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Zinc and zinc transporters in prostate carcinogenesis

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Abstract

The healthy human prostate accumulates the highest level of zinc of any soft tissue in the body. This unique property is retained in BPH, but is lost in prostatic malignancy, which implicates changes in zinc and its transporters in carcinogenesis. Indeed, zinc concentrations diminish early in the course of prostate carcinogenesis, preceding histopathological changes, and continue to decline during progression toward castration-resistant disease. Numerous studies suggest that increased zinc intake might protect against progression of prostatic malignancy. Despite increased dietary intake, zinc accumulation might be limited by the diminished expression of zinc uptake transporters, resulting in decreased intratumoural zinc levels. This finding can explain the conflicting results of various epidemiological studies evaluating the role of zinc supplementation on primary and secondary prostate cancer prevention. Overall, more research into the mechanisms of zinc homeostasis are needed to fully understand its impact on prostate carcinogenesis. Only then can the potential of zinc and zinc transport proteins be harnessed in the diagnosis and treatment of men with prostate cancer.

Introduction

Zinc is essential for life. This metal ion is second only to iron in terms of its concentration in the body and is a co-factor for more than 300 enzymes, with three major biological roles: structural, regulatory and as catalyst (Fig. 1).^{1, 2} Oysters contain more zinc per serving than any other food, but red meat and poultry provide the majority of zinc in the Western diet. Other food sources rich in zinc include beans, nuts, whole grains and dairy products.³ The importance of zinc is perhaps best illustrated by the fact that failure to accumulate zinc is a *sine qua non* of prostatic carcinogenesis. Numerous experimental studies have provided compelling evidence that zinc has a protective effect against prostate carcinogenesis both *in vitro* and *in vivo*.^{4–11} However, epidemiological investigations evaluating the role of zinc supplementation in prostate cancer development and progression have yielded conflicting results.^{12–18}

In this Review, we summarize the current data regarding the relationship between zinc and prostate carcinogenesis, focusing on the mechanistic role of zinc and its transporters in the disease. We also outline the potential opportunities for harnessing zinc for the diagnosis and treatment of prostate malignancy.

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Competing interests

The authors declare no competing interests.

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Zinc levels and prostatic malignancy

The normal human prostate accumulates the highest content of zinc of all soft tissues in the body, with a typical zinc content of $1,018 \pm 124 \mu\text{g/g}$ dry tissue.¹⁹ The high cellular accumulation of zinc results in increased levels of mitochondrial zinc that inhibit m-aconitase activity and citrate oxidation.⁵ Although this unique capability is retained in the hyperplastic tissue of BPH, which has a zinc content of $1,142 \pm 77 \mu\text{g}$ per gram of dry tissue, prostate carcinogenesis involves a dramatic reduction in zinc accumulation (to $146 \pm 10 \mu\text{g/g}$ dry tissue).^{19, 20, 21} A significant decrease in plasma zinc levels is also observed in patients with prostate carcinoma compared with healthy controls and patients with BPH.²²

The reduction in zinc concentration occurs early in the course of prostate cancer development. This trend continues during tumour progression toward castration-resistant disease in prostate cancer patients.^{5, 7, 19, 20} Failure to accumulate zinc is an exemplary feature of prostatic malignancy, a phenomenon that is observed when comparing long-term cultured normal with malignant prostate cell lines.¹⁰ Initial experimental support for this concept was provided by studies of the malignant cell lines LNCaP and PC3. LNCaP cells demonstrate low tumorigenicity compared with the highly aggressive tumorigenic PC3 cells. Correspondingly, LNCaP cells possess a higher endogenous zinc level (630 ng/mg protein) than PC3 cells (190 ng/mg protein).²³ In addition, the tumorigenic *KRAS*-transformed prostate epithelial cell line, RWPE-2, accumulate less intracellular zinc compared with the nontumorigenic parental RWPE-1 cells.²⁴ These results strongly implicate zinc concentration as a defining feature in prostate cancer development and progression.

Bypassing zinc as a tumour suppressor

The functional role of zinc accumulation in the prostate is to inhibit citrate oxidation by the highly specialized secretory epithelial cells.⁵ Blockade of this enzymatic pathway permits the production and secretion of extremely high levels of citrate, which is a major constituent of the prostatic fluid.⁵ In addition to its physiological role, zinc has associated effects and consequences that could be inhibitory to malignant cells (Fig. 2). Accordingly, the inability to accumulate zinc could potentially result in the loss of these inhibitory effects, leading to the development and progression of prostate cancer.

Metabolic and bioenergetic effects

Intramitochondrial accumulation of high levels of zinc inhibits mitochondrial aconitase activity, which, in turn, inhibits citrate oxidation.²⁵ This inhibition essentially truncates the Krebs cycle and markedly decreases cellular energy production. By undergoing a metabolic transformation to zinc-deficient citrate-oxidizing cells with a functional Krebs cycle, the energy requirements for malignancy can be met.^{23, 26}

Antiproliferative effects

Zinc seems to have a role in regulating cell division. Indeed, the intracellular accumulation of zinc inhibits proliferation of prostate cancer cells by arresting cells at the G2/M cell cycle check point.²⁷ Liang et al. demonstrate that the mechanism of the zinc-mediated inhibition of prostatic cell growth involves up-regulation of p21 gene expression. In addition, the authors suggest that the inhibitory effect of zinc may be mediated by the interaction of zinc with the p13^{suc1} subunit of Cdc2 kinase.²⁷ Further, studies by Han et al. reveal that nuclear p21 levels are depressed by zinc deficiency in LNCaP prostate cancer cells.²⁸ Reflecting the tumorigenicity of the different cell lines, sevenfold higher zinc levels were necessary to inhibit the growth of PC3 cells compared with LNCaP cells.²⁷

Effects on intracellular signalling pathways

Treatment of PC-3 and DU-145 prostate cancer cell lines with physiological levels of zinc inhibits the activity of transcription factor NF- κ B. Consequently, the expression of NF- κ B-regulated proangiogenic and prometastatic molecules is reduced in these cell lines, including vascular endothelial growth factor (VEGF), IL-6, IL-8, and matrix metalloproteinase 9 (MMP-9) in prostate cancer cells.^{11, 29} By contrast, depletion of intracellular zinc increases expression of protumorigenic cytokines in prostate cancer cell lines via a NF- κ B-dependent pathway.¹⁰ Zinc deficiency also results in hyperphosphorylation of protein kinase B (Akt) and E3 ubiquitin-protein ligase (Mdm2), as well as reduction in nuclear p53 accumulation, in human normal prostate epithelial PrEC cells.²⁸ A high level of Akt phosphorylation and low nuclear level of p21 coincides with high G1-to-S ratio in zinc-deficient LNCaP prostate cancer cells.²⁸ In addition, zinc downregulates both induced and constitutive levels of hypoxia inducible factor-1 α (HIF-1 α) in human prostate cancer cells *in vitro*.³⁰ Zinc-mediated down-regulation of HIF-1 α coincides with reduced invasiveness of C27 Human prostate cancer cells.³⁰

Apoptogenic effects

Zinc treatment results in the translocation of cytochrome c from the mitochondria to the cytosol, which triggers the activation of the caspase-9 and caspase-3, the cleavage of nuclear poly(ADP)-ribose polymerase (PARP), and, ultimately, apoptosis (Fig. 3).^{31, 32} Zinc-mediated release of cytochrome c can be potentially attributed to its effect on the mitochondrial level of the pro-apoptotic Bax protein. Indeed, treatment of PC-3 cells with zinc increases the mitochondrial and cellular levels of Bax protein and the cellular Bax/Bcl-2 ratio.³³ The increase in cellular Bax level appears to involve zinc induction of Bax gene expression.³³ The apoptogenic effect of elevated zinc concentrations in prostate cancer cells *in vitro* could also be attributable to the downregulation of antiapoptotic Bcl-2 and survivin proteins.³⁴

Invasive and migratory effects

Zinc suppresses the expression of ICAM-1, an intercellular adhesion molecule playing an important role in cell-cell and cell-extracellular matrix interactions, which coincides with reduced invasiveness and adhesion of castration-resistant PC3 prostate cancer cells.²⁹ Other studies have also demonstrated that the ability of androgen-dependent LNCaP prostate cancer cells to invade Matrigel is strongly suppressed in the presence of zinc at the concentration range of 150–250 μ M.³⁵ Furthermore, the invasive potential of these cells is associated with the ability of zinc to irreversibly inhibit aminopeptidase N.³⁶ Aminopeptidase N (APN/CD13) is a 150 kDa membrane-bound ubiquitously expressed protease, which modulates cell motility and adhesion to extracellular matrix and therefore, plays a critical role in tumor proliferation, invasiveness and angiogenesis.³⁷

Zinc transport

Although low plasma zinc concentrations have been reported in patients with prostate carcinoma (0.6+/-0.03 μ g/ml in patients with prostatic malignancies vs. 0.95+/-0.1 μ g/ml in healthy controls),³⁸ this is not the likely culprit for a decreased zinc accumulation in malignant prostate cells. Instead, prostate cancer modulates the specialized mechanisms that are required for both zinc uptake and release.³⁹ Zinc transporters are largely assigned to the two metal-transporter families: the ZIP (Zrt-like, Irt-like proteins) family, which imports zinc from extracellular fluid and the ZnT (zinc transporter) family, which functions in exporting zinc or redistributing it intracellularly in such organelles as mitochondria and endosome/lysosome compartment.^{40, 41}

Among the 10 human ZnT members identified to date, ZnT-1 is the only zinc transport protein that is localized to the plasma membrane.^{41, 42, 43} Expression of ZnT-1 is induced by high zinc concentrations in LNCaP and PC-3 human prostate cancer cells,⁴⁴ consistent with its putative role as a zinc export protein. Indeed, one *in vitro* study demonstrated that induction of *ZNT1* gene transcription is mediated by the binding of the metal-specific transcription factor MTF-1 to two metal response elements (MRE) in the ZnT-1 promoter.⁴⁵ High-level expression of ZnT-1 and ZnT-3 and low levels of metallothionein (an endogenous zinc chelator) have been demonstrated in androgen-independent cells that were derived from the initially androgen-dependent LNCaP cells.⁴⁶ In fact, this newly derived cell line demonstrated much lower zinc levels than the parent LNCaP cell line.⁴⁶ Functional implications of these findings are not well delineated in the literature. Furthermore, lack of expression of the *ZNT7* gene, a zinc transporter localized on the Golgi membrane as well as the ZnT7-positive vesicles, has been implicated in prostatic carcinogenesis in a mouse model.⁴⁷ This study clearly demonstrate that a null-mutation of the *Znt7* gene accelerates prostate tumor formation in a transgenic adenocarcinoma of the mouse prostate model (TRAMP) mice.⁴⁷

To date, 14 mammalian ZIP members have been identified;⁴³ however, only ZIP1, ZIP2, ZIP3, and ZIP4 have been shown to be localized to the plasma membrane and therefore, participate in importing zinc from extracellular fluid.^{41, 48–53} ZIP1 is important for the extraction of zinc from circulation as the primary source of cellular zinc, whereas ZIP2 and ZIP3 seem to be important for the retention of zinc in the cellular compartment.⁵⁴ All these transporters are markedly downregulated in human adenocarcinomatous prostate glands, as compared with normal peripheral zone glandular epithelium and benign hyperplastic glands, demonstrated by immunohistochemical staining of clinical tissue specimens.^{33, 34, 55} In addition, men in high-risk patient populations, such as African American men, seem to have altered prostatic zinc homeostasis, resulting in a decreased intracellular zinc accumulation that coincides with downregulation of hZIP1 and hZIP2.⁵⁶

The ZIP1 has been characterized as the major zinc uptake transporter, regulating cellular zinc accumulation in normal and transformed prostate cells.^{24, 57, 58} Overexpression of ZIP1 in transfected RWPE-2 and PC-3 cells results in a novel zinc uptake activity not found in nontransfected cells.^{24, 58} Over-expression of ZIP1 in RWPE-2 cells also results in suppression of cell growth due to increased apoptosis.²⁴ By contrast, antisense inhibition of hZIP1 expression results in a significant decrease of zinc uptake in PC3 cells.⁵⁸ Our recent studies demonstrate that overexpression of hZIP1 reduces the tumorigenic potential and growth of PC3 prostate cancer cells both *in vitro* and *in vivo*.⁹ Other studies by Chen *et al.*⁵⁵ demonstrated that overexpression of hZIP4 also inhibits proliferation and aggressive behaviour of DU145 prostate cancer cells. By contrast, silencing hZIP4 is associated with increased cell proliferation and invasiveness in 22RV1-shRNA prostate cancer cells.⁵⁵ Thus, in prostate cells, zinc uptake transporters can behave as tumour suppressors. Importantly, reduced expression of zinc uptake transporters can result in decreased intraprostatic zinc levels, regardless of the degree of supplemental zinc intake.

To escape the anti-tumor effects of intracellular zinc, malignant prostate cells could potentially silence the expression of zinc uptake transporters, an approach that may be achieved through multiple cellular mechanisms.

Epigenetic silencing

Makhov *et al.*⁵⁹ demonstrated that demethylation of the promoter region of the activator protein (AP)-2 α protein—a critical transcription factor for *SLC39A1* and *SLC39A3* gene expression—in DU-145 and LNCap cell resulted in increased hZIP1 and hZIP3 transporter

expression and augmented zinc uptake. Increased zinc uptake coincided with reduced proliferation of both DU145 and LNCap cells (Makhov P., personal communication). Interestingly, an analysis of the promoter regions of the *SLC39A1* and *SLC39A3* genes did not reveal hypermethylation in either cell line.⁵⁹ These findings suggest that hypermethylation of the *SLC39A1* and *SLC39A3* promoters is not the primary mechanism responsible for the downregulation of these genes in prostate cancer cells. Moreover, methylation patterns of the (AP)-2 α promoter region from patients' tissues with Gleason score 6 prostate cancer were found to be markedly increased in comparison with the adjacent normal prostatic tissue.⁵⁹ Gleason score 6 prostate cancer is considered to be low-risk, well-differentiated and most commonly presents as localized disease. These data suggest that the methylation of AP-2 α promoter region in prostate cancer cells is an early event in neoplastic development.

MicroRNA

Array profiling of tumour tissue specimens have shown that several microRNAs are present in higher levels than in normal prostate tissue; namely, microRNA-183, microRNA-96, and microRNA-182. These putative zinc-regulating microRNAs were further investigated *in vitro* using human primary prostate cultures and established prostate cancer cell lines. Transient transfection of microRNA-182 decreased hZIP1 protein in both normal and malignant prostate epithelial cell lines.⁶⁰ Overexpression of the entire microRNA-183-96-182 cluster suppressed five additional zinc transporters (hZIP1, hZIP3, hZIP7, hZIP9, hZnT1, and hZnT7), diminished labile zinc pools and reduced zinc uptake, demonstrating this microRNA cluster is indeed a regulator of zinc homeostasis.⁶⁰

Overexpression of RREB-1

RREB-1 is a downstream effector of the Ras-Raf-MEK-ERK pathway.⁶¹ Previous studies have demonstrated that the transfection of PC3 prostate cancer cells with constitutively active Ras inhibited hZIP1 promoter activity, whereas the transfection with dominantly negative Ras increased its promoter activity.⁶¹ These effects were shown to be mediated by RREB-1 as they were attenuated when the RREB-1 binding site in the hZIP1 promoter was mutated.⁶¹ Notably, the hZIP1 promoter contains a strong inhibitory *cis*-acting element to which the RREB-1 transcription factor binds, which represses the reporter activity.⁶¹ Overexpression of RREB-1 results in a decrease in the abundance of hZIP1 in the plasma membrane of PC3 prostate cancer cells, whereas RREB-1 knockdown with specific siRNA significantly ($P < 0.05$) increases hZIP1 expression.⁶² Indeed, studies employing prostate tissue microarrays and tissue sections confirmed an inverse relationship between RREB-1 and hZIP1 staining.⁶²

The process whereby a normal prostate epithelial cell transforms into a cancerous one involves loss of the ability to accumulate intracellular zinc. The decrease in cellular zinc content coincides with a dramatic reduction in expression of the zinc uptake transporters in malignant cells *in situ*. Given that zinc levels diminish early in the course of prostate cancer, the profile of zinc transport genes may serve as a potential tumor biomarker for early diagnosis and risk assessment for prostate cancer.

Experimental data versus epidemiology

Given the wealth of cellular data on the role of zinc and zinc transporters in prostate cancer, it is perhaps unsurprising that zinc supplementation has been investigated in the prevention and treatment of prostate cancer. Although numerous *in vitro* and *in vivo* experiments suggest that increasing zinc intake might be protective against prostate carcinogenesis,^{4–11, 63–66} the results remain controversial.

Feng *et al.* demonstrated that zinc administration by an osmotic pump inhibited the growth of PC3 xenografts in nude mice.⁶ The inhibitory effect of zinc seems to result from apoptosis, mediated by the mitochondrial membrane permeability-related Bax and Bcl-2 proteins.⁶ Experiments using the transgenic adenocarcinoma of the mouse prostate (TRAMP) model also suggest that an 'optimal' level of zinc in animal diet (30 ppm) is protective against prostate carcinogenesis.⁶⁷ Findings by Banudevi *et al.*^{68, 69} document the chemopreventative effects of zinc on prostate carcinogenesis induced by *N*-methyl-*N*-nitrosourea and testosterone in the adult male Sprague–Dawley rats. Our own studies provide evidence that hZIP1 transporter overexpression induces regression of prostate tumor growth in a PC3 xenograft mouse model.⁹ Overall, the experimental data strongly support a protective role of zinc against prostate carcinogenesis.

However, epidemiological studies evaluating the role of zinc supplementation on primary and secondary prostate cancer prevention have yielded conflicting results. Some studies reported an adverse effect with zinc supplementation,^{13, 17, 18} whereas others have reported either a protective effect with borderline significance^{15, 70} or no effect at all.^{12, 14, 16} Epstein *et al.*⁷¹ suggest that that high dietary intake of zinc is associated with a lower prostate cancer-specific mortality after diagnosis, particularly in men with localized disease. Furthermore, Platz *et al.*⁷⁰ suggest that the risk of prostate cancer is slightly lower among men with moderate and high zinc intake. Similarly, Gonzales *et al.*⁷² reported that "average intake of supplemental zinc was not associated with a reduced prostate cancer risk overall; however, risk of advanced prostate cancer decreased with greater intake of supplemental zinc". It is critical to note that the recommended dietary allowance of zinc for adult males is 11 mg/day.⁷³ A thorough study by Leitzmann *et al.*¹⁷ detected no statistically significant association between supplemental zinc intake of 100 mg/day and increased prostate cancer risk. Moreover, this study reported that zinc ingestion of 100 mg/day was actually associated with a significantly increased risk of advanced prostate cancer.¹⁷ Several potential explanations for this association between a high zinc intake and prostate carcinogenesis can be considered. One possibility is that ingestion of excessively high supplemental zinc has undesirable metabolic effects, such as immune dysfunction⁷⁴ and impaired antioxidant defense,⁷⁵ which indirectly promote prostate cancer progression. Moreover, ingestion of high levels of zinc decreases its intestinal absorption and assimilation, which paradoxically could lower circulating and tissue levels of zinc.⁷⁶ Park *et al.*⁷⁷ assessed levels of serum zinc and risk of developing prostate cancer in a multiethnic cohort of men. In this work, the investigators failed to demonstrate a relationship between serum zinc levels and prostate cancer. However, as the authors acknowledge, no evidence supports that a serum zinc level measured at random intervals reflects zinc concentration in prostatic tissues. Our studies demonstrate that failure to accumulate zinc because of a diminished expression of zinc uptake transporters might result in decreased intratumoural zinc levels despite adequate dietary zinc intake.⁹ These findings could potentially explain the conflicting results of recent epidemiological studies evaluating the role of zinc supplementation on primary and secondary prostate cancer prevention.

Another confounding factor complicating the interpretation of epidemiological studies is the likely possibility that the increased risk of advanced prostate cancer observed in men who take zinc supplements could be caused by these individuals taking additional unspecified supplements. Lawson *et al.*⁷⁸ reported that among men taking a zinc supplement, multivitamin use was associated with an increased risk of fatal prostate cancer, whereas no association with multivitamins was observed for men not taking a zinc supplement. We have previously demonstrated that 50% of men at high risk of developing prostate cancer took one or more supplements to prevent prostate cancer, and more than 25% took three or more agents concomitantly.⁷⁹ This study evaluated a population of high-risk patients in the USA, including black men, men with at least one first-degree relative or two or more second-

degree relatives with prostate cancer, or men who tested positively for the *BRCA1* gene mutation. Our data are in concordance with Leitzmann *et al.*¹⁷ and demonstrated that, compared with nonusers, men who consumed supplemental zinc also consumed more multivitamins, as well as supplemental calcium, copper, iron, vitamin E, lycopene, and folate.⁷⁹

Even the individuals solely intent on consuming commercially available zinc are at risk because of the presence of nonessential, potentially harmful trace elements contained in these supplements,⁸⁰ which might further influence study results. For example, some publications suggest that cadmium contaminants in zinc supplements could be associated with prostate carcinogenesis.⁸⁰ Studies performed in New Zealand by Krone *et al.* revealed that cadmium, a known carcinogen, was detected in all seven tested zinc-containing dietary supplements, in ratios ranging from 0.039 μg to 1.46 μg cadmium per 15 mg zinc.⁸¹ Thus, consumption of approximately 140 mg/day of zinc (the daily level of zinc supplement intake among the high-intake group studied by Leitzmann *et al.*¹⁷) could also result in simultaneous intake of as much as 13.6 μg cadmium per day. Total mean daily exposure to cadmium from foods, as estimated in the U.S. Food and Drug Administration Total Diet Study is 10 μg cadmium/person/day.⁸⁰ In addition, the bioavailability of zinc is controlled by metallothioneins, which are upregulated by the presence of heavy metals, including cadmium. Thus, as suggested by Platz *et al.*,⁷⁰ high concentrations of one metal might influence the bioavailability of another. Humans accumulate cadmium with age. It has been suggested that even small repeated low doses of cadmium could accumulate in the body and have adverse effects on prostate health associated with cadmium intake.⁸²

Therapeutic applications of zinc

Multiple studies have revealed that a decrease in the intraprostatic zinc concentration and a concomitant reduction in expression levels of zinc uptake transporters (hZIP1, hZIP2, and hZIP3) represent early steps in the development of prostate malignancy.^{2,3,33,34} Moreover, zinc concentrations diminish prior to any discernible histopathological changes, and continue to decline during progression towards hormone-independent growth.^{57,83} One cannot overemphasize the importance of early detection of prostate cancer in that it could have life-saving implications for those patients with potentially aggressive disease. Indeed, studies by Ghosh *et al.*⁸⁴ demonstrate that the progression of prostate cancer could be observed *in vivo* by monitoring zinc content in the prostates of TRAMP mice using a novel fluorescent sensor for mobile zinc. Thus, intraprostatic zinc levels, as well as the expression status of zinc transport genes, might serve as potential tumour biomarkers for the early diagnosis and risk stratification of men with prostate cancer.

Further clinical utility of zinc status on diagnostic measures in human subjects was evaluated by Cortesi *et al.*⁸⁵ They demonstrate that zinc concentration in prostate tissue segments inversely correlates with the aggressiveness of prostatic malignancy, i.e. the higher the Gleason score the greater the local zinc depletion.⁸⁵ Cortesi *et al.* suggest that local zinc concentration mapping may improve patient selection for biopsy, localize biopsy site and stratify between localized and focal therapy (e.g., Cryotherapy, Brachytherapy).⁸⁵

Overall, the described studies clearly demonstrate the value of zinc-based prostate cancer diagnostics. Thus, zinc status could serve as an adjunctive measure to PSA screening, as it provides more-specific information than elevated PSA alone. Although elevated PSA could signify the presence of multiple prostatic abnormalities (for example, carcinoma, BPH, and inflammation), reduced zinc and its uptake transporters levels offer a unique specificity for prostatic malignancy.

Development of new therapeutic strategies for advanced prostate cancer represent an urgent need in today's clinical landscape. In addition to its potential role as a diagnostic tool, zinc might underlie the development of novel therapeutic agents for the treatment of prostate cancer. Studies by Liguori *et al.*⁸⁶ demonstrated potent antitumour activity of novel heteroleptic zinc(II) complexes *in vitro*. Unfortunately, the antitumour effect of zinc could be compromised in ZIP-deficient malignant cells, which are incapable of accumulating zinc. Indeed, our recent studies demonstrate that failure to accumulate zinc because of a reduced expression of zinc uptake transporters might result in diminished intratumoural zinc levels despite adequate zinc intake.⁹ However, use of zinc ionophores, such as clioquinol, could potentially facilitate the process of zinc uptake in ZIP-deficient cells.⁸⁷ Clioquinol treatment of ZIP-deficient prostate cancer cells in the presence of physiological levels of zinc resulted in 80% inhibition of cell proliferation.⁸⁸ Our prior work showed that the treatment of PC3 and DU145 prostate cancer cells with pyrithione (an alternate zinc ionophore) under similar experimental conditions inhibited activation of NF- κ B and sensitized tumour cells to tumour necrosis factor (TNF)- α and paclitaxel-mediated cell death.¹¹ Intriguingly, the ability of paclitaxel to cause apoptosis in LNCaP prostate cancer cells was significantly reduced when cells were cultured under zinc-deficient conditions.⁸⁹ Given the prevalence of zinc deficiency, determining how chemotherapeutic action is modulated by zinc adequacy may have clinical importance. Water-soluble analogues of the zinc ionophore 1-hydroxypyridine-2-thione (ZnHPT) have been found to increase the intracellular zinc levels and suppress growth of malignant cells, both *in vitro* and *in vivo*.⁹⁰ However, systemic administration of zinc ionophores will likely increase the cellular levels of zinc in multiple bodily tissues due to the lack of target specificity for tumor tissue and might, therefore, induce unforeseen toxicities. Interestingly, Shah *et al.*⁹¹ discussed the feasibility of the direct intratumoural injection of zinc acetate in a xenograft mouse model of prostate cancer. This approach halted prostate cancer growth and substantially extended the survival durations of the experimental animals, without any detectable toxicity in other tissues. In addition, our own results demonstrated that the administration of physiological levels of zinc can prevent docetaxel-mediated mitotic arrest, thereby protecting zinc-accumulating myeloid progenitor TF-1 cells from docetaxel-mediated toxicity. Importantly, such treatment had no effect on docetaxel-mediated apoptosis in PC3 and DU145 prostate cancer cells with compromised zinc uptake.⁹² Thus, zinc status can modulate antitumour efficacy of certain chemotherapeutic agents.

Another potential approach to target prostate cancer is to use zinc-chelating agents rather than zinc ionophores. Zinc levels are markedly decreased in malignant prostate tissues,^{19, 20, 21} and in this zinc-deficient state, a normal prostate cell can compensate for decreased levels via upregulation of zinc uptake transporters. In this scenario, administration of a zinc chelator would have minimal, if any, effect on the overall intracellular zinc level. However, the situation is dramatically different in a malignant prostate cancer cell. In addition to having lower baseline zinc levels, malignant cells are also severely limited in their ability to respond to zinc chelation because of a compromised expression of zinc uptake transporters. Findings from our laboratory indicate that treatment of prostate cancer cells with the zinc specific chelator, *N,N,N',N'*-tetrakis(2-pyridylmethyl) ethylenediamine (TPEN) induces rapid and selective depletion of the antiapoptotic protein E3 ubiquitin-protein ligase XIAP (XIAP) at post-translational level.⁹³ Inhibition or downregulation of XIAP in cancer cells lowers the apoptotic threshold, thereby inducing cell death and enhancing the cytotoxic action of chemotherapeutic agents.^{94, 95} Indeed, TPEN-mediated XIAP depletion coincides with increased activation of the apoptosis-mediating caspase 3 and caspase 9, as well as increased sensitization of apoptosis-resistant tumour cells to subsequent treatment with TNF-related apoptosis-inducing ligand (TRAIL).⁹³ These findings were also supported by Zuo *et al.*,⁹⁶ who demonstrated that novel polypyridyl chelators deplete cellular zinc and destabilize XIAP in human prostate and breast cancer cells. In light of the fact that prostate

cancer cells are unable to counteract zinc chelation, a new potential therapeutic avenue opens for exploration.

Conclusions

Failure to accumulate zinc is a *sine qua non* of prostate carcinogenesis. Whereas epidemiological studies have shown mixed results, experimental data strongly suggest a protective role of zinc against prostatic carcinogenesis. Multiple *in vitro* and *in vivo* experimental studies support the concept that zinc uptake transporters might function as tumour suppressors in prostate cancer. Failure to accumulate zinc owing to a diminished expression of zinc uptake transporters might result in decreased intratumoural zinc levels, despite adequate dietary zinc. This issue was not addressed by previous epidemiologic studies. Although an interest regarding zinc's role in prostate carcinogenesis is increasingly apparent, more studies on the effects of zinc on prostate biology are necessary. Focusing on this area of research should clarify the mechanism(s) of zinc homeostasis in malignant prostate cells and provide new strategies for the screening, diagnosis, and treatment of men with prostate cancer.

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Key Points

- *In vitro* and *in vivo* experimental studies have revealed a strong association between prostate cancer and the downregulation of intracellular zinc content
- To escape the antitumour effects of intracellular zinc, malignant prostate cells can reduce expression of zinc uptake transporters through multiple mechanisms
- Failure to accumulate zinc via the diminished expression of zinc uptake transporters can, in turn, result in decreased intratumoural zinc levels despite adequate dietary zinc intake
- This finding can explain the conflicting results of various epidemiological studies evaluating the role of zinc supplementation on primary and secondary prostate cancer prevention
- The importance of changes in zinc accumulation in prostate carcinogenesis emphasizes the potential roles of zinc and zinc transport proteins for the development of novel diagnostic and therapeutic modalities

Review criteria

A Pubmed and Web of Knowledge database searches was performed for abstracts and articles in English language. The following key words were utilized: Prostate Cancer, Zinc, Transporters, Prevention, Treatment, Epidemiology, Clinical Trials, Dietary Supplements. Relevant abstracts up to 2012 were included and relevant articles and their bibliographies were reviewed.

Figure 1.

The biological roles of zinc. Second only to iron in terms of its concentration in the body, zinc is a co-factor for more than 300 enzymes, with three major biological roles: structural, regulatory and catalytic. Zinc stabilizes the structure of a number of proteins, DNA and RNA as well as ribosomes. Zinc is a component of >3,000 transcription factors, and a zinc ion is located at the active site of a various enzymes, where it participates directly in the catalytic reaction. Abbreviations: ER, endoplasmic reticulum; IAP, inhibitor of apoptosis protein; ZIP, Zrt-like, Irt-like protein; ZnT, zinc transporter.

Figure 2.

The roles of zinc in tumour suppression. In addition to its physiological role, zinc has inhibitory effects on malignant cells. Increased zinc uptake reduces the malignant potential and growth of prostate cancer cells through multiple mechanisms, whereas zinc deficiency augments tumorigenic properties of prostate cancer cells, at least in part, via activation of NF- κ B-regulated pathways.

Figure 3.

A zinc-mediated shift in the Bax to Bcl-2 ratio promotes the translocation of cytochrome c from the mitochondria to the cytosol, which triggers the activation of caspase 9 and caspase 3, cleavage of nuclear PARP and, ultimately, apoptosis. NF- κ B activation is a major pathway contributing to prostate cancer development and progression. NF- κ B regulates the susceptibility of malignant cells to apoptosis through transcriptional control of antiapoptotic genes, which act on different levels of the apoptotic pathway. The central mechanisms of IAP apoptotic suppression seem to be through direct caspase and pro-caspase inhibition. Abbreviations: IAP inhibitor of apoptosis protein; PARP, poly(ADP)-ribose polymerase.