Zinc Signaling in Prostate Cancer

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Prostate cancer (PCa) is one of the most common cancers and the second leading cause of cancer-related death among men worldwide. Despite progresses in early diagnosis and therapeutic strategies, prognosis for patients with advanced PCa remains poor. Therefore, it is necessary to develop novel strategies to prevent, diagnose and effectively treat PCa patients in clinic. Noteworthily, a unique feature of healthy prostate is its highest level of zinc content among all soft tissues in the human body, which dramatically decreases during prostate tumorigenesis. Here, we discuss clinical applications of zinc-containing compounds and proteins involved in PCa signaling pathways. Based on currently available studies, we conclude that zinc can serve as a biomarker in PCa diagnosis and therapies.

Keywords: zinc signaling ; prostate cancer ; zinc transporter ; zinc finger ; diagnosis ; immunotherapy

1. Introduction

Significantly decreased zinc levels during prostate malignancy implicated its activities in inhibiting proliferation and metastasis of tumor cells and inducing cell death, which led to the development of zinc or its related compounds in diagnostic and therapeutic applications of PCa. Due to the controversies and inconsistent results regarding the effects of zinc supplementation on PCa among different laboratory research and epidemiologic studies[1][2][3][4][5][6][7][8], we will mainly discuss the applications of zinc and its associated proteins as they relate to clinical diagnosis of PCa in this section. Additionally, we will comment on immunotherapies targeting zinc signaling.

2. Clinical Applications of Zinc Signaling in PCa

In the clinic, currently prevailing tests of PCa diagnosis can be divided into two categories: traditional and modern methods. The traditional methods include digital rectal examination and blood PSA tests, while modern methods embrace targeted magnetic resonance imaging (MRI), ultrasound fusion prostate biopsy and conventional radiological imaging[9][10][11]. Each approach may have its own disadvantages in specificity, invasiveness or targeting accuracy, which restricts its applications to patients with specific types or stages of the disease[12][13].Fortunately, PCa is the only known prostatic disease associated with a substantial decrease of zinc levels[14]; neither prostatitis nor BPHexhibit this phenomenon[12][15], suggesting that zinc serves as an excellent candidate biomarker for PCa. Indeed, based on synthetic images generated from clinical data of zinc distributions, zinc-baseddiagnostics could represent an approach superior to the serum PSA test[13][16]. Recently, several groups developed in vivo imaging strategies to simultaneously probe zinc presence and detect PCa progression[12][13][17][18][19]. Ghosh et al. employed a novel fluorescent zinc sensor ZPP1 that could precisely bind two zinc ions to monitor cell malignant transformation in the TRAMP model and observed tumor progression related to decreasing fluorescence intensity in an age-dependent manner. This study is the first report of using altered zinc levels as an innate imaging biomarker for early PCa detection[13][20]. Due to the limitations of optical imaging[12], several groups attempted to optimize zinc measurement using MRI in the following years. Jordan et al. discovered a zinc-binding gadolinium using a paramagnetic contrast agent and used it to detect extracellular zinc by proton MRI following glucose-stimulated zinc secretion. This strategy let them differentiate healthy versus malignant mouse prostates, which could provide a novel and highly specific approach for PCa diagnosis[17]. More recently, using MRI based on 19F ion chemical exchange saturation transfer (iCEST) and TF-BAPTA as a fluorinated zinc probe, Yuan et al. was able to discriminate normal and malignant prostate cells with a 10-fold higher sensitivity than the method based on glucose-stimulated zinc secretion. The iCEST-MRI allowed them to observe over 300% gradual zinc decrease in the in vivo transition of normal PrECs to cancer cells[12]. This study is the first attempt to use the 19F iCEST-MRI as a diagnostic tool for in vivo zinc imaging. Since both iCEST and 19F MRI are clinically used, this approach possesses high translational potential for clinical diagnosis of PCa. Despite these promising research and preclinical data, further exploration needs to focus on developing zinc detection strategies with high specificity, sensitivity, and economic advantage to achieve early PCa diagnosis.

Noteworthily, decreased intraprostatic zinc levels generally coincide with significantly reduced expression of the zinc transporters ZIP1, ZIP2, ZIP3 and ZIP4, which represents an early step in PCa development[1][12][21][22][23]. Based on the impacts of altered expression of these zinc transporters on PCa cell growth and metastasis, the expression levels of ZIP1, ZIP2, ZIP3 and ZIP4 genes may also serve as potential biomarkers for early PCa diagnosis. Additionally, among the upstream regulators of ZIP1 (RREB-1 and microRNA-183-96-182), the proteins modulating key zinc signaling pathways (NF-κB, PI3K and MAPK), and ZF-containing TFs (AR, PLZF and SP1), many of them have been evaluated as or determined to be potential assistant biomarkers for PCa diagnosis. In our opinion, zinc status and the genes involved in zinc homeostasis could serve as an adjunctive measure to the traditional and modern methods of PCa diagnosis.

In the past decade, immunotherapy has proven to be an effective approach in the treatment of multiple cancer types, especially melanoma and non-small cell lung cancer[24][25][26]. For PCa, immunotherapies using immune checkpoint inhibition, PSA vaccines and dendritic cell-based strategies have been intensively tested in clinical trials[27]. Ample evidence demonstrated zinc's contribution to the maintenance of host systemic immune system, and thus, its moderate levels could decrease inflammation and oxidative stress[28][29][30][31]. Generally, zinc at its physiological levels is essential to the growth, differentiation and biological function of various immune cells, including macrophages, dendritic cells, neutrophils, mast cells, T cells and B cells[32][33][34][35][36][37]. On the other hand, zinc deficiency leads to impaired immune response and an increased risk of inflammation and tumorigenesis[29][33][38]. Consistently, moderate zinc supplementation can restore or even improve host defense and reduce both morbidity and mortality of various diseases, including cancers[39][40][41]. Therefore, targeting zinc signaling to prevent immune escape of tumor cells and promote immune cells to eradicate cancers represents a logical and promising strategy in the treatments of PCa patients. However, due to the high complexity of the immune microenvironment and high heterogeneity of antitumor immune responses[27][42][43], the application of targeting zinc signaling in immunotherapies has not been tested in either preclinical models or the patients of PCa.

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