
Zinc: What Is Its Role in Lung Cancer?

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Abstract

Recently, zinc emerged as an important signaling molecule, activating intracellular pathways and regulating cell fate, although our knowledge remains incomplete. Zinc is required in many enzymatic and metabolic pathways, playing roles as enzyme cofactors. In normal cell physiology, optimal zinc availability is essential for regular growth and proliferation. Zinc accumulation has varied effects: from stimulation to inhibition of cell growth, depending on type. There is evidence that zinc is capable of inducing apoptosis in some cancers, while others proved that zinc may act as apoptosis activator depending on the dose and cell type. Upregulation of telomerase in most cancer tissues is considered to be responsible for unlimited proliferation of cancer cells, and in some cell lines, it was induced by Zn. These suggest that Zn is highly involved in cell cycle and metabolism; whether it goes to the survival or the cancer pathway depends on the concentration and the cell type involved. Nevertheless, the conclusion is that Zn is not just another trace element; but a vital one and further studies are needed to elucidate the mechanisms involved in cancer and metastatic spread in order to identify potential therapies.

Keywords: functions of zinc, zinc deficiency, high concentration of zinc, cancer, zinc, lung cancer, deficiency, homeostasis

1. Introduction

Zinc is one of the most important trace elements in the body. It has a catalytic/regulatory role in many enzymes, maintains the structural integrity of different proteins, and modulates protein-protein interactions. At the cellular level, zinc is essential for cell proliferation and

survival, contributes to genomic stability and antioxidant defense, which highlights its crucial role in aging and age-dependent degenerative diseases. Zinc is indispensable for proper immune function, its insufficiency may exacerbate immune-senescence, and zinc supplementation is beneficial to immune responses in the elderly [1]. In the intracellular environment, zinc interacts with signal transducers implicated in immune response and influences both the structural stability and function of immunologically relevant transcription factors [2]. Zinc is needed for DNA synthesis, RNA transcription, cell division, and cell activation. Programmed cell death (apoptosis) is potentiated in the absence of adequate levels of zinc under physiological conditions [3].

During the past four decades, a spectrum of zinc clinical deficiencies in human subjects has emerged. On one hand, the manifestations of zinc deficiency (ZD) may be severe, and on the other end of the spectrum, ZD may be mild or marginal [3]. Micronutrient deficiencies are an important and global public health problem. In Mexico, the first comprehensive picture of the frequency and distribution of micronutrient deficiencies was presented by the Mexican National Nutrition Survey of 1999. Zinc deficiency was the second most common micronutrient deficiency; 34% of which was found in infants [4]. Several studies have now confirmed that ZD is fairly prevalent in developing countries, affecting nearly two billion subjects and that growth retardation commonly observed in these countries may indeed be due to ZD [5]. Increased prevalence of obstructive lung disorders and lung cancer is associated with low dietary Zinc (Zn) intake and thought to be due, at least in part, to protective effects of Zn against cadmium, which is toxic and accumulates in alveolar macrophages (AM). Among the actions of Zn ions on the immune system are its effects on phagocytic cells. Hamon and colleagues [6] suggested links between lung injury, impaired phagocytosis, and Zn deficiency. In the bloodstream, zinc insufficiency may also contribute to cardiovascular risk via its association with reduced antioxidant capacity [7], endothelial dysfunction [8], arterial wall stiffness, and increased systolic blood pressure [9, 10].

The use of zinc as a nutritional supplement has become very common in many countries. However, adverse effects of high doses of zinc supplement on immunologic functions have not been clearly defined. Some studies from animal models show that high dietary zinc increased the functions of T lymphocytes and macrophages [11, 12]. Other studies reported a decrease in lymphocyte stimulation response, chemotaxis and bacterial phagocytosis of polymorphonuclear leukocytes, and monocyte function and neutropenia by high oral intake of zinc [13, 14].

2. Zinc, extracellular matrix, and cancer

Zinc was demonstrated to have the ability to neutralize free radicals protecting the body from harmful effects, immune disorders, and increased risk of cancer [15]; therefore, the deficiency of zinc may increase oxidative stress [16, 17]. Importantly, an increase of oxidative and nitrosative stress and inflammation in rat lung, in a stage of marginal zinc deficiency, was found [16, 18].

Cell-cell and cell-extracellular matrix interactions are essential in the development and maintenance of normal tissue cytoarchitecture and play an important role in the development and progression of many types of cancer [19]. Simultaneously, with the changes causing the immortalization of epithelial cells, there is a gradual evolution of the tumor microenvironment [19].

The extracellular matrix (ECM) represents a very complex network of structurally, mechanically, and biochemically heterogeneous components [20] including: collagen, elastin, fibrillin, fibulin, glycoproteins, and integrin receptors of ECM components [19, 21]. The systems that regulate deposition and stability of the ECM also include chaperones and enzymes that catalyze the post-translational processing of ECM components, as well as systems that destabilize and degrade the ECM to facilitate its renewal [20, 21].

It is known that matrix metalloproteinases (MMPs) are a family of zinc dependent endopeptidases which main function is to degrade and deposit structural proteins within the ECM. The production of MMPs is stimulated by factors such as oxidative stress, growth factors, and inflammation which lead to its up or downregulation with subsequent ECM remodeling [22]. Normally, excess MMPs activation is controlled by tissue inhibitors of metalloproteinases (TIMPs). MMPs and TIMPs imbalance has been implicated in multiple diseases [22]. Recent studies have demonstrated that ECM and basement membrane degradation by MMPs play an important role in tumorigenesis by modulating cell proliferation, apoptosis, and host immune surveillance, tumor invasion and metastasis [23]. In addition, MMP-9 acts as an important oncogene, thereby improving the invasiveness of cancer cells. It has been suggested that a high level of MMP-9 confers a poor prognosis in various cancers [24]. On the other hand, MMP2 (gelatinase A) has attracted particular interest in neoplasias, since it degrades type IV collagen, a major component of basement membrane undergoing destruction at an early stage of the invasive process [25].

It is generally accepted that a fundamental process for distant metastasis formation comprises epithelial-mesenchymal transition (EMT), during which tumor cells lose their epithelial properties and acquire a fibroblast-like phenotype; as a consequence, reduced intercellular adhesion, enhanced invasiveness, and increased apoptotic resistance of cells [26, 27]. In the early stages of tumor, several signaling pathways are activated, such as growth factors and zinc-finger transcription factors including Snail [26, 28]. In fact, Snail-1 has been shown to be crucial during cancer progression and metastasis. In colon cancer patients, enhanced levels of Snail1 are usually associated with poor clinical outcome [26, 29]. Recent studies in Snail-1 deficient mouse embryos support the idea that transcriptional repression of E-cadherin (cellular adhesion molecules) is associated with Snail-1 activity [26].

Marginal ZD was also associated with oxidative stress and inflammation in both mammary gland ductal epithelium and adipocyte-rich stromal. Excess of collagen directly inhibits mammary gland expansion and has major implications for breast disease risk [30]. Zinc-dependent enzyme MMP2 activity, a critical protein for ductal elongation and infiltration into the mammary fat pad, was also modified in ZD mice mammary glands [30].

Heat shock proteins are chaperones that play a pivotal role in cells survival under stressful conditions. Under normal conditions, Heat shock protein 27(Hsp27) is weakly expressed in cells; however, once stress occurs, Hsp27 expression increases, exerting an anti-oxidative damage function [31]. We analyzed the effect of Zn deficiency on the expression of cytoprotective factors (Hsp27 and Hsp70i) where both chaperones increased and are consistently associated with cellular stress and inflammation in lung [32, 33]. Likewise, Hsp70 has a role in iNOS induction [16, 31, 33]. In addition, proliferating cell nuclear antigen (PCNA) expression was increased in the ZD group [31, 34]. Qin and colleagues [31] demonstrated a possible association between PCNA and Hsp27 expression in retinoblastoma tumor. There is a lot of evidence that PCNA expression can be used as an index for evaluating malignant tumor cells proliferation, as well as the malignant potential and prognosis of a tumor [31, 35, 36].

Molecular mechanisms that define the pathological and physiological activities of EMT in distinct cellular contexts likely intersect. Zinc could act as trigger factor of events cascade in the ECM. Therefore, in order to understand some of the pathological mechanisms involved in cancer and metastasis, it would be necessary for more studies.

3. Zinc and apoptosis in lung cancer cells: excess or default?

Zinc plays a role in several intracellular signaling pathways, and its deregulation is present in various cancers. Levels of zinc in serum and malignant tissues of patients with various types of cancer are abnormal, supporting the involvement of zinc in cancer development. Imbalance of zinc transporters cause intracellular and serum zinc levels alteration. Patients with lung, breast, liver, and prostate cancer exhibit zinc deregulation in a meta-analysis performed in [37]. Zinc level decreases in lung cancer, but it is unclear whether hypozincaemia is a consequence of tumor, chronic stress, or a combination of both effects [38]. Stress, infection, or chronic diseases lead to redistribution of zinc between body compartments, and thus reduce zincaemia [39].

Zinc is required for both normal cell survival and for cell death via its role in apoptosis, which is strongly regulated. Its deregulation is central to the pathogenesis of a number of diseases, including cancer. As such, the factors like zinc that regulates the execution phases of apoptosis are of great interest as potential therapies. Free zinc ion does not only act as an inhibitor but also may act as an activator of apoptosis depending on dose and cell type. Franklin et al. [40] reviewed the effects of zinc on the regulation of apoptosis in malignant cells, because it is reported to both induce apoptosis in some cancers and to protect other cancer cells against apoptosis induced by other factors. They studied prostate, breast, liver, pancreas, and ovarian cancer finding that zinc is an apoptogenic agent in ovarian epithelial cells, in breast epithelial cells, and in prostate cells [40].

It is well known that lung cancer is the leading cause of cancer-related deaths in both men and women. Lung cancer is subdivided into two types based on cell type and pathology: small-cell lung cancers and non-small-cell lung cancers (NSCLCs), of which approximately 85% are NSCLCs [41]. At the advanced stages, taxane chemotherapy regimens are commonly used for the treatment of NSCLCs as first-line options, but the therapeutics results are not satisfacto-

ry. Kocdor et al. [42] found that zinc exhibited growth inhibitory and apoptotic effects in a dose-dependent manner, up to the IC_{50} concentrations for cultured lung cancer cells. Importantly, these effects were significantly increased when zinc and docetaxel (derived from the paclitaxel—natural compound isolated from pacific yew tree bark) were combined to treat lung cancer. Importantly, zinc deficiency reduces paclitaxel efficacy in cultured prostate cancer cells, whereas increased intracellular zinc concentrations sensitize prostate cancer cells to cytotoxic agents, including paclitaxel, via inhibition of NF- κ B activation [43, 44]. Therefore, authors proposed that zinc supplementation may have growth inhibitory effects against NSCLC cells and may increase docetaxel efficacy [42]. The semisynthetic form, docetaxel, primarily stabilizes cytoplasmic microtubules via binding to the β -tubulin site, causing cell cycle arrest at the G2/M phase and driving apoptosis. Therefore, the IC_{50} doses of docetaxel and zinc were higher for the p53-null H1299 cells than A549 cells. Functional p53 status may influence docetaxel and zinc-induced cytotoxicity. PTEN-PI3K-Akt-Bax signaling cascade is involved in the therapeutic effect of combined radiation/paclitaxel treatment in NSCLC without p53 expression [45].

John et al. [46] proposed that zinc depletion induces cell death via apoptosis (or necrosis if apoptotic pathways are blocked), while sufficient zinc levels allows maintenance of cell survival pathways such as autophagy and regulation of reactive oxygen species. Although in the results shown by meta-analysis zinc tissue levels are low in lung cancer [37, 38], two older studies demonstrated the contrary: they exhibit elevated zinc levels when compared with the corresponding normal tissues [47, 48]. Interestingly, while data of zinc levels in tumor tissue is limited, it has been widely recognized that ZIP is upregulated in most cancers, thereby indicating increased zinc concentrations in tumor majority [46]. Additionally, peripheral tissue surrounding lung metastasis has higher zinc content than the corresponding normal tissue or the tumor tissue itself [47]. Consequently, zinc levels regulation to promote immune cells survival and tumor apoptosis are in order. Likewise adjustments in zinc homeostasis may be a contributing factor in genetic alterations (ZNT, ZIP, metallothionein, etc.) or environmental causes (nutritional status, exposure to zinc, microbial control) playing a role in the genesis and/or maintenance of cancer [46].

Lung cancer chemotherapy treatments itself do not produce satisfactory results; however, apoptogenic effect of zinc increased docetaxel therapy efficacy against NSCLC, achieving good results. Zinc transporters are upregulated in lung cancer, but more data are needed to clarify zinc tissue tumor values and its role in the triggering and progress of apoptosis to finally found a successful therapy facing this scourge.

4. Zinc and telomerase

A telomere is a repetitive sequence of DNA that protects the ends of linear chromosomes from deterioration and repair activity [49]. Mammalian telomeres consist of repetitive TTAGGG sequences that are crucial to formation of the capping structures, which are bound by telomere-binding factors called shelterin [50]. The shelterin complex is a six subunit complex com-

posed of directly binding proteins TRF1, TRF2, and POT16 and their associated proteins Rap1, TPP1, and TIN2 [51].

Due to the inability of DNA polymerase to replicate the 5' end of the lagging strand, the length of telomeres is shortened progressively with each cell division, which eventually leads to cellular senescence when the telomere length is reduced beyond the critical level [52]. It is believed that the maintenance of telomeres is essential for the immortality of cancer cells. Telomeres are maintained by a specialized reverse transcriptase, the ribonucleoprotein telomerase, which is composed of a ubiquitously expressed RNA subunit, human telomerase RNA component [hTERC; 53], and a protein catalytic subunit, human telomerase reverse transcriptase (hTERT), the expression of which is highly regulated [54].

Zn deficiency is known to suppress the proliferation of tumor cells [55], suggesting that Zn has an important role in cell proliferation. The involvement of Zn in the proliferation of lymphocytes and other non-cancer cells also has been documented [7]. But other evidence shows that tumor size has a reverse relationship with zinc amount [56, 57].

In 2000, Nemoto et al. [58] studied how zinc modulates telomerase activity, showing that treatment with 100 μ M Zn enhanced telomerase activity in renal cell carcinoma (NRC-12) and human prostatic cancer (DU145) cells. This enhancing effect of Zn suggests that it may not be caused by cytotoxicity but rather by some biological events such as induction of Zn-binding proteins or activation of transcription factors containing Zn-finger motifs. Based on that, Zarghami et al. [59] studied the relation between Zn plasma and telomerase activity in bladder cancer patients. Nevertheless, they only found a significant relationship between Zn and Telomerase activity in the female patients, where the cancerous patients presented less Zn concentrations than the control patients, with elevated enzyme activity, consistent with the findings of Whelan et al. [60]. The study of Prasad et al. [61] also showed that patients with head and neck cancer presenting bigger tumors had zinc deficiency as well [61]. Similar results were found in lung cancer patients [62]. Therefore, there are paradoxical results regarding zinc levels and its effect on cancer.

More recently, a new embryonic stem cell marker was discovered, zinc finger and SCAN domain containing four genes (Zscan4), which has a key function in genomic stability by regulating telomere elongation, and might also have a fundamental role in the mechanism controlling telomere length regulation [63]. Zscan was also found to promote telomere elongation during reprogramming, but it is not associated with increased telomerase activity [64]. It has been shown that overexpression of Zscan4 rescues cell proliferation and causes rapid telomere extension [64]. In 2014, Lee and Gollahon [65] showed that Zscan4 binds directly to the shelterin complex member Rap1. Apparently, the binding between Zscan4 and Rap1 may be required for disrupting telomere protection dissociation of the t-loop to control telomere length in telomere biology of cancer cells.

Another zinc-finger protein involved in cell differentiation, senescence, and apoptosis is Zfp637. It belongs to the Kruppel-like protein family and comprises six consecutively typical and one atypical C2H2 zinc-finger motifs. It has been reported that Zfp637 is located in nucleus and behaves as a repression regulator in myogenic cellular differentiation by promoting

mTERT expression [66]. Recently, in [67], it was provided the first mechanism through which Zfp637 protects cells against oxidative stress-induced premature senescence. Zfp637 binds to the mTERT promoter and transcriptionally activates mTERT. mTERT expression maintains telomerase activity and telomere length and promotes cell proliferation. On the other hand, the oxidative stress-triggered downregulation of Zfp637 results in depressed binding of Zfp637 to the mTERT promoter, leading to reduced levels of mTERT-dependent telomerase activity and accelerated telomere shortening and cellular senescence, what can be reverted by overexpression of Zfp637 [67].

All these studies show that several proteins involved in the activity of telomerase have Zn-finger motifs, indirectly suggesting the involvement of this ion in cancer outcome. Unfortunately, more studies need to be done in order to assure if Zn presence or deficiency the responsible for cancer onset.

5. Conclusion

The aim of this review was to look through the state-of-the-art concerning the zinc homeostasis and cancer. Zn microenvironment may play a key role in oxidative stress, apoptosis, and/or cell signaling alterations which influences the behavior of malignant cancer cells. In fact, the study of cancer biology has mainly focused on malignant epithelial cancer cells, although tumors also contain a stromal compartment, composed by different type of cells and also includes various types of macromolecules comprising the extracellular matrix. Following this rationale, several hundred zinc supplementation studies have been conducted, investigating the effects of zinc on cancer, often with contradictory results. The mechanisms responsible for Zn accumulation and the consequence of Zn dysregulation are poorly understood, and mostly dependent of the type of cell or tissue compromised. For this reason, further studies are needed to elucidate the mechanism of this protection.

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