Role of Zinc in Breast Cancer Tumorigenesis

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It is well-known that serum and cellular concentrations of zinc are altered in breast cancer patients. Specifically, there are notable zinc hyper-aggregates in breast tumor cells when compared to normal mammary epithelial cells.

Zinc CmPn signaling network breast cancer

1. Cellular Zinc Level Is Influenced by Dietary Supplementation

1.1. Cellular Zinc Concentrations Depend on Dietary Consumption

Minerals and other trace elements are essential micronutrients for normal physiological functioning and well-being [1]. The daily intake and homeostasis of these micronutrients are largely dependent on dietary habits [1]. Although zinc is the most abundant intracellular micronutrient, the human body is incapable of storing sufficient amounts of zinc; therefore, an inadequate diet can rapidly lead to zinc deficiencies [2][3]. It is estimated that nearly 50% of United States adults over the age of 50 are consuming suboptimal amounts of zinc and nearly two billion people worldwide may be zinc-deficient [2]. In rodents, nutritional zinc deficiencies have shown to predispose subjects to a reversible carcinogenesis, in which the subsequent replenishment of dietary zinc led to a reduction in cellular multiplicity and subsequent progression of the malignancy, likely by altering cellular proliferation and gene expression [4][5]. Epidemiological studies have shown that an inverse relationship exists between dietary zinc consumption and the development of breast cancer [3][6]. Specifically, evidence shows that biopsies of breast tumor cells contained significantly higher intracellular zinc concentrations and increased zinc transmembrane protein expression compared with normal tissue cells [6]. Therefore, the aberrant expression and homeostasis of zinc in breast tumors correlates with malignancy and could contribute to the severity of this cancer subtype [6].

1.2. Zinc Cellular Specific Actions

Zinc has shown to modulate immune system functioning, as well as the regulation of various metabolic, genetic, and cell-signaling pathways [2][7]. Studies have shown that zinc plays a protective role in tumor initiation and development by reducing oxidative stress and protecting DNA from reactive oxygen species (ROS) and the subsequent development of oncogenic mutations [8]. Specifically, zinc's function as an antioxidant provides genomic stability by decreasing oxidative DNA damage [6]. However, other studies suggest that cytotoxic levels of zinc are also known to cause DNA damage, oxidative stress, and the formation of ROS [9]. Several findings suggest that zinc's function is largely concentration- and cell-specific and this property of zinc may result in both

pro-apoptotic and anti-apoptotic properties of the micronutrient [7]. While zinc has been shown to play a role in numerous malignancies, as a result of the complex nature of zinc homeostasis, a delineated relationship between zinc and tumorigenesis has yet to be established [7].

2. Zinc Plays a Significant Role in Tumorigenesis

2.1. Function of Zinc Contributes to the Progression of Cell Tumorigenesis

The biological effects of zinc can be exerted through the intra- and extracellular zinc regulatory functions and its interactions with proteins [10]. Zinc can act as either extracellular stimuli or intracellular messengers. Therefore, a precise working model of zinc regulatory mechanisms is needed to obtain a better understanding of homeostatic control for transients, subcellular distribution and trafficking, organellar homeostasis, and vesicular storage and exocytosis of zinc ions [11]. The vast majority (95%) of zinc is located intracellularly so that the extracellular concentration available is low. Intracellular zinc homeostatic molecules include cytosolic zinc-binding proteins, transporters localized to cytoplasmic and organellar membranes, and sensors of cytoplasmic free zinc ions [12]. Circulatory zinc is mainly bound to albumin, transferrin, and α2-macroglobulin but remains accessible to zinc transporters to control the cellular zinc balance [13]. Intracellular levels of zinc are largely coordinated by zinc transport channels, which are capable of both zinc influx and efflux [2]. There is evidence suggesting that zinc accumulates in elevated levels in breast cancer cells and other malignant cell lines in comparison to normal mammary epithelial cells [14]. Specifically, breast cancer cells showed a 72% increase in intracellular zinc concentrations in comparison to other, non-malignant breast cells, while serum levels of zinc were decreased from baseline [15]. One meta-analysis of 36 studies containing more than 5700 patients found significantly decreased serum zinc levels in breast cancer patients in comparison to controls and patients with benign breast diseases [16]. The findings of increased intracellular zinc concentrations were also observed at the histological level, suggesting that cellular zinc concentrations may be clinically useful in determining malignancy grading, as well as serving as predictive biomarkers for breast cancers [17]. However, the exact mechanisms that are responsible for the accumulation and dysregulation of zinc in breast tumors are not well understood and it remains unclear as to whether intracellular zinc accumulation causes the disease or is a consequence of this disease [2][14].

2.2. Zinc Transport Protein in Breast Cancer Cells

While the exact mechanisms of zinc's role in tumorigenesis is not well-understood, there are many speculations. Zinc acts as a signaling molecule, and both its intracellular and extracellular concentrations must be tightly regulated for proper physiological functioning [18]. Therefore, there is a complex regulatory system for the precise homeostatic control of cellular zinc transport, distribution, trafficking, organelle homeostasis, vesicular storage, and exocytosis of zinc ions [11][19]. There are several regulators of free intracellular zinc, such as zinc transporters, inhibitory factors, and sensors. Among the zinc transporters, Zrt-/Irt-like proteins (*ZIPs*) are most frequently studied [20][21][22]. Cellular zinc levels are strictly controlled by two families of transport proteins: ZIP channels (SLC39A) and ZnT transporters (SLC30A). ZIP channels increase cytosolic zinc levels by importing zinc into cells or releasing zinc from endoplasmic reticulum (ER) [23][24][25]. One subfamily of ZIP, estrogen-regulated LIV-1 (SLC39A6) has

been implicated in breast cancer [24][26]. For example, the gene expression levels of LIV-1, a membranous zinc transporter, have been shown to increase four-fold under exposure to estrogen treatment [3][4]. Similarly, increased expression levels of LIV-1 were also observed under progesterone (PRG) treatment [3]. LIV-1 is one of the few zinc transporters identified to contain a metalloproteinase motif, which is responsible for breaking down the basement membrane and allowing for the metastasis of breast cancer cells [5]. Likewise, studies have shown that the expression levels of another zinc transporter, ZIP10, were significantly increased in metastatic breast cancer cell lines (such as MDA-MB-231 and MDA-MB-435S) when compared to less invasive cell lines (such as T47D, MCF7, ZR75-1, and ZR75-30). In addition, attenuating ZIP10 or intracellular zinc chelation in MDA-MB-231 cell lines lead to the inhibition of malignant cell migration [6][27]. Furthermore, ZIP7 was found to be able to release zinc from the ER, which leads to zinc-mediated tyrosine kinase signaling to activate cell migration and growth. This result suggests that ZIP7 might be a novel therapeutic target for breast cancer [28]. Contradicting results for the roles of LIV1 in breast cancer tumorigenesis have been reported: some studies demonstrate that ER-positive(+) breast cancer cells, which, according to the aforementioned mechanism above, have increased LIV-1 and intracellular zinc levels, are associated with better outcomes [29], as they are responsive to anti-estrogenic therapies such as Tamoxifen and aromatase inhibitors [8]. Similarly, ZIP6 deficiency disturbs intracellular Zn(2+) homeostasis, leading to increased cell survival [26]. However, breast samples from patients showed significant increases in both ZIP7 and ZIP6 in tumors, and the Kaplan–Meier curve revealed that high ZIP7 levels are correlated with decreased overall survival of patients [30]. These contradicting results can be explained by the tumor-specific hormonal response for different members of ZIP. Another cellular zinc transport receptor, ZnT2, has been shown to function in zinc sequestration, protecting cells from the cytotoxic effects of excess intracellular zinc, ROS formation, and subsequent apoptosis [10]. This study demonstrated that increased expression levels of ZnT2 transporters in malignant breast cancer cells protects these cells from apoptosis and that, conversely, tumor cells with decreased expression levels of ZnT2 transporters were less viable [10]. As a result, attenuating intracellular zinc-sequestering mechanisms may be a viable strategy for treating malignant breast cancers [10]. One study displayed a correlation between zinc concentration and histological and molecular grading and subtypes, showing elevated zinc levels in TNBC [11]. This study also displayed that increased intracellular levels of zinc were correlated with increased aggressiveness of breast cancers, with the highest zinc concentrations being present in HER2-positive breast cancers and TNBCs [11]. Additional zinc cellular regulatory factors are zinc inhibitory factor (ZIF) and zinc-sensing G-protein coupled receptor (ZnR/GPR39). ZIF reduces free intracellular zinc by inhibiting zinc transport in the oocyte before ovulation [31]. As a G-protein coupled receptor, ZnR/GPR39 triggers intracellular Ca^{2+} release and subsequently activates downstream MAPK or PI3K/AKT pathways controlling cell proliferation [32]. ZnR/GPR39 activity has been found to be enhanced in breast cancer [33][34][35].

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