaling pathways and genes transcription. Balanced zinc homeostasis, therefore is vital for normal cell growth and differentiation; and deviations from optimal zinc levels may contribute to pathophysiologic consequences observed in many zinc-related diseases. Most of these zinc-affected pathways are also deregulated in many types of cancer and this further highlights the importance of zinc homeostasis in oncogenesis.

5. Zinc and the prostate gland

The human prostate gland is divided into three distinct morphological regions which include the peripheral, central and transition zones (McNeal, 1981). The peripheral zone contains the majority of the glandular tissues present in the normal prostate and accounts for 70% of the volume in the young adult prostate. The central zone consists of larger acini and has a more complex ductal branching while the transition zone comprises of glands lobules with shorter ducts in comparison to those in the peripheral zone. The central and transition zones account for 25% and 5% of the prostate volume, respectively.

The normal peripheral zone of the prostate gland accumulates the highest concentrations of zinc in comparison to other soft tissues of the body (Kar & Chowdhury, 1966; Lahtonen, 1985). The ability to accumulate zinc in the peripheral zone is due to the presence of highly specialized secretory epithelial cells that is not found in the central zone of the prostate. hZIP1 transporter is an important transporter for uptake from the circulation and accumulation in the prostate gland (Costello et al., 1999; Desouki et al., 2007) while hZIP-2 and hZIP-3 retain zinc in the cellular compartment (Desouki et al., 2007).

hZIP1 transporters are downregulated in adenocarcinoma cells and in prostate intra-epithelial neoplastic loci (PIN) (Rishi et al., 2003). This causes not only a decrease in zinc

uptake (Franklin et al., 2005a; Franklin et al., 2003; Franklin et al., 2005b) but also reduces the capacity to accumulate zinc (Huang et al., 2006). The downregulation of hZIP1 is also associated with high prostate cancer risk in African American male population in comparison with Caucasians (Rishi et al., 2003). hZIP2, hZIP3 and ZnT4 are also found downregulated in malignant tissues in comparison to nonmalignant and Benign prostatic hyperplasia (BPH) tissues (Beck et al., 2004; Desouki et al., 2007). These findings collectively suggest that alterations of intracellular zinc due to changes in zinc transporters expression are associated to the development prostate cancer. It is suggested that human *ZIP1*, *ZIP2* and *ZIP3* genes may be tumor suppressor genes (Desouki et al., 2007) and zinc may be a tumor suppressor agent (Franklin & Costello, 2007).

5.1 Association of zinc with prostate cancer

It is still unclear of the role of zinc in malignant diseases but abnormal levels of zinc in serum of cancer patients and malignant tissues are widely reported. Serum zinc levels are increased in melanoma patients (Ros-Bullon et al., 1998) but more often, reduced serum zinc levels are reported in breast (Sharma et al., 1994; Yucel et al., 1994), gallbladder (Gupta et al., 2005), lung (Diez et al., 1989; Issell et al., 1981), Hodgkin's disease (Cunzhi et al., 2001), colorectal (Gupta et al., 1993), neck (Buntzel et al., 2007), leukemia (Zuo et al., 2006) and thyroid (Al-Sayer et al., 2004) cancer patients. Elevated zinc levels in malignant tissues are observed in breast (Margalioth et al., 1983), intestinal (Kucharzewski et al., 2003), metastatic nasopharyngeal (Bay et al., 1997) cancers but are decreased in kidney carcinoma tissues (Margalioth et al., 1983). It is also high in bone marrow of patients with non-Hodgkin lymphomas (Schmitt et al., 1993). In prostate cancer, decreased zinc levels are consistently observed in malignant tissue samples from different populations and at various stages of malignancy (Vartsky et al., 2003; Zaichick et al., 1997). Analysis of malignant prostate tissues showed a 60-70% reduction of zinc levels in comparison to those of the normal peripheral zone tissues (Zaichick et al., 1997). The plasma zinc level between patients with malignancy is also significantly lower than normal patients (Goel & Sankhwar, 2006).

5.1.1 Epidemiologic studies

It is reported that dietary zinc supplementation protects against oxidative damage, reduces cancer risk (Ho, 2004) and is beneficial against prostate tumorigenesis (Franklin & Costello, 2007). Findings from several epidemiologic studies, however, attain no consensus on the effectiveness of zinc against prostate cancer, partly because of differences in experimental design, amount of zinc administered and methods in determining plasma/serum zinc status (Haase et al., 2008). Several studies showed that there are either no beneficiary effects of zinc or there are no potential adverse effects of dietary zinc on prostate cancer risk (Andersson et al., 1996; Kolonel, 1996; Vlajinac et al., 1997; West et al., 1991). In contrast, there are reports which concluded that zinc reduces prostate cancer risk (Epstein et al., 2011; Key et al., 1997; Kristal et al., 1999). Gonzalez et al. (2009) reported that dietary zinc was not associated with prostate cancer and 10-year average intake of supplemental zinc does not reduce the overall risk of prostate cancer. However, they found that risk of advanced prostate cancer decreases with greater intake of supplemental zinc in their VITamins And Lifestyle (VITAL) cohort study (Gonzalez et al., 2009). There are also reports that showed high zinc intake increases the risk of advanced prostate cancer (Gallus et al., 2007; Lawson et al., 2007; Leitzmann et al., 2003) and higher intake of dietary zinc could also potentiate the development of BPH and progression towards cancer (Lagiou et al., 1999; Moyad, 2004). Although further studies are

required in this area, these reports nevertheless, raised concern for potential detrimental outcomes of long-term use of high zinc-supplements in men.

5.1.2 *In vitro* studies

The beneficial effects of zinc in prostate cancer intervention and treatment were investigated *in vitro* and *in vivo* but yielded contradictory observations as well. Several *in vitro* zinc studies showed that zinc inhibits prostate cancer cells proliferation and invasion through the induction of necrotic cell death and caspase-mediated mitochondrial apoptogenesis (Feng et al., 2002; Feng et al., 2000; Iguchi et al., 1998; Liang et al., 1999). Other suggested inhibitory mechanisms include increased levels of Bax or decreased Bcl-2 and survivin expression-mediated apoptosis effect (Ku et al., 2010) and zinc-induced proteasomal degradation of HIF-1α, a protein often upregulated in tumors leading to more aggressive tumor growth and chemoresistance (Nardinocchi et al., 2010). In addition, zinc was reported to repress the metastatic potential of prostate cancer cells through various mechanisms. These include inhibition of NF-κB activities (Uzzo et al., 2006), suppression of the invasive potentials of human prostate aminopeptidase N and urokinase-type plasminogen activator (Ishii et al., 2001a; Ishii et al., 2001b) as well as inhibiting proteolytic activities of prostate specific antigen (PSA) (Ishii et al., 2004). In contrast, it is also reported that zinc promotes cancer cell growth by enhancing telomerase activity, an enzyme thought to be responsible for the continuous proliferation of tumor cells (Nemoto et al., 2000) and suppressing the inhibitory potential of bisphosphonates on tumor cell invasion (Boissier et al., 2000). Our studies also showed that restoration of high zinc for a prolonged period could only inhibit zinc proliferation transiently, after which the malignant cell growth was restored and acquired a more aggressive behaviour (Wong & Abubakar, 2008a; Wong & Abubakar, 2010).

5.1.3 *In vivo* studies

The association of zinc with prostate cancer and the therapeutic potentials of zinc in prostate cancer were also investigated *in vivo* (Table 1). Two early studies using xenograft mice inoculated with PC-3 cells (Feng et al., 2003) and PC-3-hZIP1 cells (Golovine et al., 2008) showed that zinc treatment resulted in inhibition of tumor growth. Feng et al. (2003) showed that inhibition of tumor growth was due to zinc-induced apoptosis. Golovine et al. (2008) showed that overexpression of hZIP1 transporter in PC3 cancer cells resulted in increased zinc uptake, decreased tumor volume and inhibition of NFκB activity which are usually high in PC3 cells at physiological zinc serum range (0.5–1.5 μg/ml). Direct intratumoral injection of zinc in mM range was also shown to halt prostate cancer cell growth in xenograft mice (Shah et al., 2009) but the practicality of using intratumoral administration in human remains in question. Prasad et al. (2010) used a more relevant mouse model i.e. transgenic adenocarcinoma of the mouse prostate (TRAMP) mice in their study to determine the role of zinc in the development of prostate cancer. TRAMP mice develop spontaneous autochtonous disease which enables studies on the transformation of normal prostatic cells, progression and metastasis of prostate cancer (Gingrich et al., 1996). These mice were given 0.85 ppm zinc (deficient), 30 ppm zinc (optimal) and 150 ppm zinc (high) for 14 weeks. Their results showed that prostate tumor weights were higher at both zinc-deficient and high zinc-supplemented mice which led them to suggest that zinc at optimal levels is preventive whereas at both deficient and higher levels it may enhance tumor growth (Prasad et al., 2010).

Animal models	Zinc concentrations given	Duration of treatment	Findings	References
Nude mice inoculated with PC3	0.25 µL/h	28 days (4 weeks)	Inhibition of tumor growth	Feng et al., 2003
C.B17/ICR-SCID mice inoculated with PC-3-hZIP1 in the flank region	2000 ppm	23 days (3.3 weeks)	Decreased tumor volume	Golovine et al., 2008
NOD/SCID inoculated with PC3 cells in the dorsum of animals	200 µL of 3 mM zinc acetate per injection	direct intratumoral injection every 48 hours for a period of two weeks	Halted prostate cancer cells growth	Shah et al., 2009
TRAMP mice	zinc deficient (0.85 ppm), optimal (normal) zinc (30 ppm) and high zinc (150 ppm)	14 weeks	Significantly higher tumor weights in zinc-deficient or high-zinc fed mice	Prasad et al., 2010
Sprague-Dawley rats using N-methyl-N-nitrosourea MNU+ testosterone (MNU + T)	100 ppm	3 times / week	Fewer incidences of hyperplasia, dysplasia, and prostatic intraepithelial neoplasia in the ventral prostate zinc-treated mice	Banudevi et al., 2011
Sprague-Dawley rats using MNU+ cyproterone acetate + testosterone propionate	227 mg/L (equivalent to 227 ppm)	20 weeks	Increased incidence of prostate intraepithelial neoplasm	Ko et al., 2010

Table 1. *In vivo* zinc studies using murine models

To investigate the chemopreventive potential of zinc, Banudevi et al. (2011) treated prostate cancer induced Sprague-Dawley rats using N-methyl-N-nitrosourea MNU+ testosterone (MNU + T) with zinc (100 ppm) thrice a week. The zinc-treated mice showed fewer incidences of hyperplasia, dysplasia, and prostatic intraepithelial neoplasia in the ventral prostate compared to the non-treated group (Banudevi et al., 2011). They concluded that zinc may act as a potential chemopreventive agent in targeting prostate cancer. However, in another study on prostate cancer induced Sprague-Dawley rats using MNU+ cyproterone

acetate + testosterone propionate fed with zinc sulfate heptahydrate dissolved in drinking water (227 mg/L or 227 ppm) for 20 weeks, they found high dietary zinc increased intraprostatic zinc concentrations and promoted prostate intraepithelial neoplasm (Ko et al., 2010). A much higher zinc and longer duration of treatment may be responsible for the observations made by Ko et al. (2010), it nevertheless suggests that high zinc treatment for a prolonged period may have detrimental outcomes.

5.2 Mechanisms of zinc-induced prostate cancer pathogenesis

It is established that zinc deficiency is associated with prostate cancer development based on the observation of significantly low/absence of zinc in cancerous prostate tissues and indirect evidences from *in vitro* and animal studies. It remains to be unraveled whether the absence of zinc is a consequence of cells transformation or whether zinc deficiency directly contributes to transformation.

A number of studies showed that zinc exerts both growth and metabolic effects on prostate cells and contribute to the development of prostate malignancy by altering citrate metabolism (Costello et al., 2004; Singh et al., 2006). It is reported in these studies that zinc inhibits *in vitro* cultured human prostate cell lines (LNCaP, PC3 and BPH-1) and rat ventral prostate epithelium cells proliferation by inducing mitochondrial apoptogenesis by releasing cytochrome *c*, which then activates subsequent caspase mediated-apoptotic cascading events leading to apoptosis. It is also shown that zinc inhibits the gene expression and activity of m-aconitase in prostate cells (Costello et al., 1997; Tsui et al., 2006). These findings led to the proposal that the presence of high zinc in normal prostate limits citrate oxidation via the Krebs cycle resulting in accumulation of high citrate levels for the secretion of prostatic fluids (Costello et al., 1997). In the transformed prostate cells, where zinc concentration is very low or absent, citrate oxidation can proceed via the Krebs cycle to generate ATP, thus, providing unlimited energy for malignant cells growth (Costello et al., 2004; Costello & Franklin, 2006). Concurrently, as intracellular zinc decreases, the apoptogenic effects of zinc are also removed, hence encourages malignant cells proliferation (Costello et al., 2004). Based on these observations, these authors suggest that restoration of zinc to prostate may be an effective treatment for prostate cancer.

Although the proposed mechanisms are plausible, it is also discussed above that zinc has diverse effects on cellular processes and mediates various signaling transduction pathways including those that are implicated in the development and progression of prostate cancer. This point was exemplified in another study that showed the involvement of zinc in Akt pathway (Han et al., 2009). Akt/protein kinase B (PKB) gene is amplified in cancerous prostate tissues and increase in its kinase activities are associated with hormone-resistant prostate cancer (Edwards et al., 2003). Activation of Akt pathway promotes the survival and protection of cancer cells from apoptosis by inhibiting downstream death proteins such as Bad, caspase-9 and forkhead transcription factors (FHTF) (Cantley, 2002). Phosphatase and TENsin homolog (PTEN), a tumor suppressor, negatively regulate the phosphorylation of Akt and maintains it at basal level. Normal prostate cells accumulates high zinc and during zinc deficiency, Han et al. (2009) showed that Akt is hyperphosphorylated in prostate normal epithelial cells (PrEC) and led to Mdm2 phosphorylation and decreased nuclear accumulation of p53. This resulted in reduced tumor-suppressive effect of p53, hence, maintaining the progression of the cell cycle and promoting cell survival through an Akt-Mdm2-p53 signaling axis. In LNCaP prostate cancer cells where PTEN is deleted and mutated, Akt phosphorylation becomes

uninhibited. In zinc-deficient LNCaP cells, it is suggested that Akt phosphorylates p21, inhibits its nuclear entry and promotes cytoplasmic degradation. Hence, zinc-deficient LNCaP cells could survive and progress through the G0/G1 phase of the cell cycle. This study showed that zinc is important in maintaining the survival of normal prostate cells and in its absence, the malignant cells uses alternative pathway to promote cell survival instead.

Difference in response to zinc between normal and malignant cells was also observed in our previous studies. We demonstrated an increasing percentage of senescent normal prostate PNT2 cells when treated with a high zinc concentration but this was not observed in LNCaP cells (Wong & Abubakar, 2008b). Hence, high zinc in the normal prostate regulates healthy prostate cell growth by maintaining senescence but this regulatory role is lost in zinc-deficient cancerous tissues. Han et al. (2009) also showed that cell growth was unchanged for LNCaP cells supplemented with high zinc although G2/M populations was depressed, which is similar to our observation (Wong & Abubakar, 2008a). Since there was no change in nuclear p21 level in high zinc-treated LNCaP cells in the study by Han et al., (2009), restoration of high zinc to LNCaP cells may have affected other pathways. We showed that restoration of high zinc to LNCaP for a longer period (5 weeks) resulted in upregulation of protein expression of Vaccinia H1-related (VHR) phosphatase, zeta chain-associated protein-70 (ZAP-70) kinase and phosphorylated extracellular signal-regulated protein kinase 1 and 2 (p-ERK 1 and 2) which declined after chelation of Zn^{2+}, highlighting the possible association of zinc with VHR/ZAP-70-associated pathways in the modulation of LNCaP prostate cancer cell growth.

To further determine the effects of prolonged high zinc treatment on global gene expressions in LNCaP prostate cancer cells, we continuously cultured LNCaP cells for at least five passages over a 5 week period in growth medium supplemented with supraphysiologic concentrations of Zn^{2+} (Wong & Abubakar, 2010). Various methods were employed to demonstrate the intracellular accumulation of zinc and these are correlated with the cancer cell growth and proliferation. Specific gene expression analysis using microarray was used to examine the different gene expression levels and validated using quantitative real time polymerase chain reaction amplification. Using this approach it was observed that high intracellular zinc initially inhibited prostate cell growth and colony formation on soft agar. The inhibition, however, is transient as the cancer cell growth rate recovers to the pre-zinc treatment cancerous cell growth rate. Results from microarray studies using these prolonged high zinc-treated cells suggest that the recovery is accompanied by high expression of genes known to promote prostate cancer cell proliferation, migration and aggressiveness. Genes such as *FASN*, *FAD*, *TACSTD1*, *FBL*, *ADRM1*, *E2F3*, *CD164* and *STEAP1* are highly expressed. In addition, *CD164*, *FBL* and *TACSTD1* were also found upregulated in increasing presence of high zinc in normal prostate PNT2 cells. Collectively, these findings suggest that zinc initially suppresses cell growth, perhaps by repressing the expressions of selected growth promoting genes but the ability of zinc to regulate these genes in the cancerous tissues are eventually lost, resulting in the superinduction of the expression of these genes which in turn promote the survival of the prostate cancer cells even when the intracellular zinc level is high. These observations, thus, support the epidemiologic findings that high zinc intake is associated with the progression to advanced aggressive prostate cancer. In another gene profiling study of normal human prostatic cell line HPR-1 and androgen-independent malignant prostate cancer PC3 cells treated with zinc (20 μM) for 1-6 hours, it was also observed that zinc affects many genes involved in oncogenesis pathways although genes associated with zinc accumulation and zinc-induced apoptosis are also found responsive (Lin et al., 2009). In

their study, Fos, which codes for a transcription factor associated with AP-1, was dramatically up-regulated by short-term zinc treatment in PC-3 cells and up-regulation of c-Fos protein is known to occur in advanced human prostate cancer (Ouyang et al., 2008). They also showed that expression of the Akt1 and PIK3 genes, associated with the Akt pathway, was dramatically upregulated in normal cells but remained unaffected in the cancer cells. However, the long-term effect of zinc on the expression of these genes is not known since cells were only treated for 6 hours in this study. This observation nevertheless supports the role of zinc in regulating malignancy promoting genes in normal cells but its control is lost in the cancerous tissues. The consequences following the loss of zinc regulation of cancer-promoting genes warrant further research.

6. Conclusion

Despite the contrasting reports on the effects of zinc on prostate cancer cells, these studies collectively affirmed the importance of zinc in the regulation of prostate health under normal physiologic conditions. Adverse consequences are apparent with zinc deficiency as well as with high zinc supplementation. The diverse effects of zinc on prostate cells reflects the immensity of zinc interactions with various cellular kinases, phosphatases, signaling transduction molecules and transcription factors in the regulation of normal cellular processes and immune responses, thereby also affecting those of the tumor cells and tumor microenvironment (John et al., 2010) once the normal cells transformed. Because of the extensive involvement of zinc in cellular signaling networks which includes its potential role in regulating cancer-promoting genes, simple restoration of high intracellular zinc concentration to the cancerous tissues may not be corrective. Instead, it may further fuel aberrant signaling in cancer cells leading to deleterious consequences. The use of zinc therapy based on its ability to induce apoptosis is effective perhaps when given intratumorally but dietary supplementation of zinc faces with issues of bioavailability and difficulties in achieving therapeutically meaningful dose in diseased prostate. The effects of chronic use of zinc still require further research with standardized zinc preparations, methods of zinc measurement, patient selection and statistical analysis to achieve a final consensus of the effectiveness of zinc in prostate cancer prevention and treatment. On the other hand, research focus on developing methods of using endogenous zinc (Ghosh et al., 2010) for early detection and progression of prostate cancer in human as well as utilizing zinc-regulated genes for diagnosis or targeting them for treatment of prostate cancer may be more relevant in this regard.

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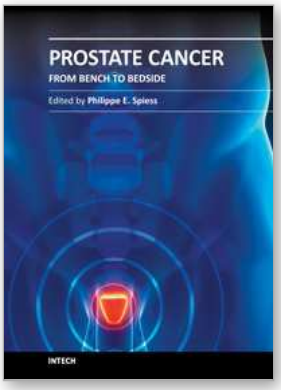

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The present textbook highlights many of the exciting discoveries made in the diagnosis and treatment of prostate cancer over the past decade. International thought leaders have contributed to this effort providing a comprehensive and state-of-the art review of the signaling pathways and genetic alterations essential in prostate cancer. This work provides an essential resource for healthcare professionals and scientists dedicated to this field. This textbook is dedicated to the efforts and advances made by our scientific community, realizing we have much to learn in striving to some day in the not too distant future cure this disease particularly among those with an aggressive tumor biology.

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