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Trace Elements and Tumor: Research Progress

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Abstract: This review systematically summarizes the core advances in the field of trace elements and tumors, and clarifies the dual roles of key elements such as Zn, Cu, Fe, Se, Mn, and Ni in tumorigenesis (e.g., DNA damage repair), tumor progression (e.g., tumor microenvironment regulation), and therapeutic response—these elements not only possess tumor-suppressive potential but can also contribute to tumorigenesis. Meanwhile, it confirms the breakthrough value of multi-omics technologies and organoid models in deciphering the "element-cell-tumor" interaction mechanisms, which overcomes the limitations of traditional in vitro experiments and also points out the core directions for subsequent clinical research.

Keywords: Tumor; Trace elements; Treatment

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1. Introduction

Cancer remains one of the major public health challenges seriously threatening the health of Chinese residents. According to the cancer registration data released by the National Cancer Center, approximately 482.47 thousand new cancer cases and 257.42 thousand new cancer-related deaths were reported in China in 2022. In recent years, with the accelerated aging of the global population and shifts in lifestyles, the incidence and mortality patterns of cancer have evolved. This has led to a continuous increase in disease burden and an increasingly severe situation for cancer prevention and control. As a result, the mechanisms underlying how trace elements act in tumor development and treatment have been thoroughly explored, with the key findings outlined as follows: Copper serves a crucial function in the signaling pathways that drive cancer initiation, with key examples including the MAPK-ERK, P38MAPK, ULK, and PDK1-AKT pathways [1]. These pathways are closely associated with the regulation of cell proliferation and survival in the early stages of carcinogenesis. Manganese chloride functions as an agonist for the cGAS-STING pathway and thereby facilitates the generation of type I interferons. Furthermore, the expression of glutathione (GSH) in tumors can be downregulated by manganese molybdate nanoparticles, while manganese dioxide facilitates the generation of reactive oxygen species (ROS). All these mechanisms collectively contribute to the induction of ferroptosis in tumor cells [2]. Zinc exerts a suppressive impact on

tumor progression through two key pathways: first, via negative modulation of the functional activity of NF-κB transcription factors; second, by exhibiting antioxidant capacities [3]. This dual action helps alleviate chronic inflammation and oxidative stress, which are key drivers of tumor progression. Selenium's antitumor actions are likely mediated through a range of mechanisms, which include the following aspects: specifically, reducing the expression of hypoxia-inducible factors (HIFs); restricting tumor angiogenesis; facilitating DNA repair processes; and impeding the proliferation of tumor cells [4]. These mechanisms collectively target the malignant phenotypes of tumor cells. This review summarizes the recent research progress on the relationship between trace elements and tumors. It aims to provide a reference for the regulation of trace elements, as well as the prevention and treatment of trace element-related tumors.

2. Zinc and tumors

2.1. Zinc homeostasis

Zinc stands among the most plentiful trace elements found within nearly all organs and tissues of the human body. It serves a vital function in stabilizing the structural integrity of a range of proteins, with particular relevance to those participating in DNA synthesis and RNA transcription. This action, in turn, modulates key cellular processes including the regulation of cell growth, development, and differentiation, the maintenance of immune responses, and the mediation of oxidative stress and cell apoptosis. Collectively, these roles help prevent cancer development [5]. Zinc homeostasis could modulate the tumor immune microenvironment through the modulation of T cell activation, specifically helper T cell polarization toward distinct subsets, including Th1, Th2, Th17, and Treg [6]. Choi et al. (2018) found that zinc can inhibit endothelial cell proliferation via Orai1-mediated intracellular calcium ion fluctuations, and they revealed the molecular mechanisms underlying zinc-induced anticancer effects and the Orai1-SOCE signaling pathway in cancer cells [7].

2.2. Zinc and gastrointestinal tumors

Zinc deficiency can contribute to colorectal cancer and esophageal cancer. A study conducted in Linxian County, Liaoning Province, China, showed a negative correlation between dietary zinc intake and the risk of colorectal cancer (CRC), and this relationship may be modified by the SLC30A8 rs3802177 polymorphism [8]. Findings derived from a systems assessment demonstrated that an incremental increase in daily zinc supplement consumption, specifically by a daily increment of 5 mg, was associated with a 15% reduction in the risk of developing esophageal cancer. This is because Zinc can regulate the immune system, transcription factors, cell differentiation and proliferation, the synthesis and repair of DNA and RNA, and the activation or inhibition of enzymes, as well as stabilize cell membranes and maintain the integrity of cell structures. Zinc deficiency may induce the expression of inflammatory genes and oncogenic microRNAs, thereby promoting the development of esophageal squamous cell carcinoma [9]. Animal-based research has shown that esophageal squamous cell carcinoma cells exhibited a faster proliferation rate in murine models maintained on a zinc-insufficient diet, which was associated with the induced overexpression of COX-2, P38, PCNA, and NF-κB [10]. Furthermore, a study by Fong et al. (2005) showed that zinc intake could reduce the mRNA level of the COX-2 enzyme (involved in inflammatory responses) by 80%, which provides the possibility of zinc supplementation for the prevention or treatment of esophageal cancer (EC) [11]. In addition, Zinc supplementation exerts an effective protective effect on the Barrett's esophageal epithelium, preventing its transformation into malignant esophageal cancer cells; this, in

turn, serves to confirm its role in providing protection [12].

2.3. Zinc and thyroid cancer

Some studies have demonstrated zinc's influence on papillary thyroid cancer and follicular carcinoma [13]. According to Al-Sayer's study, the preoperative serum zinc levels in patients with thyroid cancer are significantly lower compared to healthy individuals, while surgery to resect malignant thyroid tissue returns these zinc levels to normal [14].

2.4. Zinc and gynecological tumors

Bengtsson et al. (2022)'s study demonstrated that moderate/high zinc intake, high phosphorus intake, and high serum zinc levels may be associated with improved breast cancer survival rates [15]. Additionally, in patients with ovarian cancer—particularly those with the high-grade serous ovarian cancer subtype—circulating zinc concentrations were significantly lower than those in healthy control groups [16].

2.5. Zinc and prostate cancer

Shahrokhi et al. (2024)'s meta-analysis included 52 studies with a total of 163,909 participants. It found that serum zinc levels and zinc levels in prostatic fluid or tissue were significantly lower in prostate cancer patients, while there were no significant differences in nail zinc levels or zinc intake between prostate cancer patients and healthy controls [17].

3. Copper and tumors

3.1. Copper homeostasis

Copper is an essential trace element in the human body, with a dual role—it is beneficial to cellular health while also potentially exerting toxicity. It serves a vital function in numerous biological processes, encompassing preserving genomic DNA integrity, producing critical metabolites, transporting oxygen to the mitochondrial electron transport chain, and functioning as a metabolic cofactor at active sites to engage in redox reactions. Contemporary research has demonstrated that copper functions as an active signaling metallic element and a metallallosteric modulator, taking part in biological processes encompassing cell growth and proliferation, autophagy, and antioxidant defense, in turn modulating the progression of cancer [18]. However, excessive copper intake may cause free radical damage and reduce protein or enzyme activity. This process induces cellular injury through excessive activation of oxidation-driven stress, lipid peroxidation, inflammatory responses, and DNA impairment, and eventually facilitates tumor angiogenesis [19].

3.2. Copper and pancreatic cancer

A comparative analysis of serum copper levels between 100 individuals diagnosed with Pancreatic Ductal Adenocarcinoma (PCA) and 100 healthy controls revealed that these levels were elevated in the PCA group. This finding suggests that elevated copper levels have the potential to raise the likelihood of developing PCA. Meanwhile, urine sample testing revealed that copper levels were also higher in the urine of PCA patients [20]. Copper's enhancement of anti-pancreatic cancer (APCA) activity primarily takes place via five key mechanisms: stimulating apoptotic processes, boosting ferroptotic events, suppressing metastatic spread, aiding autophagic

activities, and directing actions toward tumor DNA impairment. Exogenous copper can bind to cysteines C107 and C148 of Glutathione Peroxidase 4 (GPX4), increase the ubiquitination and aggregation of GPX4, and thereby enhance ferroptosis in PCA cells through GPX4-mediated autophagy [21]. Additionally, it also promotes ferroptosis by activating the MAPK pathway, demonstrating anti-pancreatic cancer activity [22]. Furthermore, studies have indicated that copper-toluate can inhibit PCA growth, while upregulating TP53 and DDIT3 expression levels and downregulating the expression levels of Sp1, ErbB2, as well as STAT3. As common tumor suppressor genes, TP53 and DDIT3 can promote cancer cell apoptosis, whereas Sp1 inhibits cell apoptosis [23].

3.3. Copper and gynecological tumors

By estimating the average copper intake in 21 communities in Shanxi, China, Chen et al. (1992) found that the breast cancer mortality rate in these regions was significantly higher than the average level, thereby confirming a negative correlation between copper intake and breast cancer mortality [24]. Furthermore, in a study by Sohrabi et al. (2021), the copper levels in tissue samples obtained from endometrial cancer patients were notably reduced when contrasted with tissues from non-cancerous cases [25]. At the same time, Zhuang et al. (2022) further investigated the therapeutic effectiveness of copper-based nanoparticles for the treatment of endometrial cancer through the utilization of their antioxidant activity [26]. Nevertheless, within India's Kashmir Valley—a region with high risk for endometrial cancer, Mir et al. (2007) demonstrated that the plasma copper levels in patients with endometrial cancer were significantly higher than those in the control group, suggesting that plasma copper level dysregulation may be a contributing factor to the development of the disease [27].

4. Iron and tumors

4.1. Iron homeostasis

Iron serves as a vital constituent of key heme molecules, iron-sulfur proteins, and enzymes. It is involved in a variety of biological-related pathways, encompassing oxygen delivery, ferroptosis, immune reactions, cell-based energy metabolism, and a host of additional enzymatic reactions. Both iron overload and iron deficiency are associated with pathological conditions. Contemporary research has centered on ferroptosis—a type of iron-dependent cellular death that serves a critical function in the biological activities of cancer cells.

4.2. Iron and gastrointestinal tumors

Both iron deficiency and iron excess can induce gastrointestinal tumors. Sohrabi et al. (2021) assessed the difference in iron concentration between esophageal cancer (EC) tissues and normal tissues, and the findings demonstrated that the iron content within cancerous tissues exhibited a higher level. The mechanism may be related to the overexpression of iron importer proteins, DNA damage, ferroptosis, and oxidative stress [28]. Meanwhile, non-coding RNAs associated with ferroptosis are related to the prognosis, tumor microenvironment, and treatment sensitivity of EC [29]. However, there are differences between total iron intake, heme iron intake, and EC risk. Total iron supplements are significantly negatively correlated with EC risk, especially in the Asian population and the esophageal squamous cell carcinoma subgroup. Dose-response assessments demonstrated that with each 5 mg daily increment in total iron supplementation, the relative risk of EC is reduced by 15%. However, heme iron intake is positively correlated with EC risk, particularly in the USA. With each daily 1 mg increment in heme iron supplements, the risk of developing EC rises by 21% [30]. A population study found that patients with

iron deficiency anemia (IDA) have a significantly increased risk of developing cancer, and gastrointestinal tumors are more common in men and postmenopausal women with IDA [31]. In addition, abnormal iron metabolism in gastric cancer cells, such as the upregulation of TFR1 and dysregulation of ferritin storage, can significantly enhance ferroptosis sensitivity. Ferroptosis inducers (e.g., Erastin and RSL3) can enhance chemosensitivity and reverse drug resistance by inhibiting GPX4 or system Xc- [32].

4.3. Iron and gynecological tumors

Triple-Negative Breast Cancer (TNBC) is an iron- and lipid-rich tumor, and inducing ferroptosis is considered a novel approach to kill breast tumor cells. Furthermore, ferritin deposition exerts effective immunosuppressive effects on the tumor immune microenvironment (TIME) by influencing innate and adaptive immune responses [33].

5. Selenium and tumors

5.1. Selenium homeostasis

Selenium constitutes a naturally existing element, and it is mainly acquired by humans via dietary consumption, air exposure, water intake through drinking, as well as dietary supplements. Appropriate quantities of selenium play a vital role in sustaining the normal operation of organismal functions, while excessive intake may induce toxic reactions. Studies have shown that selenium exhibits antitumor effects, specifically manifested in suppressing the proliferative activity of cancerous cells, preventing tumor formation in cell populations exposed to carcinogens, reducing carcinogen-induced DNA mutations, and exerting antioxidant and anti-inflammatory effects [34].

5.2. Selenium and esophageal cancer

There is a significant negative correlation between serum selenium concentration and esophageal cancer incidence. Selenium plays a significant chemopreventive role through mechanisms that involve downregulating Ki-67 expression, inducing apoptosis, alleviating inflammatory responses, and oxidative DNA damage. Additionally, methylselenocysteine can downregulate the differentiation grade of esophageal squamous cell carcinoma (ESCC) from high-grade to low-grade by regulating the KLF4/miR-200a/Keap1/Nrf2 axis [35]. Steevens et al. (2010) measured selenium levels in toenail samples and observed that serum selenium levels exhibited a negative correlation with the risk of esophageal cancer; however, this negative correlation only manifested in cases of esophageal adenocarcinoma (EAC) among female non-smokers [36].

5.3. Selenium and pancreatic cancer

High-concentration selenium can reduce the risk of pancreatic cancer, and the mechanisms of selenium against pancreatic cancer primarily encompass facilitating cancer cell apoptosis, triggering ferroptosis, restraining tumor metastasis, and suppressing uncontrolled proliferative activity. Organic selenium can release iron from mitochondria to enhance the sensitivity of pancreatic cancer cells (PCACs) to ferroptosis, thereby inhibiting tumor growth [37]. Moreover, novel methylseleninates exhibit toxic effects on PCACs; the mechanism involves inducing cell detachment by downregulating cell division control protein 42 homolog (CDC42) and its downstream effector β1 integrin (CD29), which further triggers entosis and entotic cell death [38]. Meanwhile, sodium selenite can downregulate the expression of genes that promote pancreatic cancer (PCA) metastasis (CEMIP, DDR2, PLOD2, and P4HA1) and upregulate the expression of the ATF3 gene that promotes ferroptosis in PCACs, thereby

specifically reducing PCAC activity and inhibiting tumor growth [39]. Additionally, novel selenoaspirin derivatives can inhibit NF-κB signaling by inducing caspase-mediated apoptosis and G1-phase cell cycle arrest to block PCAC proliferation, while also enhancing the cytotoxicity of gemcitabine against PCA [40].

6. Nickel and tumors

6.1. Nickel homeostasis

Ni can induce DNA damage through direct DNA binding and reactive oxygen species (ROS) stimulation. Additionally, Ni can inhibit the DNA damage repair system, including repair pathways such as direct reversal, nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), homologous recombination repair (HR), and non-homologous end joining (NHEJ). Nickel promotes tumor growth through multiple mechanisms, such as inducing DNA aberrations and deletions, inhibiting intercellular communication mechanisms, impairing the maintenance of nucleotide excision repair, triggering oxidative DNA distortion, and causing methylation.

6.2. Nickel and pancreatic cancer

A case-control study involving 118 PCA patients and 399 healthy individuals demonstrated that high nickel concentrations were negatively associated with the risk of PCA [41].

6.3. Nickel and breast cancer

A meta-analysis on serum and hair nickel levels in relation to breast cancer showed that, compared with the healthy control group, the serum nickel levels in breast cancer patients were significantly elevated [42].

7. Manganese and tumors

7.1. Manganese homeostasis

Manganese (Mn) is one of the essential trace elements. It acts as a cofactor for various cellular enzymes and participates in the metabolism of carbohydrates, nitrogen, neutralization of oxygen-free radicals, glycosaminoglycans, and cholesterol. At the cellular level, excessive Mn^{2+} accumulates in mitochondria, causing inhibition of mitochondrial enzymes and overproduction of superoxide dismutase. This leads to increased reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby resulting in toxicity or carcinogenesis.

7.2. Manganese and pancreatic cancer

Manganese-based nanoparticles can promote ferroptosis through multiple pathways and exhibit anti-pancreatic cancer (APCA) activity. Experiments have shown that gene delivery using manganese-doped zinc selenide quantum dots can induce sequence-specific silencing of oncogenic Kras mutations in pancreatic cancer (PCA), thereby inhibiting PCA tumorigenesis [43]. Meanwhile, manganese-based Prussian blue nanoparticles can induce ferroptosis in PCA via the MAPK pathway [44], and pH-sensitive PtMn nanoparticles can specifically recognize pancreatic cancer cells (PCACs) and increase intracellular reactive oxygen species (ROS) production to enhance ferroptosis, thereby suppressing the proliferation and metastasis of PCA [45].

8. Conclusion

In conclusion, the mechanisms of trace elements in tumorigenesis, progression, and treatment have exhibited distinct and diverse characteristics. Zinc exerts a protective effect against tumors in multiple systems, including the gastrointestinal tract, thyroid, gynecological system, and prostate, by regulating cellular functions, the immune microenvironment, and the expression of specific genes. Copper possesses both beneficial and toxic properties: it can provide therapeutic targets for tumors such as pancreatic cancer (e.g., promoting ferroptosis and inhibiting proliferation), while abnormal levels (either excessively high or low) may also be involved in the pathological progression of breast cancer and endometrial cancer. Relying on key pathways like ferroptosis, iron, whether in excess or deficiency, may induce gastrointestinal tumors, serving as a critical node in regulating the biological behavior of cancer cells. These findings not only systematically clarify the correlation patterns between "trace elements and tumors" but also offer new insights for clinical tumor prevention and treatment. Precision regulation of trace element levels (e.g., targeted zinc supplementation and rational intervention in copper-iron metabolism) may become a potential approach to reduce the risk of specific tumors and improve patient prognosis. Furthermore, the application of multi-omics technologies and organoid models has effectively overcome the limitations of traditional in vitro experiments, laying a technical foundation for in-depth analysis of the complex interaction mechanisms among "elements, cells, and tumors."

In the future, with the further advancement of research on trace element homeostasis regulation mechanisms and the promotion of the concept of personalized medicine, it is expected to establish a tumor risk assessment system and precision intervention strategies based on trace element detection. This will enable trace elements to play a more effective role in tumor prevention and treatment, providing more solid scientific support for reducing the disease burden of cancer and improving public health.

Disclosure statement

The authors declare no conflict of interest.

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