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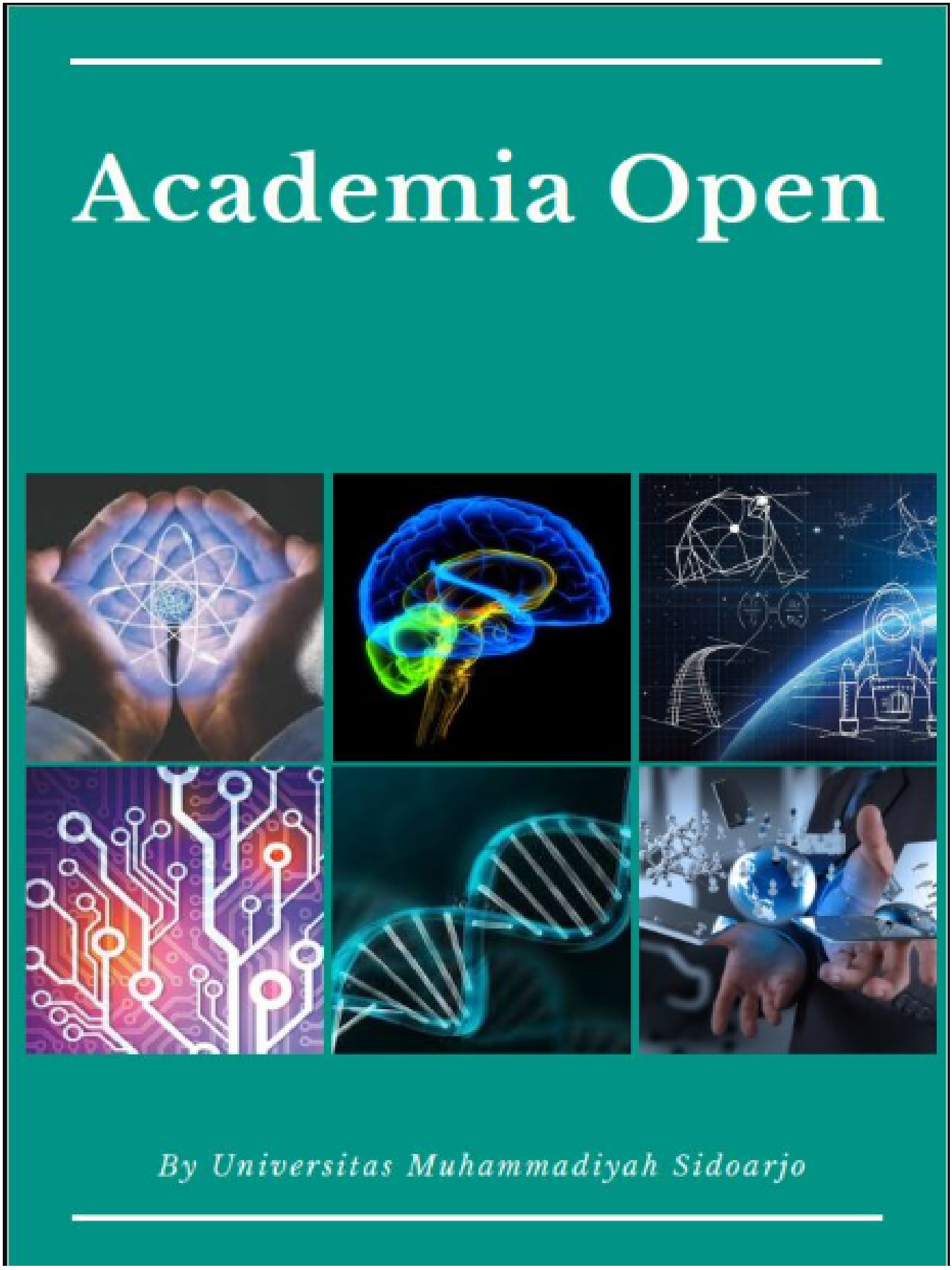

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The Biochemical Role of Zinc, Copper, and Iron in Carcinogenesis / Review: Peran Biokimia Zinc, Tembaga, dan Besi dalam Karsinogenesis / tinjauan

Hala Sabry Al-Atbi, zainab.alkhazragie@buog.edu.iq (*)

Department of Chemistry, Sciences College, University of Basrah, Basrah 61004, Iraq

Zainab Kadhim Al-Khazragie, zainab.alkhazragie@buog.edu.iq

3Department of Polymers and Petrochemicals Engineering, College of Oil and Gas Engineering, Basrah University for Oil and Gas, Basrah 61004, Iraq

Karrar Hassan Thamir, zainab.alkhazragie@buog.edu.iq

3Department of Polymers and Petrochemicals Engineering, College of Oil and Gas Engineering, Basrah University for Oil and Gas, Basrah 61004, Iraq

(*) Corresponding author

Abstract

General Background Trace elements such as zinc, copper, and iron are essential regulators of cellular metabolism and redox balance, playing fundamental roles in genomic stability and immune function. Specific Background In cancer biology, disturbances in zinc, copper, and iron homeostasis are associated with oxidative stress, DNA damage, angiogenesis, and uncontrolled cell proliferation. Zinc contributes to antioxidant defense and DNA repair, whereas copper supports tumor vascularization and migration, and iron promotes reactive oxygen species formation through redox cycling. Knowledge Gap Although these metals have been individually examined, their integrated molecular interactions and collective implications in carcinogenesis remain insufficiently synthesized. Aims This review evaluates the biochemical roles of zinc, copper, and iron in oxidative stress, genomic instability, angiogenesis, and regulated cell death, and explores their diagnostic and therapeutic relevance. Results Evidence indicates that zinc supports genomic integrity, copper participates in both tumor progression and cuproptosis-related cell death, and iron contributes to ferroptosis and tumor metabolic adaptation. Alterations in metal transporters, storage proteins, and redox regulators influence tumor behavior and therapeutic responsiveness. Novelty This article provides an integrative perspective on trace element homeostasis by connecting zinc, copper, and iron within a unified carcinogenic framework. Implications Modulating metal balance through chelation, targeted delivery systems, and nutritional strategies represents a promising avenue for personalized cancer management.

Keywords: Trace Elements, Zinc Homeostasis, Copper Metabolism, Iron Dysregulation, Carcinogenesis

Key Findings Highlights

1. Zinc supports genomic stability through antioxidant and DNA repair pathways.
2. Copper participates in angiogenesis and respiration-linked programmed cell death.
3. Iron imbalance drives reactive oxygen species formation and lipid peroxidation pathways.

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Introduction

Carcinogenesis, the process of cancer development, is widely recognized as a multistep and multifactorial phenomenon characterized by the slow accumulation of genetic and epigenetic alterations. These modifications disrupt normal biological processes, leading to uncontrolled cell proliferation, evasion of apoptosis, sustained angiogenesis, and metastasis [1,2]. The technique typically comprises three primary components. Figure 1: Initiation, Promotion, and Progression. DNA damage occurs during initiation due to spontaneous mutations, oxidative stress, or carcinogenic exposure. If this damage is not rectified, it may result in permanent genetic alterations. The clonal growth of these initiated cells transpires during the promotion phase, often due to hormonal imbalance, chronic inflammation, or dysregulated signaling pathways. Increased genetic instability and phenotypic changes that enhance the malignancy potential of tumor cells are indicators of progression[3].

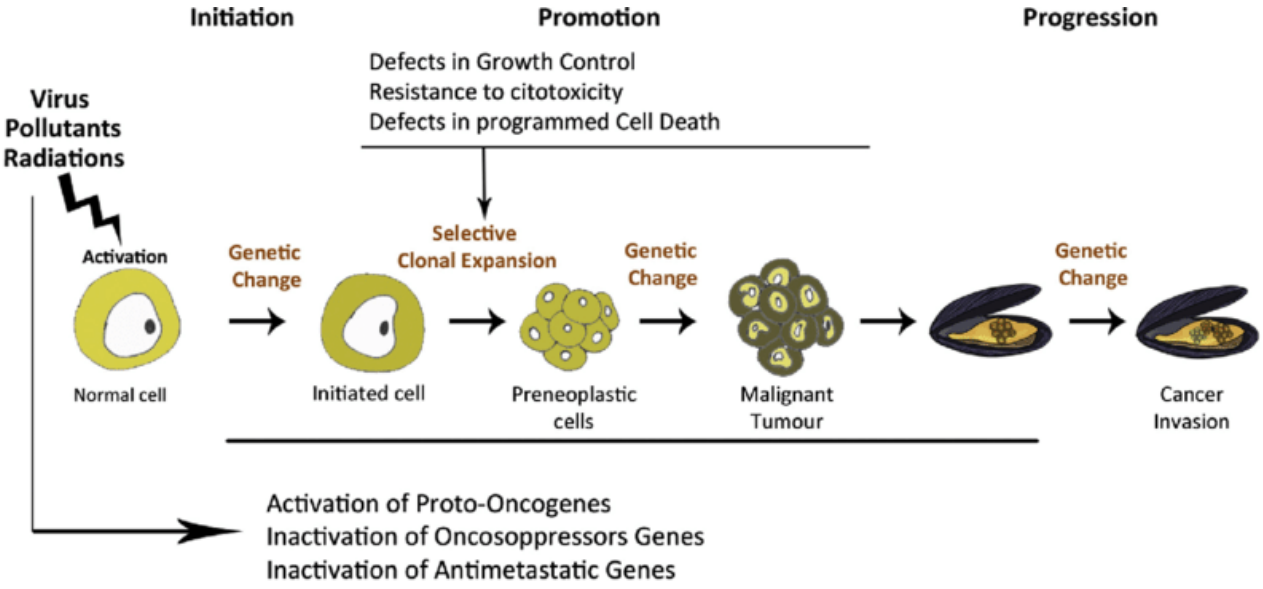

Figure 1. Figure 1. Cancer Development Stages [4]

Recent studies have underscored the importance of trace elements, such as iron, copper, and zinc, in influencing various stages of carcinogenesis. These are essential trace elements required for maintaining redox balance, enzymatic function, and cellular homeostasis. Their biochemical activities are closely associated with processes frequently disrupted during carcinogenesis, including DNA synthesis, repair mechanisms, cell cycle regulation, and oxidative stress response.[5] An imbalance in these metals may contribute to the development and proliferation of cancer through mechanisms such as elevated reactive oxygen species (ROS) generation, altered gene expression, and dysregulation of cellular signaling pathways [6,7]. Identifying potential targets for early detection, prevention, and treatment necessitates comprehension of the multistep process of carcinogenesis.

Natural Sources and Physiological Importance of Trace Elements

Micronutrients, sometimes referred to as trace elements, are minerals that are needed by living things in very small amounts, usually less than 100 mg per day, to maintain a variety of biological processes [8]. Trace elements are necessary for cellular signaling, enzymatic processes, antioxidant defenses, and homeostasis, even though the body has very little of them. Iron (Fe), copper (Cu), and zinc (Zn) are some of the most physiologically significant trace elements; they are all essential for metabolic and regulatory processes.

Though their bioavailability from different sources varies, trace elements are mostly acquired through diet. Other routes of exposure include water, soil, and even dust particles inhaled from the environment. Rich sources of zinc are red meat, shellfish, whole grains, legumes, and seeds. More than 300 enzymatic processes, such as DNA synthesis, wound healing, immunological response, and antioxidant defense, depend on zinc as a cofactor[9]. Nuts, dark leafy greens, seafood, and organ meats—particularly liver—all contain copper. Copper is involved in the creation of neurotransmitters, connective tissue, iron metabolism, and mitochondrial respiration [10]. Heme iron, found in animal sources such as liver and red meat, and non-heme iron, found in plant-based sources like lentils, beans, and fortified cereals, are the two types of iron. Hemoglobin and cytochromes, which are vital for oxygen transport and cellular respiration, contain iron. Additionally, it affects DNA replication and immunological response [11,12].

Even though trace elements are needed in trace amounts, their toxicities or deficiencies can cause serious health problems such as anemia, neurotoxicity, and an increased risk of infections or cancer.

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Zinc in Carcinogenesis

Zinc is an important mineral that helps cells fight damage from harmful substances and keeps our genes stable. It helps many enzymes and proteins that control genes work correctly. These include those that fix DNA, protect against damage, and control cell death. Zinc helps superoxide dismutase (SOD), a key enzyme, get rid of harmful molecules called superoxide radicals, protecting cells from damage caused by reactive oxygen species (ROS). Zinc helps keep proteins and DNA stable, and it helps regulate p53, an important gene that fights tumors [5,13]. It also helps fix damaged DNA through processes like BER and NER Figure 2. When someone doesn't have enough zinc, these repair systems don't work as well, which can make DNA unstable and cause more mutations. This can lead to cancer [14]. Zinc has a complicated double role in cancer development. It can stop tumors when it's at the right level in the body, but it might help cancer grow when its levels are not normal. Zinc is needed for many enzymes to work correctly, such as those that control genes, fight damaging molecules, and fix DNA. Because of this, zinc is important for keeping DNA stable, protecting against damage, controlling cell growth, and causing cell death. On the other hand, not having enough zinc can lead to DNA damage, problems with DNA repair, issues with important cell signals (p53 and NF κB), and long-term swelling.

All of these things can start and help cancer grow [15,16]. In cancers like prostate, breast, pancreatic, and esophageal, changes in how zinc transporters work (like ZIP1, ZIP6, ZIP7, ZIP10, ZnT2) cause either too little or too much zinc. This affects how the tumor grows, spreads, moves to other places in the body, and resists hormone treatments [17,18]. For instance, in breast cancer, more zinc in the tissue and too much ZIP6/ZIP7 have been linked to changes in cell type and resistance to tamoxifen[19]—new research, like the work of Bendellaa et al. and Chen et al.[20,21] suggests treatments that involve aiming at zinc carriers, adding zinc, and using zinc oxide nanoparticles. These methods are designed to specifically cause cell death, enhance the efficacy of chemotherapy, and reduce overall harm in lab tests.

A deficiency in zinc can hinder one's immune response, increase oxidative damage, and lower the ability to repair DNA, all of which can lead to a higher risk of developing cancer. There are both epidemiological and experimental studies that demonstrate the relationship between lower zinc levels and higher risks of developing certain types of cancer. Compared to normal prostate cells, prostate tumor tissues have a significantly lower concentration of zinc. It is thought that zinc can prevent the advancement of prostate cancer by slowing down cell growth and promoting apoptosis [22]. Breast cancer patients exhibit changes in zinc transporter expression alongside lower zinc levels, indicating potential involvement in tumor growth and advancement [23]. Additionally, zinc supplementation has demonstrated protective effects in animal models of colon cancer by bolstering antioxidant mechanisms and mitigating inflammation [24].

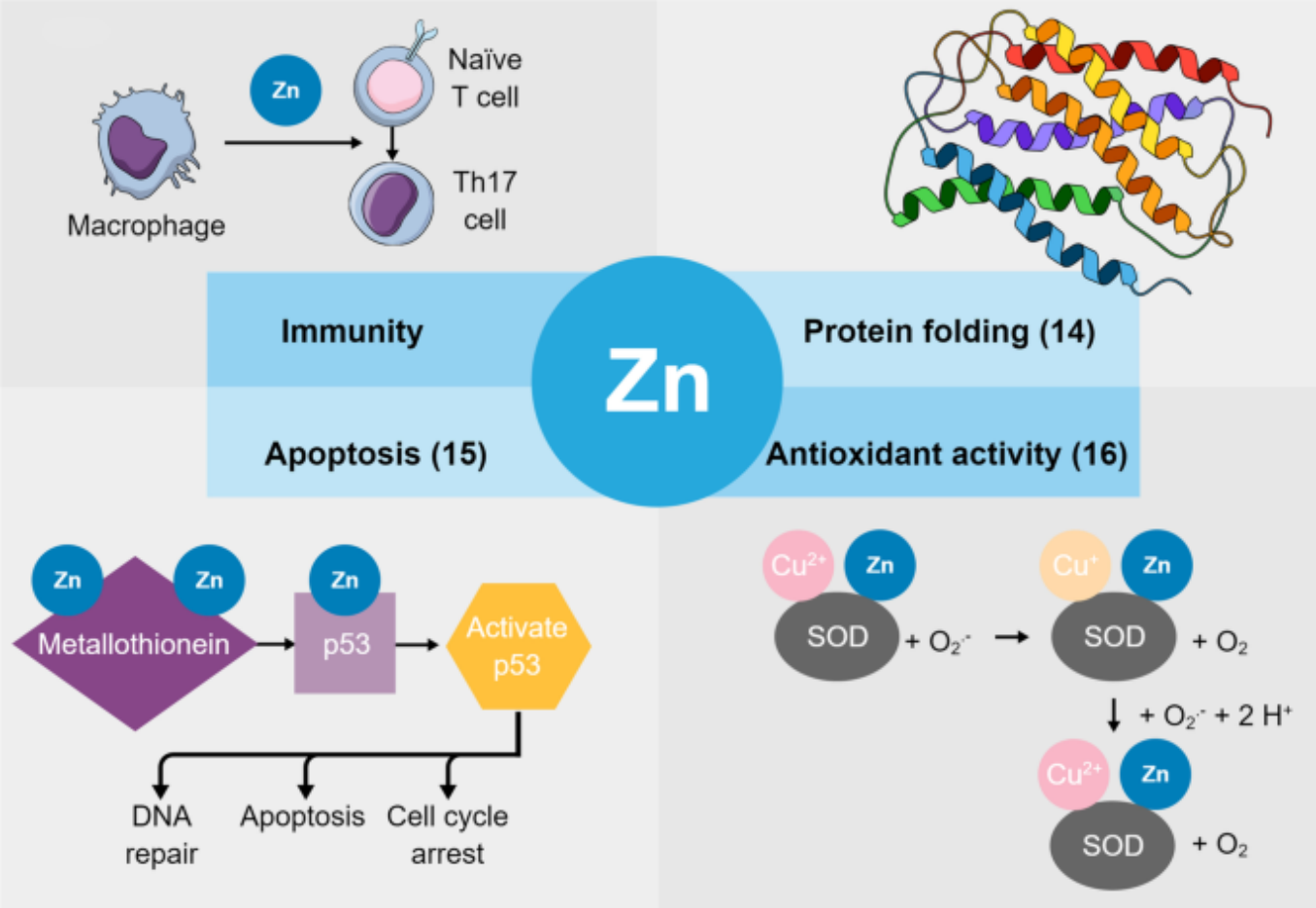

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Figure 2. Figure 2. The roles of zinc in human physiology [25].

Copper's Role in Carcinogenesis

Copper is a trace element of significant importance due to its involvement in various physiological functions, including mitochondrial respiration, antioxidant defences, and the oxidation of metabolites. The redox activity is crucial for life, particularly during the malignant alterations of a cell. Copper serves as a cofactor for numerous oxidative enzymes, including cytochrome c oxidase, superoxide dismutase (Cu/Zn-SOD), lysyl oxidase, and ceruloplasmin. These enzymes participate in energy metabolism, collagen crosslinking, and the detoxification of free radicals. Furthermore, an excess of copper might facilitate the production of reactive oxygen species (ROS) via Fenton-like mechanisms, leading to oxidative DNA damage, lipid peroxidation, and, in certain instances, an increase in carcinogenesis [26].

Copper is a trace element that has dual roles in cancer research. On one hand, it is essential for the proper functioning of a cell, serving as a redox cofactor for specific enzymes. Conversely, its disrupted equilibrium promotes certain markers of cancer and facilitates the eradication of malignant cells. Numerous investigations have recorded elevated serum and tissue copper concentrations in breast, colon, prostate, and lung malignancies. Copper's metabolic dysregulation correlates with an elevation in tumor grade, tumor progression, and tumor-related metastasis, positioning it as a potential diagnostic and therapeutic target [27,28]. This heightened level has been observed in various cancer types and is associated with tumor proliferation, metastasis, advanced stages, unfavorable prognosis, and angiogenesis; copper is instrumental in angiogenesis, the process of generating new blood vessels from pre-existing ones, which is a critical aspect of tumor progression. It helps boost the activity of pro-angiogenic factors like vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and angiogenin. These actions encourage the formation of new blood vessels, which give tumors more nutrients and oxygen, helping them grow and spread to other parts of the body [29]. Mechanically, copper helps support enzymes and signaling pathways that are involved in promoting metastasis and helping tumors avoid the immune system [30,31].

On the other hand, too much copper that is easily released can cause different types of cell death. Scientists found that cuproptosis happens when copper builds up in the mitochondria, which then directly binds to certain proteins in the TCA cycle that have lipoyl groups. This causes these proteins to clump together, lose important Fe–S cluster proteins, create toxic stress in the proteins, and lead to controlled cell death in cells that rely on respiration [26,32]. This shows a dual role of copper—on one hand, it can support tumor growth (called cuproplasia), and on the other, it can help fight tumors (called cuproptosis). Because of this, researchers are actively working on new treatments. For example, they are studying ways to reduce copper levels, like using copper chelators such as tetrathiomolybdate, to slow down blood vessel growth and stop tumors from spreading. At the same time, they are developing drugs that help move copper into cells, such as copper ionophores like elesclomol and disulfiram–Cu complexes, and copper-based nanoparticles, to trigger cuproptosis in cancer cells that are sensitive to this process [30,32]. Important molecules that control how tumors handle copper include proteins that bring copper in and out of cells (like CTR1/SLC31A1, ATP7A/B), copper-carrying proteins (like ATOX1, CCS), metallothioneins, and antioxidant systems (like GSH). Changes in how these molecules work, either through gene expression or mutations, can affect how sensitive a tumor is to copper and how well treatments work [31,33]. Although early research and clinical tests show promise, translating these findings into real-world use requires accurate biomarkers to identify patients whose tumors depend on copper or are sensitive to copper-related cell death. Careful management is also important because changing copper levels in the body can be harmful and might damage healthy tissues. Recent studies highlight both the potential for new treatments and the need for carefully controlled clinical trials along with better ways to deliver copper-targeted therapies specifically to tumors [30,32].

Iron in Carcinogenesis

Iron has two main roles in the body. It is needed for many important chemical reactions, but when it's not controlled properly, it can cause harm. One way iron causes cancer is through a process called the Fenton reaction. In this reaction, a type of iron called ferrous iron (Fe^{2+}) reacts with a substance called hydrogen peroxide (H_2O_2) to create very harmful molecules called hydroxyl radicals (•OH). These harmful molecules, known as reactive oxygen species (ROS), can damage DNA, fats in cell membranes, and proteins. This damage can lead to mutations and make the genes unstable, which can help cancer develop [34]. When there is too much iron in the body, like in a condition called hemochromatosis or when iron metabolism is not working properly, the extra iron is stored in the form of ferritin or hemosiderin. But if the body can't store all the iron, some of it becomes labile iron. This type of iron can cause oxidative stress, which can harm DNA and help start cancer Figure 3. Too much iron has been linked to liver cancer, especially in people who inherit a form of hemochromatosis or have ongoing liver inflammation [35]. Also, high iron levels may play a role in colorectal cancer, possibly because they increase the production of harmful substances called ROS and boost the growth of cells in the gut [36]. Iron helps cancer grow by supporting the way cells multiply, form new blood vessels, and spread to other parts of the body. Because of this, scientists are looking at ways to stop cancer by controlling iron levels, such as using drugs that remove iron or change how the body handles it. Cancer cells often act in a way that makes them dependent on iron. They have more of a certain protein that brings iron into cells and less of another protein that releases iron. This causes more iron to be available inside the cell, which helps the cells grow, use energy better, and multiply more quickly [37,38]. Changing how iron is used in the body can help cancer grow and make it more harmful. This need for iron makes cancer cells vulnerable to a type of cell death called ferroptosis, which happens when iron causes damage to fats inside cells. Ferroptosis acts as a way to stop tumors from growing and is now seen as a useful target for treatment, either on its own or along with other cancer treatments like chemotherapy and immunotherapy [39,40]. Ferroptosis can have different effects in cancer, depending on the situation. In some cases, the body's reaction to lipid peroxidation might actually help cancer grow [40].

Studies show that having too much iron in the body, especially from eating red meat and processed meat, increases the

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chance of getting colon and liver cancer [36,41]. Studies show that too much iron can turn on cancer-causing signals like WNT, MAPK, and EGFR. In some cases, it can also cause a type of cell death called ferroptosis, which is linked to oxidative stress [38]. Inside a tumor, how iron is handled affects the support cells and the immune cells around it, which can change how the body fights cancer and how well treatments work [42]. For example, the p53 protein helps control the production of hepcidin, a hormone that affects iron levels in the body and in tumors, especially in liver cancer [43]. New treatment ideas are exploring ways to alter how cancer cells utilize iron, including drugs that remove iron, prevent iron from entering cells, promote iron release, or accelerate ferroptosis. These methods try to use cancer's need for iron against it without causing the whole body to lose too much iron or leading to anemia [38].

On the other hand, iron deficiency has been increasingly recognized as a factor that may contribute to cancer growth. This is because iron is important for the immune system to work properly. Immune cells, like T cells and natural killer (NK) cells, need enough iron to function well. These cells play a crucial role in identifying and eliminating cancer cells. When there's not enough iron, these cells don't work as well. They produce fewer signaling proteins called cytokines, are less effective at killing cancer cells, and have a reduced ability to present cancer cells to other immune components. This weakens the body's ability to spot and destroy tumors. This makes it easier for cancer to start and spread. Also, long-term iron deficiency can cause ongoing inflammation, which can lead to more DNA damage and help cancer cells grow [43].

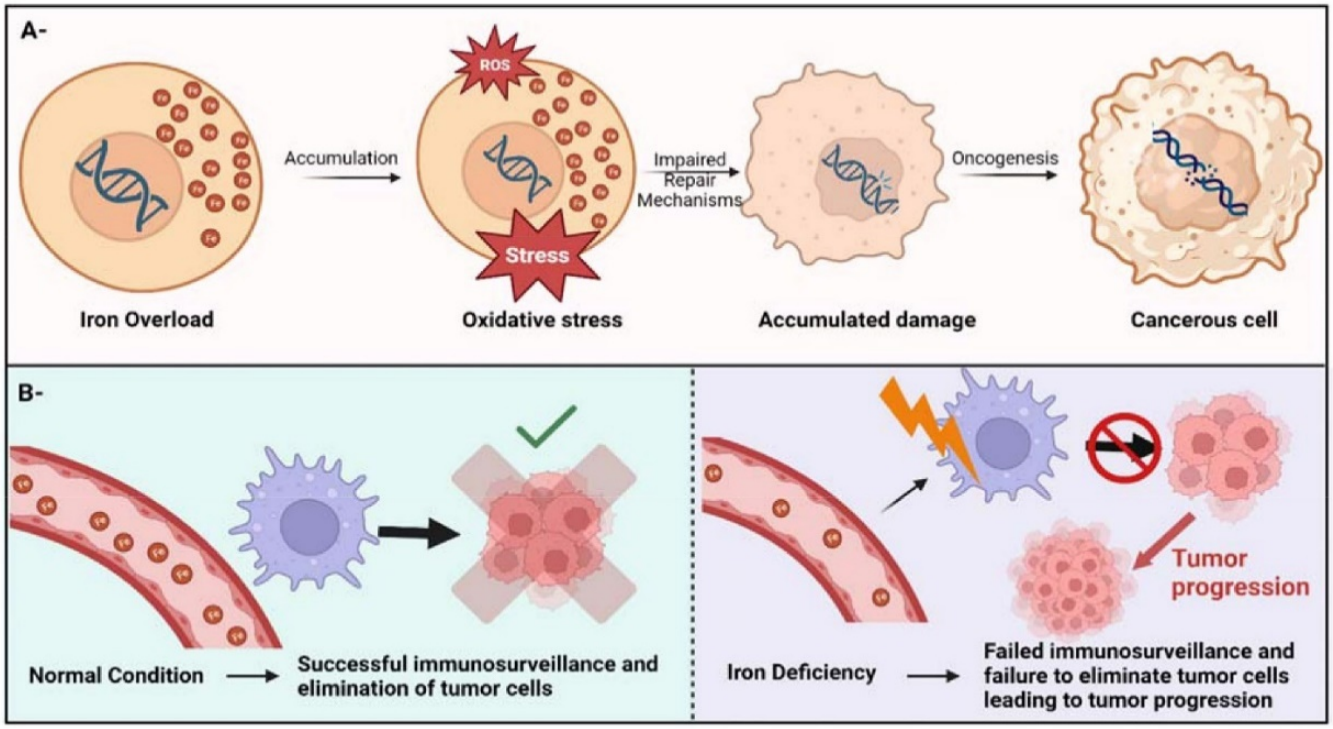

Figure 3. Figure 3. Iron imbalance can cause cancer through different mechanisms [44].

Therapeutic and Diagnostic Implications

Trace elements like zinc, copper, and iron play two important roles in cancer biology, which has led to more research on using them as tools to detect cancer and treat it. One way scientists are working on this is by using metal chelators, which are substances that bind to excess amounts of these elements. This helps stop them from causing harmful reactions that support cancer growth. For example, deferoxamine and triapine are being studied for their ability to remove excess iron from cancer cells, which can slow down how quickly tumors grow [45]. Similarly, copper chelators such as tetrathiomolybdate have shown effectiveness in stopping the formation of new blood vessels that feed tumors and in reducing tumor size in breast and liver cancer studies [46]. In the field of diagnosing diseases, higher levels of certain metals in the body's tissues or blood can act as early warning signs, helping doctors detect cancer, predict how it might progress, or check how well treatments are working. Studies have found that people with breast, colon, and liver cancers often have higher-than-normal levels of copper and iron in their blood and tissues, which suggests these metals could be useful for cancer screening and determining who is at higher risk [47].

Along with medical care, a person's diet also plays an important role. Eating foods rich in antioxidants, such as selenium, vitamin C, and zinc, may help the body balance chemicals that cause damage and reduce the harmful effects of metals. However, taking too much of certain metals like iron and copper, especially in people who are already at risk, can be harmful and may even increase the chance of cancer [48]. These results show that tailored nutrition plans and treatments that target metals could be valuable tools to support standard cancer care.

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Conclusion

Trace elements such as zinc, copper, and iron play crucial roles in the body; nevertheless, imbalances in their levels may be associated with the onset and progression of many cancer types. These metals influence mechanisms such as oxidative stress, DNA repair, apoptosis, and angiogenesis—all of which are crucial to cancer development. Zinc safeguards the organism from damage and maintains genetic material stability; nevertheless, excessive copper and iron, which are required in minimal quantities, can induce detrimental chemical reactions that produce hazardous chemicals known as reactive oxygen species (ROS). Numerous studies have identified alterations in these trace elements in individuals with prostate, breast, colon, and liver cancers, indicating their potential utility in diagnosis and disease progression prediction. Moreover, modifying the body's metal equilibrium through techniques such as chelation therapy, dietary alterations, or targeted medicines may provide novel approaches for cancer prevention and treatment. Understanding the interactions of these factors with cancer mechanisms is crucial for developing enhanced therapy strategies that integrate conventional care with metabolic modifications. Future studies should focus on enhancing these procedures and tailoring them to individual trace element levels to achieve optimal outcomes.

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