REVIEW

Zinc and metallothionen in prostate cancer: A review

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Zinc is an essential and the second most abundant trace element in humans. Zinc is a structural component of different proteins involved in the transcriptional machinery, such as transcription factors and ribosomes and the presence of zinc is also necessary for DNA synthesis. Zinc not only improves cell mediated immune functions but also functions as an antioxidant and anti-inflammatory agent. Oxidative stress and chronic inflammation have been implicated in development of many cancers. Various types of tumor cell lines have been used to investigate the cellular effects of zinc ions and its connection with metallothioneins (MTs). Dietary zinc deficiency is associated with oxidative stress in the reproductive organs with consequent decline in MTs levels indicative of association of MTs expression and apoptosis and perturbation of homeostatic zinc level. Treatment of prostate cancer with zinc causes an increase in MTs expression, which is significantly associated with resistance to cisplatin chemotherapy and radiotherapy in prostate cancer. We review the role and recent advances of zinc and MTs in prostate cancer in the last years.

Keywords: Zinc; metallothionein; cancer; prostate cancer

1. Zinc in medicine

Zinc is the second most common trace metal in the human body. It is involved in numerous aspects of biology cellular, zinc is known to be an essential component of DNA-binding proteins with zinc fingers, as well as copper/zinc superoxide dismutase and several proteins involved in DNA repair. Thus, the zinc plays an important role in immune function, protein synthesis, DNA synthesis and cell division [1, 2]. The role of zinc in cancer has received increasing attention in last years. Dietary deficiencies in the intake of zinc can contribute to oxidative modifications to DNA that increase risk for cancer development [3, 4]. Various types of cancer have been used to investigate the cellular effects of zinc ions and its connection with MTs [5]. MTs are low weight proteins involved in several key cellular processes such as metal ions homeostasis, detoxification and scavenging of free radicals [5, 6]. In humans, MTs are encoded by 17 genes, from which thirteen code for MT-1, two for MT-2 and one gene each codes for MT-3 and MT-4 [7, 8]. MTs were shown to protect cells against oxidative stress damage and participate in differentiation, proliferation and apoptosis of normal and cancer cells [9]. Their altered mRNA expression has been correlated with metal toxicity and a variety of cancers. The different MTs genes have been found in normal human prostatic tissue. Different studies showed the relationship between the gene expression of MTs and the cellular zinc homeostasis in relation to the diseases of the prostate and the potential of MTs as a candidate biomarker for prostate cancer and the utilization of zinc in prostate cancer prevention and treatment [10, 11]. For this reason, we show in this review an overview the importance of the regulation of zinc and/or relationship with the MTs in prostate cancer in recent years.

2. Zinc in medicine

Zinc is an essential and the second most abundant trace element in humans. It is critical for the growth, development and differentiation of cells, as well as for RNA transcription, DNA synthesis, cell division and cell activation [12]. The major manifestations of zinc deficiency include growth retardation, hypogonadism in males, cell-mediated immune dysfunctions, rough skin, hyperammonemia and cognitive impairment. Zinc is a structural component of different proteins involved in the transcriptional machinery, such as transcription factors and ribosomes and the presence of zinc is also necessary for DNA synthesis. Furthermore, zinc is a second messenger of mitogenic signaling [13]. Zinc also plays an important role in synaptic function. At cellular level, zinc is a modulator of synaptic activity and neuronal plasticity in both development and adulthood [14]. Zinc has many beneficial roles in normal growth and development, cellular homeostasis, cell survival, and numerous biochemical functions, including protein synthesis, gene expression, and nucleic acid metabolism [15, 16]. Zinc deficiency affects cells involved in both innate and adaptive immunity at the survival, proliferation and maturation levels. These cells include monocytes, polymorphonuclear-, natural killer-, T-, and B-cells. T cell functions and the balance between the different T helper cell subsets are particularly susceptible to changes in Zinc status [17]. Zinc affects the monocytes/macrophages in several ways. Zinc is required for the development of monocytes/macrophages and regulates their functions such as phagocytosis and proinflammatory cytokine production. LPS stimulation of zinc sufficient monocytes results in down-regulation of inflammatory cytokines such as TNF, IL-1, IL-6 and IL-8 [18, 19, 20, 21, 22]. Zinc deficiencies occur due to malabsorption syndromes and other gastrointestinal disorders, chronic liver and renal diseases, sickle cell disease, malignancy, cystic fibrosis, pancreatic insufficiency, rheumatoid arthritis and other chronic conditions [23]. Several other diseases including infectious diseases, cancer, chronic diseases such as bronchial asthma and Alzheimer disease, skin lesions, growth retardation, impaired wound healing, anemia, mental retardation which were observed even in mild zinc deficiency and/or alterations in zinc status [24, 25]. Zinc has a key role in apoptosis regulation. Zinc chelation in cell culture medium causes apoptosis and subsequent addition of Zinc protects cells against the undergoing apoptosis even if it was added to the cell culture only a short time after an apoptotic agent [26].

Beneficial therapeutic response of zinc supplementation has been observed in the diarrhoea of children, chronic hepatitis C, shigellosis, leprosy, tuberculosis, pneumonia, acute lower respiratory tract infection, common cold, and leishmaniasis [27, 28]. Zinc supplementation was effective in decreasing incidences of infections in the elderly, in patients with sickle cell disease (SCD) and decreasing incidences of respiratory tract infections in children. Zinc supplementation was effective in decreasing oxidative stress and generation of inflammatory cytokines such as TNF-alpha and IL-1 beta in elderly individuals and patients with SCD [20, 29, 30].

3. Zinc in cancer prevention

Zinc not only improves cell mediated immune functions but also functions as an antioxidant and anti-inflammatory agent. Oxidative stress and chronic inflammation have been implicated in development of many cancers [31]. The role of zinc in cancer has received increasing attention. In patients with head and neck cancer, Prasad et al showed that nearly 65% of these patients were zinc deficient based on their cellular zinc concentrations. Natural killer (NK) cell activity and IL-2 generation were also affected adversely. Th2 cytokines were not affected. In these patients, zinc status was a better indicator of tumor burden and stage of disease in comparison to the overall nutritional status. NF-κ B is constitutively activated in many cancer cells, and this results in activation of antiapoptotic genes, VEGF, cyclin DI, EGFR, MMP-9 and inflammatory cytokines. Zinc inhibits NF-κ B via induction of A-20 [32]. Increased amounts of zinc transporter LIV-1 (SLC39A6) are present in estrogen receptor–positive breast cancer

and in tumors that spread to lymph nodes. The LIV-1 subfamily of ZIP zinc transporters consists of nine human sequences. It is a highly conserved group of eight transmembrane domain proteins, which are situated on the plasma membrane and which are responsible for zinc transport into cells. LIV-1 has been used as a reliable marker of luminal A type clinical breast cancer [33]. In different publications there has been showed the concept that zinc is involved in the pathogenesis of prostate cancer (PCa); and that zinc could be efficacious in the prevention and treatment of prostate cancer [34, 35].

4. Zinc and metallothionein in cancer

MT has been found to be involved in apoptosis, immunomodulation, transcription regulation, cell proliferation, and activation of enzymes via administration of zinc to the proteins [36]. In Figure 1, we show schematic representation of the MTs functions. Many of these interactions are driven by zinc(II) ions. Disturbing of zinc homeostasis can lead to formation of reactive oxygen species, which can result in oxidative stress causing alterations in immunity, aging, and civilization diseases, but also in cancer development [5]. Various types of tumor cell lines have been used to investigate the cellular effects of zinc ions and its connection with MTs. The human genome contains at least 11 functional MTs genes that may be divided into four subgroups (MT1-4). Given their stress--inducible nature and their capacity to chelate toxic metals and electrophiles, many studies have proposed MTs expression to confer resistance to many toxic drugs [37, 38]. Several lines of evidence indicate that MTs may play a role in various carcinogenic processes, as high levels of MT expression have been reported in association with progressive disease and poor prognosis in several tumors [39, 40]. Han et al showed by microarray and validation analyses that MT1H, is down-regulated in many human malignancies. Low expression of MT1H was associated with poor clinical outcomes in both prostate and liver cancer. The promoter region of MT1H was hypermethylated in cancer and that demethylation of the MT1H promoter reversed the suppression of MT1H expression [41]. A number of studies have demonstrated altered MT2A expression in various human tumors, including prostate cancer. Forma et al conducted an association study to examine whether MT2A gene polymorphisms are associated with a risk of prostate cancer. They suggested

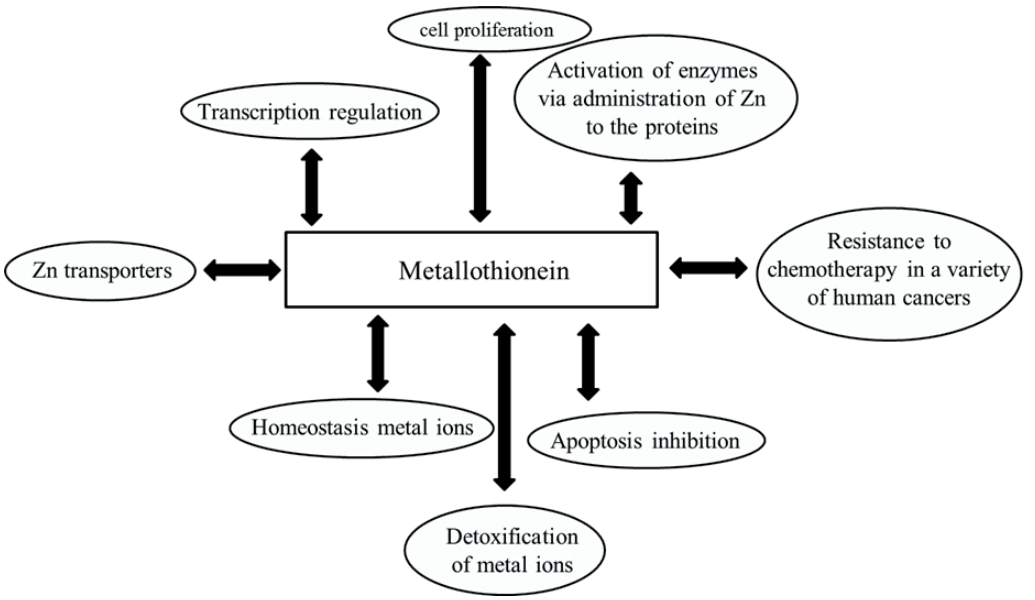

Figure 1: Schematic representation of the MTs functions

that the gen polymorphism rs28366003 SNP in MT2A is associated with the risk of prostate cancer in a Polish population [42].

4.1. Metallothionein and zinc in prostate cancer

Dietary zinc deficiency is associated with oxidative stress in the reproductive organs with consequent decline in MTs levels [43] indicative of association of MTs expression and apoptosis and perturbation of homeostatic zinc level [44]. Several reports have demonstrated MTs overexpression to be a useful prognostic factor for tumor progression and implicated in causing resistance to chemotherapy in a variety of human cancers [45, 46]. MTs are evaluated as trace metal-responsive genes. The different MTs genes have been found in normal human prostatic tissue. MTs protein in the normal human prostate is supported by transcription of mRNA from the MT-1A, MT-1E, MT-1X, and MT-2A genes. Expression of MT-1X mRNA is down-regulated in advanced prostate cancer [47]. Treatment of prostate cancer with zinc causes an increase in MT expression, which is significantly associated with resistance to cisplatin chemotherapy and radiotherapy in prostate cancer and the effect of MTs induction by zinc on resistance to radiotherapy and cisplatin treatment in prostate cancer cells, which may provide unique opportunities to manipulate the cellular events in a prostate cell [48]. Gumulec et al showed also provided evidence of the association between MT expression and prostate tumor progression [49]. Hlavna et al showed that significantly increased microRNA levels, are a large class of single-stranded RNA molecules involved in post-transcriptional gene silencing, of MT2A isoform in tumor cell lines. Contrary to mRNA, significantly reduced level of MTs protein in tumor lines was observed. None of the miRNA analyzed here correlated with MT mRNA level after zinc treatment in the prostate cell lines. It can be assumed according to results that miRNAs act differently in each cell line [50]. The disturbance of zinc homeostasis featured with a significant decrease of cellular zinc level was well documented to associate with the development and progression of human prostate malignancy. Hua Wei et al showed for the first time provided new evidence on zinc regulation of MTs gene expression and elucidated the relationship between the gene expression and the cellular zinc homeostasis in relation to the pathogenesis status of the prostate tissues [10]. The expression of MTs genes was induced by zinc and cadmium in the RWPE-1 and BPH-1 human prostate epithelial cell lines the human prostate gland has low basal expression of the MT-1 and MT-2 proteins. In prostate cancer, MTs protein expression is variable and correlates directly with the increasing Gleason score of the tumor. Albrecht et al showed that the RWPE-1 cells may be a valuable system to define the interplay that occurs between zinc concentration, cadmium exposure, citrate and MT in the normal and malignant prostate epithelial cell [51].

5. Conclusion

Zinc ions contribute to a number of biological processes. Disturbing of zinc homeostasis can lead to formation of reactive oxygen species, which can result in oxidative stress causing alterations in immunity, aging, and civilization diseases, but also in cancer development. It is clear from literature that zinc is of extraordinary and diverse importance in cancer biology. MTs may play a role in various carcinogenic processes, as high levels of MTs expression have been reported in association with prognosis in several tumors. This review reports on the roles of zinc in differential regulation of MTs gene expression in human prostate normal and malignant cell lines. We believe that this review delivered important insight to a new field of research on zinc and its roles in the prevention and intervention of prostate cancer. It is however still necessary to clarify the ambiguity of the association between MTs staining and prostate tumors.

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Conflicts of Interest

The authors declare no conflict of interest.

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