Semi-Review Article ISSN 2693-2504

Journal of Medical Clinical Case Reports

Zinc(II) Induced Suppressive Oncology for Prostate Cancer Prevention, Progression, and Angiogenesis

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Submitted : 7 Aug 2023; Published : 25 Sept 2023

Citation: Tsuneo I. (2023). Zinc(II) Induced Suppressive Oncology for Prostate Cancer Prevention, Progression, and Angiogenesis. J Medical Case Repo, 5(2):1-6.

Abstract

Zinc(II) induced oncological suppressive effects on prostate cancer (PCa) prevention and development with PCa Stage 1, Stage 2, and Stage 3 have been investigated, subsequently, the zinc-ions binding prostate anti-cancer molecular mechanism is clarified.

For PCa prevention, adequate dietary zinc intake status can prevent the prostate cancer disease through restoration of high zinc levels, protective preventative PCa progressing by using chemotherapeutic agents.

At PCa Stage 1, zinc can inhibit PCa proliferation and cell growth, and can prevent PCa progressing that Zn^{2+} ions can diminish androgen receptor (AR), proliferating cell nuclear antigen (PCNA), proliferation index. At PCa Stage 2, zinc suppresses the progression of PCa by proliferation, migration, and invasiveness that zinc is confirmed to function as a tumor suppressor in PCa cells, in which zinc, zinc transporters, and zinc and ZRT- and Irt-like proteins1 (ZIP1) can suppress tumor growth, invasive and migratory tumor malignant cell, and regional lymph nodes in PCa cancer. At PCa Stage 3, metastatic prostate cancer is composed of prolife-ration, neovascularization, extravasation, and bone or bone marrow metastasis with angiogenesis that MAZ regulates PCa bone metastasis, intercellular zinc levels inhibit metastatic and angiogenic malignant cells, and ZMYND8 inhibits tumor angiogenesis.

Zinc induced ROS generation in PCa cell is involved that ROS-mediated oxidative stress on prostate cancer can be modulated by rich antioxidants and accumulated zinc, resulting paclitaxed (PTX) to mitochondrial dysfunction, leading to apoptotic tumor cells.

Zinc coordinated molecular apoptosis mechanism in PCa cells is involved that Zn^{2+} ions having Zn^{2+} ions-centered tetrahedral geometric coordination pattern bind with each PCa stage tumor proteins, causing Zn^{2+} ions-several protein complex formation and apoptosis of PCa cells, leading to molecular apoptosis of prostate cancer tumor cells.

Keywords: Zinc(II), PCa proliferation and growth, Invasive and migratory malignant cell, Regional lymph nodes, Bone and bone marrow metastasis, Tumor angiogenesis, ROS and oxidative stress.

Abbreviation

ADT	=	androgen deprivation therapy,	PCa	=	prostate cancer,
AR	=	androgen receptor,	PCNA	=	proliferating cell nuclear antigen,
BAX	=	Bcl-2-associated X protein,	PSA	=	prostate specific antigen,
BPH	=	benign prostate hyperplasia,	PTX	=	paclitaxel,
BPNs	=	black phosphorus nanosheets,	SASP	=	senescence-associated secretory phenotype,
LNCaP	=	human prostate tumor cell line,	TME	=	tumor microenvironment,
LNM	=	lymph node metastasis,	TRAMP	=	transgenic adenocarcinoma of the mouse prostate,
MAZ	=	Myc-associated zinc-finger protein,	VEGF-A	=	vascular endothelial growth factor A,
MMPs	=	matrix metalloproteinases,	ZFX	=	Zinc finger protein X-linked,
NF-κB	=	nuclear factor-kappa B,	ZIPs	=	ZRT- and Irt-like proteins,

ZMYND8 = Zinc finger MYND-type containing 8,
ZnAAs = zinc amino acid conjugates

Introduction

Prostate cancer (PCa) is most common among men that the characteristics of canonical cancer metastasis is the major cause of death in PCa patients, include epithelial-to-mesenchymal transformation (EMT), migration, invasion, extracellular matrix (ECM) interactions and angiogenesis that angiogenesis, the sprouting of new blood vessels from pre-existing vessels, is essential for tumor growth and metastasis [1]. PCa procedure is composed of PCa primary malignant tumor formation and growth within the prostate, malignant tumor proliferation outside the prostate, migration and invasion, and metastasis. Specially, prostatic cancer carcinogenesis occurs in prostatic malignancy, anti-proliferative effect, apoptogenic effect, and invasive and migratory effect [2]. PCa is an aged-related malignancy and has a cellular senescence in man that androgen receptor (AR) target agnonist and androgen deprivation therapy (ADT) induced cellular senescence are carried out, the therapy induced senescence-associated secretory phenotype (SASP) of regulation and reduction of tumor growth is performed by tumor microenvironment [3].

While, zinc(II) ions have important anti-cancer effects for cancer tumor cells of malignant proliferation, local invasion, and metastasis [4]. Zinc acts as the maintenance of prostate health that zinc suppresses tumor progression and protects DNA integrity in prostate cells, and zinc transporter functions as tumor suppressor [5]. Furthermore, zinc regulates cell proliferation and growth, apoptotic characteristics appearance in prostate tumor cells that zinc has apoptotic effects on the regulation of normal and malignant cell growth and proliferation under physiological of cellular zinc distribution and concentration [6].

The other, angiogenesis in PCa tumor growth progression plays an important role of vascular endothelial growth factor A (VEGF-A) in angiogenic prostate cancer and this prostate cancer angiogenesis mechanism should be clarified in order to be elucidated that anti-angiogenesis therapy may be effective in the treatment of PCa [7]. However, it is unclear whether zinc could inhibit initial tumor formation as PCa prevention and metastasis with angiogenesis in PCa.

In this semi-review article, zinc(II) induced suppressive oncology on prostate cancer prevention, prostate cancer development, and prostate cancer angiogenesis with prostate cancer Stage 1, Stage 2, and Stage 3 are investigated, subsequently, the zinc-ions coordinated binding PCa protein molecular apoptosis mechanism is clarified.

Prostate cancer progressing and development in PCa Stage 1, Stage 2, and Stage 3

Prostate cancer (PCa) process on PCa Stage 1, 2, 3 is considered that Staging of PCa is composed of primary malignant tumor, neovascularisation, local invasion and the migration, regional lymph node, and metastases with angiogenesis [8].

The staging is as follows;

PCa Stage 1 (Malignant tumor formation and proliferation); Cancer tumor is in half or less half and in more than half of the prostate, without spread outside of the prostate.

PCa Stage 2 (Local invasion, regional lymph node); Cancer tumors spread beyond the outer layer of the prostate, but not to lymph
nodes.

PCa Stage 3 (Metastasis, bone metastasis, and angiogenesis); Tumor has spread to nearby tissues, lymph nodes or other organs of the body, beyond the outer layer. Angiogenic PCa relies on angiogenesis for growth, progression, and the dissemination of tumor cells.

Thus, PCa Stages are thought to be composed of PCa Stage 1 with malignant tumor formation and growth, PCa Stage 2 with local invasion and regional lymph node, and PCa Stage 3 with bone and bone marrow metastasis and angiogenesis.

Zinc(II) ions induced PCa prevention

Zinc induced Inhibitory effect on the progression of prostate malignancy is efficient to be used as PCa prevention [9], and zinc induced PCa suppressive tumor cells and apoptosis of human melanoma cells may be used for PCa prevention [10].

Zn^{2+} ions can prevent the PCa that high zinc levels in the prostate are essential for prostate health and protect prostate cells, DNA integrity in the prostate [11], and that enhancing zinc uptake and accumulation can prevent PCa in the premalignant cell that restoration of high zinc levels in malignant cells could be efficacious in the treatment and prevention of PCa [12].

Zinc homeostasis induces regression of prostate growth, protective role of zinc against prostate carcinogenesis, and zinc can modulate anti-tumor efficacy of certain chemotherapeutic agents [13]. Adequate dietary intake of zinc may be critical in the PCa prevention of age-related diseases. Especially in the prostate, adequate zinc status will help to prevent prostate disease from developing or further progressing, thereby acting as a vital anti-benign prostate hyperplasia (BPH), anti-PCa agent, and Zinc Amino Acid Conjugates (ZnAAs), should be considered [14].

Thus, adequate dietary zinc intake status can prevent the prostate cancer disease through restoration of high zinc levels, protective preventative PCa progressing with inhibitory effects on the progression of prostate malignancy and suppressive tumor.

Zinc induced proliferative and malignant suppressive tumor growth in PCa Stage 1

At PCa Stage 1, zinc can inhibit proliferation of PCa cell that zinc suppresses the expression androgen receptor (AR) and prostate specific antigen (PSA), AR-mediated transaction in androgen receptor-sufficient (AR(+)) PCa cells, and then $ZnCl_2$ (0~300 μM) functions as a negative growth regular for (AR(+)) PCa cells [15]. Zinc concentration (100~1000 ng/mL) can

inhibit PCa cell growth and prevent the PCa progressing [16]. Zinc exist a state of Zn^{2+} dyshomeostasis in prostate cell that 10 μMZn^{2+} reduces PC3 cell proliferation and induces HIF1α in normal HK-2 renal tubular cells and PC3 cell survival under oxidative stress [17].

In PCa patients, plasma zinc level is mild-moderate disease 10.49±2.89μmol/L, severe disease 7.64±2.33μmol/L, advanced disease 6.98 ± 1.97μmol/L in PCa patients that zinc status in PCa disease is inversely associated with disease grades which to define the disease stage, in which low zinc status influences the severity and progression of PCa disease [18].

Zinc regulates proliferation and growth, apoptogenesis in prostate cancer cells that Zinc (15 μM) increases the Bax-associated mitochondrial pore forming process and cellular production, and the Bax/Bcl-2 ratio, leading to apoptotic effect [19]. Zinc suppresses the growth of tumor xenografts and the development of normal prostate that the AR, the proliferating cell nuclear antigen (PCNA), and proliferation index can be diminished by 10, 20 mg/kg $ZnCl_2$-treated prostate cancer tumors [20]. Zn^{2+} induced coordinations can gain intrinsic stability effects for black phosphorus nanosheets (BPNSs) through chemo-photo thermal therapy [21].

Thus, at PCa Stage 1, zinc can inhibit proliferation PCa cell growth, proliferation, and can prevent PCa progressing that Zn^{2+} ions can diminish AR, PCNA, proliferation index, and can gain intrinsic stability effect for BPNSs by chemo-photo thermal therapy.

Zinc induced suppressive local invasion and migration, and regional lymph node in PCa Stage 2

At PCa Stage 2, zinc has anti-proliferative effects of prostatic malignancy and tumor suppressor, apoptogenic effects, invasive and migratory effects that zinc uptake transporter function as tumor suppressor, and invasive and migratory effects [2]. The significant heterogeneity of lymph node metastasis (LNM) in PCa luminal and interstitial cells contributes to tumor progression and results in tumor microenvironment (TMA) immunosuppression.

Malignant cells in LNM were already present in the initial stage of PCa, and the cells with metastatic ability were a specific population in PCa cells, indicating that these luminal cells may have characteristics of strong tumor growth, metastasis, and immune evasion, the heterogeneity of luminal cells, tumor infiltrating immune cells, and fibroblasts contributed to the special TME in metastasis of PCa, which was characterized by high cell growth capacity, high levels of immune suppression [22].

Zinc and zinc transporters can inhibit the PSA and uPA activities that zinc such as 50-150 μM zinc acetate and zinc transporters such as ZIP1 protein can suppress the proliferation, migration and invasion of PCa cells. The proliferation and the invasion of LNCaP cells and overexpression of ZIP1 reduced cell growth and invasion by Inhibition of NF-κB activity, in which the intake of Zinc 15 mg/day may be beneficial for advanced PCa [23]. Zinc has an anti-tumor growth and a cytotoxic effect in prostate malignant cells that the malignant cells evolved with condition that silence ZRT- and Irt-like proteins1 (ZIPs1) expression, and zinc intake (Zn Ligands containing 20 μM Zn) increases accumulation of zinc and its cytotoxic effects in PCa regional lymph nodes [24].

Zinc may inhibit the tumorigenic phenotype and suppresses invasiveness and adherence in PCa cells that physiological concentration of zinc (0.12-0.5μg/ml) suppresses pro-angiogenic and pro-metastatic reduced invasiveness of highly invasive PC-3 cells [25].

Zinc supplementation may be an effective therapy for prostate cancer that suppressive development of malignancy leads to ZIP1 downregulation and a subsequent zinc decrease in prostate cancer and zinc show decreased expression in prostate cancer to suppress invasion and metastatic potential of prostate cancer cells by increasing telomerase activity or suppressing the anti-tumor potential of bisphosphonates [26].

Thus, at PCa Stage 2, zinc suppresses the progression of PCa by proliferation, migration, and invasiveness that zinc is confirmed to function as a tumor suppressor in PCa cells, in which zinc, zinc transporters, and ZIPs1 can suppress tumor growth, invasive and migratory tumor malignant cell, and regional lymph nodes in PCa cancer.

Zinc induced PCa anti-metastasis and angiogenesis inhibitions in PCa 3 Stage

At PCa Stage 3, metastasis characters are migration companying interaction with host immune system, endothelium bonding, trans-migration, and metastasis formations, in which local invasion is early steps in metastasis that proliferates and / or coalesces with other metastasized cells to form a micro-metastasis characterization is proliferation, neovascularization and extravasation at the primary site. Then, metastatic prostate cancer in the bone or bone marrow is expressed in both primary tumors and bone metastasis of PCa [27].

Use of zinc supplement 25-40 mg/day may be relatively safe for PCa, while use of 75 mg/day may increase risk of lethal and aggressive PCa [28]. Zinc finger protein X-linked (ZFX) inhibits tumor proliferation and metastasis in PCa cells that ZFX expression, as well as the presence of lymph node metastasis and TNM stage, is negatively correlated with post-operative survival, suggesting that high ZFX expression is a risk factor [29]. Myc-associated zinc-finger protein (MAZ) regulates PCa bone metastasis [30]. Zinc finger MYND-gene type containing 8 (ZMYND8) knockdowns suppressed angiogenesis that ZMYND8 is suitable drug target for inhibition of tumor angiogenesis [31].

Angiogenesis is essential for tumor growth and metastasis that vascular endothelial growth factors (VEGFs) are part of the platelet-derived growth factor family among the angiogenic growth factors, and matrix metalloproteinases (MMPs) play a crucial role in regulatory angiogenesis [1].

Zinc could inhibit angiogenic activity in PCa cells that tumor cell migration and invasion are accompanied with angiogenesis that is regulated by angiogenic stimulating factors, such as angiogenin, VEGF and basic fibroblast growth factor (bFGF) [32]. Intracellular zinc levels can inhibit the angiogenic and metastatic malignant cells through suppressive nuclear factor-kappa B (NF-κB) signaling that progressive growth and metastasis of prostate cancer is mediated by the secretion of angiogenic and metastatic factors, in which the suppressive effect of zinc on the angiogenic and metastatic potentials of PCa cells was not simply attributable to cell death but rather was mediated through the inhibition of specific pathways regulating progression of prostate cancer [25].

Thus, at PCa Stage 3, metastatic prostate cancer is composed of proliferation, neovascularization, extravasation, and bone or bone marrow metastasis, and angiogenesis that ZFX, MAZ regulate PCa bone metastasis, intercellular zinc levels inhibit metastatic and angiogenic malignant cells, and zinc, MMPs, and ZMYND8 inhibit tumor angiogenesis.

Zinc induced ROS generation in PCa cell

Zinc induced NAD(P)H oxidase (NOXs) activation occurring reactive oxygen species (ROS) generation in PCa cell is involved that in role of ROS, a moderate level of ROS guaranteed by redox balance is essential for physiological activities via the activation or inactivation of metabolic enzymes that once the redox status deviates to oxidation, increased ROS can cause oxidative damage, in which zinc regulates signaling pathways, further affecting several cancer facts such as proliferation, angiogenesis, invasion, and metastasis [33]. Zinc increases production of ROS and hydroxyl radicals, resulting in an decrease in mitochondrial aconitase (ACO2) activity, oxidative stress, and apoptosis of prostate cancer cell, and leading to ROS increase and accumulation in PCa cells, in which zinc combined with p53 can increase the antitumor effect, accumulated ROS activity leads of paclitaxel (PTX) to mitochondrial dysfunction, resulting in apoptosis tumor cells [34]. Increased ROS enhance genetic instability, promote cell proliferation, oxidative stress, and alter somatic DNA mutations that ROS-mediated oxidative stress on prostate cancer can be modulated by dietary components rich in antioxidants [35].

Thus, a higher level of ROS in PCa causes inflammation, proliferation, oxidative damage of proteins, lipids, DNA, and RNA, accumulation of DNA damage disrupting genome stability, involving tumorigenesis and tumor progression. ROS-relevant alternation in these cells contributes to inflammation, proliferation, angiogenesis, and metastasis. ROS, as a direct DNA mutagen, activate several oncogenes and inactivate several tumor suppressor genes. ROS, as a common proliferative and apoptotic convergent point, regulate the biological behaviors subtly in terms of different cellular environments.

Accordingly, as mentioned above, zinc(II) induced PCa prevention and PCa suppressive progressing with Stage 1 (Malignant formation and proliferation), Stage 2 (Local invasion and regional lymph nodes), and Stage 3 (Bone and bone marrow metastasis, angiogenesis) can be summarized in Table 1.

Zn^{2+} ions	PCa Prevention	PCa Stage 1 • Primary tumor • Malignant tumor • Tumor proliferation	PCa Stage 2 • Invasiveness and migration • Local invasion, regional lymph nodes	PCa Stage 3 • Metastasis • Bone and bone marrow metastasis • Angiogenesis
$Zn^{2+} \rightarrow$	$\rightarrow Zn^{2+}$ • Zinc induced inhibitory and suppressive effects on tumor cell and progression of prostate malignancy for PCa prevention • Zinc can modulate anti-tumor efficacy of therapeutic agents • Adequate zinc status helps to prevent PCa as a vital anti-benign prostate hyperplasia (BPH), anti-PCa agent	$\rightarrow Zn^{2+}$, ROS • $ZnCl_2$(0~300μM); suppresses growth tumor cell • Zn (100~1000ng/mL); PCa cell growth inhibition, preventive PCa progressing • Zn^{2+}10 M reduces PCa cell proliferation, oxidative stress • Zn^{2+} concentration (1000 ng/mL); highest PCa growth inhibition	$\rightarrow Zn^{2+}$, ROS • Zn induced invasive and migratory effects • Zn ligands containing 20 μM Zn increases accumulation of zinc and cytotoxic effect in PCa regional lymph nodes • Zinc, zinc transporters, and ZIPs1 can suppress tumor growth, invasive and migratory tumor malignant cell, and regional lymph nodes	$\rightarrow Zn^{2+}$, ROS • ZEX knockdown inhibits PCa cell growth and metastasis • MAZ regulates PCa bone metastasis • Intracellular zinc levels can inhibit metastatic malignant cells through suppressive NF-κB • Zinc, MMPs, and ZMYND8 promote tumor anti-angiogenesis

Table 1: Zinc induced oncological suppressive effects for prostate cancer prevention and development with prostate cancer stages 1~3

Zinc coordinated molecular apoptosis mechanism in PCa cells Zinc has apoptogenic effects for inflammation, proliferation, invasiveness and migration, metastasis, angiogenesis, and oxidative damage of proteins in PCa cells. These zinc coordinated molecular apoptosis mechanism is involved that Zn^{2+} ions is liable to bind with each cancer proteins, in which Zn2+ ions having Zn^{2+} ions-centered tetrahedral geometric coordination pattern bind with each PCa stage cancer tumor proteins, causing Zn^{2+} ions-several protein complex formation, oxidative stress, and apoptosis of PCa cells, leading to molecular apoptosis of prostate cancer tumor cells.

Conclusions

Zinc(II) induced suppressive tumor cell on prostate cancer prevention and prostate cancer development with prostate cancer Stage 1, Stage 2, and Stage 3 are investigated, subsequently, the zinc-ions binding prostate anti-cancer molecular mechanism is clarified.

For PCa prevention, adequate dietary zinc intake status can prevent the prostate cancer disease through restoration of high zinc levels, protective preventative PCa progressing, and using inhibitory effects on the progression of prostate malignancy and suppressive tumor.

At PCa Stage 1, zinc can inhibit proliferation PCa cell growth, proliferation, and can prevent PCa progressing that Zn^{2+} ions can diminish AR, PCNA, proliferation index, and can gain intrinsic stability effect for BPNSs by chemo-photo thermal therapy.

At PCa Stage 2, zinc suppresses the progression of PCa by proliferation, migration, and invasiveness that zinc is confirmed to function as a tumor suppressor in PCa cells, in which zinc, zinc transporters, and zinc and ZIP1 can suppress tumor growth, invasive and migratory tumor malignant cell, and regional lymph nodes in PCa cancer.

At PCa Stage 3, metastatic prostate cancer is composed of proliferation, neovascularization, extravasation, and bone or bone marrow metastasis that MAZ regulates PCa bone metastasis, intercellular zinc levels inhibit metastatic and angiogenic malignant cells, and zinc, MMPs, ZMYND8 inhibit tumor angiogenesis.

Zinc induced ROS generation in PCa tumor cells is causes inflammation, proliferation and growth, and oxidative stress.

Zinc coordinated molecular apoptosis mechanism is involved that Zn^{2+} ions having Zn^{2+} ions-centered tetrahedral geometric coordination pattern bind with each PCa stage cancer tumor proteins, causing Zn^{2+} ions-several protein complex formation, oxidative stress, and apoptosis of PCa cells, leading to molecular apoptosis of prostate cancer tumor cells.

Conflicts of Interest

Author declares there is no conflicts of interest.

Sources of Funding

No source funding by author own's expense.

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