

Zinc(II) Mediated Suppressive Prostate Cancer for Progression with Stages 1~3, and Zinc Ions-Coordinated Prostate Anti-Cancer Molecular Mechanism

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Abstract

Zinc(II) induced prostate cancer (PCa) suppressive development Stage 1, Stage 2, and Stage 3 have been investigated, the PCa anticancer activity and apoptosis molecular mechanism is subsequently elucidated on the basis of anti-cancer activities of Zn-CysHis Ligands complexes formed by zinc ions-coordinated tetrahedral geometry.

For the PCa Stage 1, zinc can prevent PCa progressing, inhibit PCa cell growth and proliferation, and lead to apoptogenesis that zinc concentration (100~1000 ng/mL) can prevent the PCa progressing, ZnCl₂(0~300 μM) regulates as a negative growth for PCa cells, 10, 20 mg/kg ZnCl₂-treated prostate cancer tumors can be diminished, and zinc (15 μM) increases the Bax-associated mitochondrial pore Bax/Bcl-2 ratio, leading to apoptotic effect.

For 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.

For 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 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, leading to apoptotic tumor cells.

Zinc coordinated anticancer and apoptosis molecular mechanism in PCa cells is involved that Zn²⁺ ions having Zn²⁺ ions-centered Zn-CysHis Ligands complexes with tetrahedral geometry bind with each other PCa stages tumor proteins, causing Zn²⁺ ions-several protein complexes formed and apoptosis of PCa cells, leading the Zn-CysHis Ligands complexes to molecular anti-cancer activities and apoptosis for 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; Zn-CysHis ligands complexes

Introduction

Prostate cancer (PCa) is most common among men with an aged-related malignancy having a cellular senescence in man that 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 with angiogenetic effect [1]. PCa angiogenesis in 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 [2]. The other, zinc(II) ions have important anti-cancer effects for cancer tumor cells of malignant proliferation, local invasion, and metastasis [3]. 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 [4]. Zinc also 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].

Adequate dietary zinc intake status can prevent the prostate cancer disease through restoration of high zinc levels, protective preventative PCa progressing, and by using chemotherapeutic agents such as a vital anti-benign prostate hyperplasia (BPH), anti-PCa agents [6]. In PCa patients, plasma zinc level is mild-moderate disease $10.49 \pm 2.89 \mu\text{mol/L}$, severe disease

$7.64 \pm 2.33 \mu\text{mol/L}$, advanced disease $6.98 \pm 1.97 \mu\text{mol/L}$ 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 [7]. In this semi-review article, zinc(II) induced prostate cancer suppressive development with prostate cancer Stage 1, Stage 2, and Stage 3 are investigated, the PCa anticancer and apoptosis molecular mechanism is subsequently elucidated on the basis of anti-cancer activities for zinc-ions coordinated Zn-CysHis Ligands complexes formation.

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, neovascularization, local invasion and the migration, regional lymph node, and metastases [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); The tumor has spread to nearby tissues, lymph nodes or other organs of the body, beyond the outer layer. In addition, PCa angiogenesis process has tumor growth and angiogenetic progression that anti-angiogenesis therapy may be elucidated in the treatment of PCa [9].

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, bone marrow metastasis, and angiogenesis in PCa tumor growth progression.

Zinc induced prostate PCa initial Stage 1 with tumor malignant cell

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 [10].

In the PCa Stage 1, zinc can inhibit proliferation of PCa cell that zinc suppresses the expression androgen receptor (AR), prostate specific antigen (PSA), and the proliferating cell nuclear antigen (PCNA), and then ZnCl_2 ($0 \sim 300 \mu\text{M}$) functions as a negative growth

regular for (AR(+)) PCa cells and proliferation index can be diminished by 10, 20 mg/kg ZnCl_2 -treated prostate cancer tumors can be diminished [11]. Zinc concentration ($100 \sim 1000 \text{ ng/mL}$) can prevent the PCa progressing and inhibit PCa cell growth [12]. Zinc exists a state of Zn^{2+} dyshomeostasis in prostate cell that $10 \mu\text{M}$ Zn^{2+} reduces PC3 cell proliferation and induces HIF1 α in normal HK-2 renal tubular cells and PC3 cell survival under oxidative stress [13]. Zinc regulates proliferation and growth, apoptogenesis in prostate cancer cells that zinc ($15 \mu\text{M}$) increases the Bax-associated mitochondrial pore forming process and cellular production, and the Bax/Bcl-2 ratio, leading to apoptotic effect [14]. Zn^{2+} induced coordination's can gain intrinsic stability effects for black phosphorus nanosheets (BPNSs) through chemo-photo thermal therapy [15]. Thus, in PCa Stage 1, zinc can prevent PCa progressing, inhibit PCa cell growth and proliferation, and lead to apoptogenesis that zinc concentration ($100 \sim 1000 \text{ ng/mL}$) can prevent the PCa progressing, ZnCl_2 ($0 \sim 300 \mu\text{M}$) functions as a negative growth regular for PCa cells, 10, 20 mg/kg ZnCl_2 -treated prostate cancer tumors can be diminished, and zinc ($15 \mu\text{M}$) increases the Bax-associated mitochondrial pore Bax/Bcl-2 ratio, leading to apoptotic effect.

Zinc induced PCa moderate Stage 2 with local invasion and migration, and regional lymph node

In the 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 [1]. The significant heterogeneity of lymph node metastasis (LNM) in PCa luminal and interstitial cells contributes to tumor progression and results in tumor microenvironment (TME) 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 [16]. Zinc such as $50\text{-}150 \mu\text{M}$ zinc acetate and zinc transporters such as ZIP1 protein can suppress the proliferation, migration and invasion of PCa cells that zinc and zinc

transporters can inhibit the PSA and uPA activities, the proliferation, the invasion of LNCaP cells and overexpression of ZIP1 reduced cell growth and invasion by inhibition of NF- κ B activity, in which the intake of Zinc 15 mg/day may be beneficial for advanced PCa [17]. 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 μ M Zn) increases accumulation of zinc and its cytotoxic effects in PCa regional lymph nodes [18]. 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 [19]. Zinc may suppress invasiveness and adherence in PCa cells that zinc concentration (0.12-0.5 μ g/ml) suppresses pro-angiogenic and pro-metastatic reduced invasiveness of highly invasive PC-3 cells [20]. Thus, in 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 metastasis and angiogenic tumor growth Stage 3

In the PCa Stage 3, metastasis characters are migration accompanying 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 [21].

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 (Tumor, Lymph nodes, Metastasis) stage, is negatively correlated with post-operative survival, suggesting that high ZFX expression is a risk factor [22]. Myc-associated zinc-

finger protein (MAZ) regulates PCa bone metastasis [23]. Up-regulation of intracellular zinc levels can inhibit the PCa metastatic and angiogenic malignant cells that the suppressive effect of zinc on the metastatic and angiogenic potentials of PCa cells is mediated through the inhibition of specific pathways regulating progression of prostate cancer [20]. Zinc finger MYND-gene type containing 8 (ZMYND8) knockdowns suppressed angiogenesis that ZMYND8 is suitable drug target for inhibition of tumor angiogenesis [24]. 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 [25]. Thus, in 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 ZMYND8 inhibits 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 [26]. Zinc increases production of ROS and hydroxyl radicals, resulting in a 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 [27]. 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 [28].

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, metastasis and angiogenesis. 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.

Zinc(II) coordinated anti-cancer and apoptosis PCa molecular mechanism in PCa tumor cells

Zinc(II) has apoptogenic effects for inflammation, proliferation, invasiveness and migration, metastasis, angiogenesis, and oxidative damage of proteins in PCa cells. Zinc(II) (Zn^{2+} ion) is liable to bind with each cancer proteins that Zn^{2+} ions having Zn^{2+} ions-centered tetrahedral geometric coordination pattern binds with each PCa stage cancer tumor proteins. Zinc coordinated molecular apoptosis for zinc-based anticancer drugs with the cellular redox homeostasis and considering chemical properties of the respective anticancer metal complexes currently either in clinical routine in oncology.

Zn(II) complex has great therapeutic potential and identifies the mechanisms of apoptotic cell death and to reduce the toxicity of Zn(II) complex on control cells that these Zn-CysHis Ligands complexes formations play an important role in anticancer metal-based drugs such as antitumor efficacy, inhibition of

migration and invasion activities, and cell senescence [29]. Structural zinc sites typically consist of four Cys and/or His ligands that Zn-CysHis Ligands complexes with tetrahedral geometry are formed by zinc binding of CysHis type Zn-protein [30]. Zinc complexes comprising Nitrogen-donor Ligands in Zn complexes are important as anti-cancer agents that zinc can coordinate various donor atoms and zinc complexes comprising N-donor ligands are very effective as anticancer agents [31].

Therefore, this 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 these Zn-CysHis Ligands complexes to molecular anti-cancer activity and apoptosis of prostate cancer tumor cells. Accordingly, as mentioned above, zinc(II) induced suppressive PCa progressing with Stage 1 (Malignant formation and proliferation), Stage 2 (Local invasion and regional lymph nodes), and Stage 3 (Bone and bone marrow metastasis, anti-angiogenesis), and zinc coordinated anticancer activities and apoptosis molecular mechanism in PCa cells can be summarized in Table 1.

Table 1: Zinc induced anti-proliferative, anti-invasive, and anti-metastatic functional activities for PCa suppressive development with PCa Stages 1~3, and the zinc coordinated PCa anticancer and apoptosis molecular mechanism in PCa tumor cells

Zn^{2+} ions	PCa Stage 1 Primary tumor, Tumor proliferation, Malignant tumor	PCa Stage 2 Invasiveness and Migration, Local invasion, Regional lymph nodes	PCa Stage 3 Metastasis, Bone and bone marrow, Meta-stasis with angiogenesis
Zn^{2+} 	 Zn^{2+} , ROS • ZnCl ₂ (0~300 μ M) suppresses growth tumor cell • Zn (100~1000 ng/mL) inhibits PCa cell growth, prevents PCa progressing • Zn^{2+} 10 M reduces PCa cell proliferation, oxidative stress • Zn^{2+} concentration (1000 ng/mL); highest PCa growth inhibition	 Zn^{2+} , ROS • Zn induced invasive and migratory effects • Zn ligands containing 20 μ M Zn increase 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	 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- κ B • ZMYND8 promotes tumor anti-angiogenesis
Zinc coordinated PCa anticancer and apoptosis molecular mechanism in PCa cells; Zn^{2+} ions that having Zn^{2+} ions-centered tetrahedral geometric coordination pattern, bind with each other PCa stages cancer tumor proteins, causing Zn^{2+} ions-several protein complex formation, oxidative stress, and apoptosis of PCa cells, leading the Zn-CysHis Ligands complexes to the molecular anticancer activities and apoptosis in prostate cancer tumor cells.			

Conclusions

Zinc(II) induced prostate cancer suppressive development with prostate cancer Stage 1, Stage 2, and Stage 3 are investigated, the PCa anticancer and apoptosis molecular mechanism is subsequently elucidated on the basis of anti-cancer activities of the Zn-CysHis Ligands complexes formed by zinc-ions coordinated tetrahedral geometry. For the PCa Stage 1, zinc can prevent PCa progressing, inhibit PCa cell growth and proliferation, and lead to apoptogenesis that zinc concentration (100 ~ 1000 ng/mL) can prevent the PCa progressing, ZnCl₂ (0 ~ 300 μM) regulates as a negative growth for PCa cells, 10, 20 mg/kg ZnCl₂-treated prostate cancer tumors can be diminished, and zinc (15 μM) increases the Bax-associated mitochondrial pore Bax/Bcl-2 ratio, leading to apoptotic effect. For the 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. For the 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 ZMYND8 inhibits tumor angiogenesis. Zinc induced ROS generation in PCa tumor cells is causes inflammation, proliferation and growth, and oxidative stress. Zinc(II) coordinated anti-cancer and apoptosis molecular mechanism has been subsequently elucidated that Zn²⁺ ions which having Zn²⁺ ions-centered tetrahedral geometric coordination pattern and Zn-CysHis Ligands complexes with tetrahedral geometry formed, bind with each PCa stage cancer tumor proteins, causing Zn²⁺ ions-several protein complex anti-cancer drugs and oxidative stress to PCa cells, leading the Zn-CysHis Ligands complexes to molecular anticancer activities and apoptosis of prostate cancer tumor cells.

Abbreviations

ADT=androgen deprivation therapy
AR=androgen receptor
BAX=Bcl-2-associated X protein
BPH=benign prostate hyperplasia
BPNs=black phosphorus nanosheets
LNCaP=human prostate tumor cell line

LNM=lymph node metastasis
MAZ=Myc associated zinc-finger protein
NF-κB=nuclear factor-kappa B
NOXs=NAD(P)H oxidase
PCa=prostate cancer
PCNA=proliferating cell nuclear antigen
PSA=prostate specific antigen
PTX=paclitaxel
ROS=reactive oxygen species
SASP=senescence-associated secretory phenotype
TME=tumor microenvironment
TNM=Tumor, Lymph nodes, Metastasis
TRAMP=transgenic adeno-carcinoma of the mouse prostate
VEGF-A=vascular endothelial growth factor A
ZFX=Zinc finger protein X-linked
ZIPs=ZRT-and Irt-like proteins
ZMYND8=Zinc finger MYND-type containing 8

Declarations

Conflicts of Interest

Author declares there is no conflicts of interest.

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