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Biometallic ions and derivatives: a new direction for cancer immunotherapy

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Abstract
Biometallic ions play a crucial role in regulating the immune system. In recent years, cancer immunotherapy has become a breakthrough in cancer treatment, achieving good efficacy in a wide range of cancers with its specificity and durability advantages. However, existing therapies still face challenges, such as immune tolerance and immune escape. Biometallic ions (e.g. zinc, copper, magnesium, manganese, etc.) can assist in enhancing the efficacy of immunotherapy through the activation of immune cells, enhancement of tumor antigen presentation, and improvement of the tumor microenvironment. In addition, biometallic ions and derivatives can directly inhibit tumor cell progression and offer the possibility of effectively overcoming the limitations of current cancer immunotherapy by promoting immune responses and reducing immunosuppressive signals. This review explores the role and potential application prospects of biometallic ions in cancer immunotherapy, providing new ideas for future clinical application of metal ions as part of cancer immunotherapy and helping to guide the development of more effective and safe therapeutic regimens.

Keywords Metalloimmunology, Biometallic ions, Metal materials, Cancer immunotherapy

Introduction

Cancer immunotherapy has been one of the major breakthroughs in cancer treatment in recent years, and its importance and status have attracted much attention [1, 2]. The importance of immunotherapy lies in its unique mechanism of action. Immunotherapy can activate the patient's innate immune system, enabling it to attack and destroy cancer cells. With better specificity and fewer side effects than traditional treatments have, immunotherapy can more accurately identify and attack cancer cells, thereby reducing damage to normal cells. In addition, immunotherapy has the advantage of durability: Some treatments stimulate the establishment of long-term immune memory, allowing the immune system to recognize and attack cancer cells over the long term and thus reducing the rate of cancer recurrence. Immunotherapy has now become an important part of the treatment regimen for a variety of cancers, including malignant melanoma [3], non-small cell lung cancer [4], uroepithelial carcinoma [5], colorectal cancer [6] and Hodgkin's lymphoma [7].

The main approaches to cancer immunotherapy include immune checkpoint inhibitors [8], CAR-T-cell therapy [9] and tumor vaccines [10]. On the one hand, immune checkpoint inhibitors restore the immune system's attack on cancer cells by blocking the T-cell immunosuppressive pathway, while CAR-T cell therapy works by modifying the patient's T-cells so that they can specifically recognize and attack cancer cells. On the other

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hand, tumor vaccines inhibit tumor growth by stimulating the immune system to produce antibodies and T-cell responses to specific tumor antigens. Despite some notable successes in cancer immunotherapy, several challenges remain. Immune tolerance is one of the major problems, and some patients become resistant to immunotherapy, making it less effective. Furthermore, immune escape is an important challenge [11], as some cancer cells can evade the immune system by altering their surface antigens, leading to treatment failure [11]. Immunotherapy can also produce several side effects, such as immunotoxin reactions and cytokine release syndrome, which must be managed promptly [12].

Metal ions play a variety of important roles in living organisms, particularly immune functions. They maintain the normal functional state of the immune system by regulating immune cell function, participating in inflammatory responses and antioxidant defenses. Accordingly, recent studies have shown that metal ions and their derivatives have promising applications in cancer immunotherapy. These biometallic ions, which include mainly iron, zinc, copper, magnesium, and manganese [13–16], play important physiological roles in living organisms and influence the function of the immune system (Table 1). Metal ions and their derivatives (nanomaterials and alloy materials, etc.) have several possible effects in cancer immunotherapy, including directly affecting the growth and metastasis of tumor cells, modulating the function of immune cells, and enhancing the effectiveness of immunotherapy [17, 18]. First, metal ions and their derivatives can directly affect the growth and metastasis of tumor cells (Table 2). Second, metal ions and their derivatives can regulate the function of immune cells, mainly T cells, B cells, and macrophages [2, 19, 20] (Table 3). In addition, metal ions and their derivatives can enhance the effect of immunotherapy [21] (Table 3).

Biometallic ions represent a major transformation in cancer immunotherapy as they can modulate the immune response and optimize immune cells and improve the tumor microenvironment through unique biological mechanisms, thus potentially overcoming some of the key limitations in existing immunotherapies [22, 23].

Table 1 Effects and applications of representative metal ions or metal ion derivatives [23, 31, 48, 61, 163]

Metal ion	Pathway		Brief effects	Potential applications
Zn^{2+}	Innate immunity	cGAS–STING	Zn^{2+} promotes the phase separation of DNA-cGAS complexes, which are involved in the biosynthesis of cGAMP	Immune supplements Immune-cell reprogramming Immunotherapy sensitizer
		NLRP3 inflammasome	The depletion of Zn^{2+} activates NLRP3 inflammasomes via destabilization of lysosomes	
		NF-κB	Zn^{2+} downregulates the activation of NF-κB via IKK inhibition	
	Adaptive immunity	NFAT	Zn^{2+} inhibits calcineurin and NFAT-dependent gene expression	
		TCR-Lck	Zn^{2+} promotes the formation of a complex between CD4/CD8 and Lck, which is involved in T cell activation	
Mn^{2+}	Innate immunity	cGAS–STING	Mn^{2+} increases the affinity between STING and cGAMP	Immune supplements Immune-cell reprogramming Immunotherapy sensitizer Immunogenic cell death
		NLRP3 inflammasome	Mn^{2+} activates NLRP3 inflammasomes and propagates the exosomal release of ASC	
Mg^{2+}	Innate immunity	NKG2D	Low intracellular levels of Mg^{2+} decrease NKG2D expression in natural killer cells and impair their cytotoxicity	Immune supplements Immune-cell reprogramming Immunotherapy sensitizer
		NF-κB	Decreases in the extracellular levels of Mg^{2+} upregulate the expression of NF-κB	
	Adaptive immunity	TCR–ITK	Mg^{2+} binds with ITK to enhance TCR signalling	
		NKG2D	Mg^{2+} induces NKG2D expression on CD8 T cells, enhancing their cytolytic responses	
		LFA-1	Extracellular Mg^{2+} can promote an active conformational change in the T cell co-stimulatory molecule LFA-1, augmenting T cell activation and cytotoxicity	
Cu^{2+}	Innate immunity	NF-κB	Cu^{2+} promotes the release of inflammatory cytokines, such as TNF-α and IL-6, which accelerates the immune response.	Immune supplements Immune-cell reprogramming Immunotherapy sensitizer
		SOD	Cu^{2+} modulate immune cell activity by influencing oxidative stress pathways.	
	Adaptive immunity	TCR	Cu^{2+} is one of the metal ions required for T-cell receptor (TCR) signaling, which enhances TCR signal strength and promotes T-cell activation and functional development.	
		mTOR	Cu^{2+} affect the metabolism and proliferation of T and B cells by regulating mTOR activity.	

Table 2 Direct effects of biometallic ions or derivatives on tumorigenesis and development [29, 35, 37, 46, 53, 164–167]

Metal ion	Main mechanism of action	Direct effects in tumor cells	Impact on tumor development	Clinical relevance and application
Zn^{2+}	Cofactor for DNA synthesis and repair; Antioxidant effect, reduce ROS accumulation; Regulates apoptosis	Enhances DNA repair by activating p53 oncogene; Stabilizes cell membrane and inhibits ROS-induced DNA damage	Zinc deficiency leads to DNA repair damage and accelerated cell proliferation; High zinc levels inhibit tumor growth by inducing apoptosis	Prostate cancer, breast cancer; zinc supplementation studies for cancer prevention
Mg^{2+}	Maintains cytoskeletal stability and energy metabolism; Essential for ATP production; Regulates cell cycle and DNA repair	Supports ATP production and cellular metabolism to maintain rapid growth requirements; Influences cell cycle progression by regulating cell cycle proteins	Magnesium deficiency causes cell cycle arrest and inhibits tumor proliferation; Magnesium excess contributes to the anti-tumor effects of the immune system	Pancreatic cancer, colorectal cancer; magnesium deficiency and increased risk of colorectal cancer
Cu^{2+}	Promotes angiogenesis (VEGF); Cofactor for redox reactions; Regulates cell migration and infiltration	Activate angiogenic signaling (e.g. VEGF) to enhance nutrient supply; Increase ROS production to promote oxidative stress and migration of tumor cells	High copper environment promotes tumor angiogenesis and enhances invasiveness; Copper chelators are used to inhibit angiogenesis and delay tumor progression	Breast and colorectal cancer; copper chelators as an antitumor strategy
Mn^{2+}	Antioxidant defense (MnSOD core component); Regulates proliferation and anti-apoptotic signaling; Maintains cellular homeostasis	Resist ROS-induced oxidative stress damage through MnSOD; Activates survival signaling such as PI3K/Akt and enhances anti-apoptotic ability	High Manganese Levels Enhance Tumor Cell Viability and Anti-Apoptotic Capacity; MnSOD overexpression in some tumors correlates with drug resistance	Gastric and breast cancer; MnSOD overexpression correlates with radiotherapy resistance

Table 3 Effect of biometallic ions or derivatives on immune cells and the efficacy of cancer immunotherapy [31, 39, 60, 66, 148, 168–170]

Metal ion	Regulated immune cells	Mechanisms of action	Potential role in cancer immunotherapy
Zn^{2+}	T cells, NK cells, macrophages, etc.	Promotes T cell proliferation, enhances NK cell killing activity, and regulates macrophage polarization, etc.	Enhance anti-tumor immune activity; maintain intracellular antioxidant balance and reduce inflammatory response, etc.
Mg^{2+}	T cells, B cells, macrophages, etc.	Stabilizes cell membrane structure to support cell metabolism and survival, etc.	Enhancement of immune cell viability and immune persistence; enhancement of immune function in the tumor microenvironment, etc.
Cu^{2+}	Macrophages (M1/M2), T cells, etc.	Promotes macrophage M1 polarization and activates T cells, etc.	Stimulating anti-tumor immune responses, modulating inflammatory responses in the tumor microenvironment, and limiting tumor proliferation, etc.
Mn^{2+}	Macrophages, NK cells, T cells, etc.	Activation of cGAS-STING pathway to enhance interferon response, etc.	Activation of tumor immune surveillance mechanisms by increasing interferon levels; enhancement of anti-cancer recognition by immune cells, etc.

Current immunotherapies, such as immune checkpoint inhibitors (PD-1/PD-L1 inhibitors) and CAR-T cell therapy, have achieved notable efficacy in certain cancer patients but still face significant challenges. First, not all cancer patients benefit from immunotherapy, especially in cases where robust tumor immune evasion mechanisms are present. For instance, immunosuppressive factors within the tumor microenvironment can inhibit the effective response of the immune system [24–26]. Secondly, biometallic ions such as zinc, iron, and copper possess multiple biological functions, including involvement in immune cell activation, signal transduction, and redox reactions. These ions can regulate the function of immune cells, such as T cells and dendritic cells, thereby promoting antitumor immune responses [23, 27]. By improving the tumor microenvironment, metal ions can enhance tumor antigen presentation capacity, thereby increasing the immune system's ability to recognize and attack cancer cells. Additionally, bio-metal ions may lower immune tolerance by modulating immunosuppressive signaling pathways, thereby enhancing the effectiveness of immunotherapy [28]. Consequently, biometallic ions offer new potential breakthroughs for cancer immunotherapy, particularly in terms of improving therapeutic

efficacy, reducing side effects, and overcoming immune evasion.

In summary, biometallic ions and derivatives show promising applications in cancer immunotherapy, and they provide new therapeutic options and hope for cancer patients by influencing tumor cell growth and metastasis, modulating immune cell function and enhancing immunotherapeutic effects. In this review, the applications and potential mechanisms of action of these metal ions (nanomaterials and alloy materials, etc.) in cancer immunotherapy, as well as their biosafety and specific delivery systems, are thoroughly investigated. These studies not only reveal the important role of metal ions in cancer therapy, but also provide valuable insights and new directions for future basic research and clinical development, which are expected to further improve the selectivity and efficacy of cancer therapy.

The role of metal ions in tumor immunomodulation

Metal ions play important roles in immune regulation with several mechanisms of action. First, metal ions can affect the growth and function of immune cells. Copper ions can influence the immune response by regulating the proliferation and activation of T cells, thus regulating the activity of the immune system [29]. In addition, zinc ions influence macrophage activity, thereby modulating tumor-associated inflammatory responses [30]. Metal ions can also affect the migration and localization of immune cells, affecting their distribution and activity in the body [31]. Second, metal ions can affect the complex interactions between different cells in the immune system, including intercellular signaling and intercellular interactions [32]. Metal ions can affect the overall function of the immune system by modulating these interactions. Iron ions can affect the activity of dendritic cells and thus their ability to recognize and process antigens [33]. Finally, metal ions can regulate the differentiation and secretion of immune cells, affecting the strength and direction of the immune response. Some studies have shown that copper ions affect the differentiation of Th17 cells and the secretion of IL-17, which in turn influence the occurrence and development of the tumor-associated inflammatory response [34]. Overall, metal ions play an important role in immune regulation, and their mechanism of action involves several aspects (Fig. 1), including influencing the growth and function of immune cells, influencing the interactions between immune cells, and influencing the differentiation and secretion of immune cells. Further studies on the mechanisms of metal ions in immune regulation can help elucidate the regulatory mechanisms of the immune system and provide new ideas and methods for the treatment of immune regulation-related diseases. Below, we summarize and analyze the specific roles of some of the important metal ions (Zn^{2+}, Cu^{2+}, Mg^{2+}, and Mn^{2+}) in cancer immunomodulation.

Zinc ions (Zn^{2+})

Zinc is the second most abundant transition metal element in living organisms. It always exists in the form of divalent cations (Zn^{2+}) under physiological conditions. As a signaling ion, free Zn^{2+} can regulate the innate and adaptive immune responses of immune cells and affect their functions [35], including the maturation of dendritic cells, the phagocytosis of macrophages, the toxicity of natural killer cells, and the activation of T cells. The immunomodulatory effects of Zn^{2+} in immune cells have been reported. However, the specific molecular mechanisms of antitumor immune responses mediated by Zn^{2+} in tumor cells or the tumor microenvironment are not fully understood, which hinders the development of zinc-based antitumor drugs and the development of metal

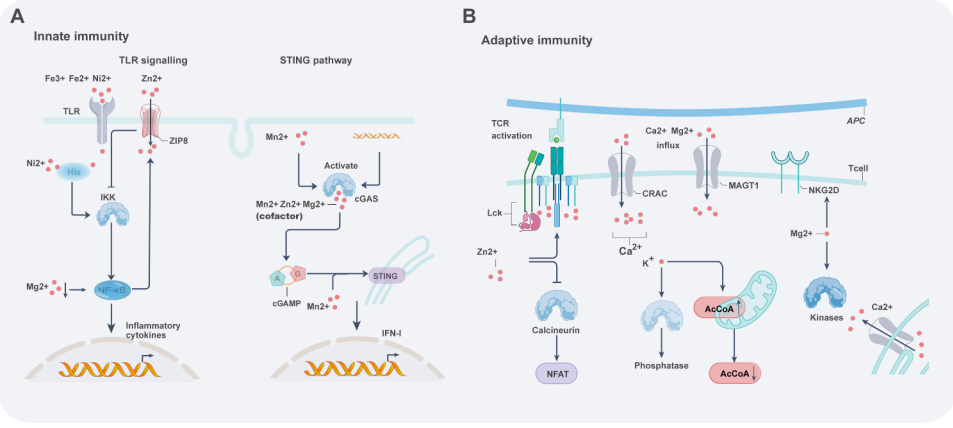

Fig. 1 Metal ion-related immune processes. **(A)** Metal ions and metal-ion containing substances can modulate innate immunity. For example, Ni^{2+}, Fe^{2+}, Fe^{3+}, Zn^{2+} and Mg^{2+} can affect the TLR signaling pathway; Mn^{2+}, Zn^{2+}, Mg^{2+}, K^{+} and Ca^{2+} can regulate the activation and signaling of cGAS-STING. **(B)** Ca^{2+}, Mg^{2+}, and Zn^{2+} are involved in key signaling pathways of T cell function, and hence modulate adaptive immune responses

immunotherapy. Therefore, comprehensively exploring the molecular mechanism of Zn^{2+} in tumor immunoregulation and its potential application in antitumor immunotherapy is highly important.

Zinc ions are key regulators of immune cell function. They exert immunomodulatory effects by influencing the expression and function of immune cell receptors, modulating gene expression, and regulating cell differentiation. For example, zinc affects T cell and B cell functions through modulation of the NF-κB signaling pathway [35]. In T cells, zinc ions regulate the NFAT (nuclear factor of activated T cells) signaling pathway, thereby promoting cytokine secretion and T cell proliferation [35]. Zinc ions may indirectly impact NFAT activation by affecting calcium ion flux, calcium-dependent enzyme activity, or directly interacting with calcium channels and calmodulin. For instance, zinc ions can regulate the expression of zinc finger proteins, which influences intracellular calcium balance, thereby modulating the NFAT pathway [35, 36]. Additionally, zinc modulates immune inhibitory responses by affecting immune checkpoint molecule expression, thus inhibiting tumor immune evasion.

Additionally, zinc ions have multiple possible effects on the function of immune cells in the tumor microenvironment. First, zinc ions can affect the activity of a variety of immune cells [37], including T cells, B cells, and NK cells. Appropriate amounts of zinc ions can promote the activity of immune cells and increase their ability to recognize and kill tumor cells. Second, zinc ions have anti-inflammatory effects [30]: They can inhibit the release of inflammatory mediators and reduce inflammatory responses in the TME, thereby reducing the immunosuppressive state of the TME. Zinc ions are involved in regulating a variety of cell signal transduction pathways, including the NF-κB and STAT pathways, and thereby affect the activity and function of immune cells [35]. Third, zinc ions are cofactors of multiple antioxidant enzymes, which can reduce oxidative stress, protect immune cells from oxidative damage, and enhance their resistance to the tumor microenvironment [38]. Finally, some studies have shown that an appropriate amount of zinc ions can increase tumor antigen presentation and the ability of immune cells to recognize antigens, thereby strengthening antitumor immune responses [35].

Studies have shown that Zn^{2+} overload in tumor cells induces ROS production through two mechanisms: electron leakage from mitochondrial aerobic respiration and NOX1 oxidation of NADPH [39]. The accumulation of ROS and the resulting damage to mitochondrial DNA activate multiple signaling pathways, leading to the production of high levels of interferons and inflammatory cytokines [40]. Additionally, excess Zn^{2+} in tumor cells triggers tumor cell pyroptosis through the canonical caspase-1/GSDMD-dependent pathway and the alternative caspase-3/GSDME-dependent pathway, resulting in the exposure of numerous DAMPs [27]. Furthermore, research has demonstrated that a cyclometalated Pt(IV)-terthiophene complex disrupts zinc homeostasis in tumor cells while inducing DNA damage, leading to excessive cytosolic Zn^{2+} accumulation and redox imbalance and thus ultimately inducing pyroptosis and cytoskeletal remodeling, activating a potent antitumor immune response in vivo [41]. This is the first reported metal complex that modulates zinc homeostasis to activate antitumor immunity, suggesting that zinc homeostasis-targeting drugs have significant potential in cancer chemotherapies and immunotherapies.

In summary, zinc ions play various biological roles in cancer immunotherapy, including promoting the functions of T cells and NK cells, maintaining macrophage activity, regulating inflammatory responses, inhibiting tumor cell proliferation and invasion, and enhancing the efficacy of immunotherapy. The supplementation and regulation of zinc ions are highly important for improving the outcomes of cancer immunotherapy. Future research will further elucidate the specific mechanisms of zinc ions in immune regulation, offering new insights and approaches for cancer treatment.

Copper ions (Cu^{2+})

Copper ions play multiple critical roles in the body, participating in various biochemical processes and physiological functions [42]. As cofactors for many essential enzymes, copper ions are crucial in antioxidant defense (e.g., superoxide dismutase), energy production (e.g., cytochrome oxidase), and pigment synthesis (e.g., tyrosinase) [42]. Copper ions support the health of connective tissues by promoting the cross-linking of collagen and elastin through lysyl oxidase, thereby enhancing tissue structure and function [43]. The nervous system relies on copper ions for neurotransmitter synthesis and myelination, ensuring efficient nerve signal transmission [44]. Additionally, copper ions enhance macrophage phagocytic capacity and antioxidant defense in the immune system, protecting cells from oxidative damage. Their broad-spectrum antimicrobial activity inhibits pathogens such as bacteria, viruses, and fungi, and in wound healing, they promote angiogenesis and cell proliferation, accelerating tissue repair [45]. These combined functions make copper ions essential for maintaining health and normal physiological functions.

Additionally, copper ions play critical roles in the activation and function of immune cells, involving various mechanisms and cell types. As an essential trace element, copper promotes the proliferation and activation of T cells by regulating T-cell receptor (TCR) signaling, thereby enhancing the response to antigens. Copper ions also regulate T cell proliferation and differentiation by

activating multiple signaling pathways, such as the MAPK and PI3K/Akt pathways [29, 46]. The MAPK pathway, particularly the ERK pathway, is essential for T cell activation and proliferation. By activating the ERK pathway, copper ions enhance T cell proliferation and immune responses, boosting their ability to target tumors. Studies have shown that copper deficiency may lead to reduced T cell immune function, whereas adequate copper supplementation can strengthen T cell immune responses. However, copper overload can also result in T cell apoptosis or impaired proliferation [47]. Moreover, copper ions also increase the antioxidant capacity and pathogen-phagocytizing function of macrophages by increasing the activity of copper–zinc superoxide dismutase (Cu/Zn-SOD) within these cells [48]. copper can modulate the cytotoxicity and cytokine secretion of natural killer (NK) cells, increasing their ability to eliminate virus-infected cells and tumor cells [29]. The antigen-presenting function and T-cell activation role of dendritic cells (DCs) are also influenced by copper ions, which play crucial roles in adaptive immunity. By regulating inflammatory signaling pathways such as the NF-κB pathway, copper ions modulate the inflammatory response, affecting the secretion of inflammatory factors and the intensity of inflammation [29]. Copper ions also support the metabolism and energy supply of immune cells, ensuring that they have sufficient energy during activation and function. By influencing intercellular communication, copper ions regulate the migration and localization of immune cells, ensuring an effective immune response. These multifaceted roles highlight the importance of copper ions in maintaining the normal function of the immune system and ensuring effective immune responses.

Copper ions play crucial regulatory roles in cancer immunotherapy by enhancing antitumor immune responses through various mechanisms. Copper ions promote the proliferation and activation of T cells and natural killer (NK) cells [29], increasing their ability to recognize and kill cancer cells. Additionally, copper ions increase the phagocytic function and cytokine secretion of macrophages, thereby enhancing their antitumor effects. Copper ions also regulate the tumor microenvironment, influencing the polarization state of tumor-associated macrophages and angiogenesis, and thus indirectly inhibit tumor growth and metastasis. Specifically, copper can promote the M1 (proinflammatory) polarization of tumor-associated macrophages, thereby strengthening the antitumor immune response [48]. Furthermore, by regulating angiogenesis [49], copper ions influence the blood supply and oxygen delivery to tumors, indirectly affecting tumor growth and metastasis. Copper ions also play essential roles in antioxidant defense by increasing the activity of antioxidant enzymes, protecting immune cells from oxidative stress damage, and maintaining their functional activity. Oxidative stress not only impacts tumor cell growth but also suppresses the function of immune cells [50]. By maintaining antioxidant defenses, copper ions help protect immune cells and enhance their antitumor effects. Copper ions are also involved in regulating cell signaling and gene expression, influencing the behavior of both immune cells and tumor cells to further strengthen the antitumor immune response. For example, copper ions can influence gene expression by regulating metal response elements (MREs) and metal transcription factors (MTF-1) [51, 52]. These gene regulatory networks are involved in cell growth, differentiation, and metabolism, ensuring normal cell function and health. The regulation of the expression of specific genes by copper ions helps to increase the antitumor activity of immune cells and inhibit the malignant behavior of tumor cells. Through these multiple regulatory functions, copper ions significantly increase the effectiveness of cancer immunotherapy. These effects suggest new therapeutic strategies and insights.

Magnesium ions (Mg^{2+})

As a macronutrient in the human body, magnesium plays an indispensable role in a variety of life activities, such as enzymatic reactions, bone formation, and nerve excitation. Low magnesium dietary intake and hypomagnesemia are associated with the development of various diseases, including infections and cancer [53]. It was previously reported that feeding mice a diet deficient in magnesium ions accelerated the spread and metastasis of cancer cells [54]; furthermore, magnesium ions play an important role in the immune response and can promote the activation of CD8 + T cells by binding to LFA-1 [31]. These findings suggest that magnesium ions may have important clinical significance as immunomodulators in cancer immunotherapy.

Magnesium ions have multiple key regulatory functions in cancer immunotherapy: maintaining immune cell activity, regulating cell signaling, promoting immune cell migration and adhesion, and modulating the tumor microenvironment. Magnesium ions are important cofactors for immune cells, such as T cells, B cells and natural killer (NK) cells [31], and enhance the overall antitumor capacity of the immune system by promoting the proliferation and differentiation of these cells. Magnesium regulates intracellular signaling pathways and supports immune cell activation and response by influencing calcium signaling and ATP stabilization [55]. Magnesium ions also enhance the antitumor immune response by influencing the cytoskeleton and promoting the localization and infiltration of immune cells in the tumor microenvironment [53]. In addition, magnesium ions indirectly inhibit tumor growth and metastasis by modifying the immune status of the tumor microenvironment through

the regulation of the extracellular matrix and angiogenesis [56]. The antioxidant and anti-inflammatory effects of magnesium protect immune cells from oxidative damage and maintain their normal function. By regulating gene expression, magnesium ions influence immune cell function and antitumor capacity, which in turn enhances the effectiveness of cancer immunotherapy and improves treatment outcomes.

Magnesium ions influence the NF-κB pathway through multiple mechanisms [57]. In immune cells, magnesium ions may participate in regulating the activity of the IκB kinase complex, inhibiting IκB phosphorylation and degradation, thereby suppressing NF-κB activation. This mechanism plays a critical role in immune responses, as magnesium's regulation of the NF-κB signaling pathway aids immune cells in responding effectively within inflammatory environments. Changes in magnesium ion concentrations within immune cells can directly impact cytokine secretion. For instance, in macrophages and T cells, magnesium regulates calcium signaling and the NF-κB pathway, controlling the production of cytokines such as IL-2, TNF-α, and IFN-γ [58, 59]. These cytokines play key roles in immune responses, especially in tumor and infection immunity.

In summary, the regulatory function of magnesium ions in cancer immunotherapy involves several aspects and enhances antitumor immune responses through multiple mechanisms. Magnesium ions act as cofactors for a variety of enzymes and participate in the metabolism, proliferation and differentiation of immune cells, maintaining the activity and function of T cells, B cells and natural killer (NK) cells. Magnesium ions influence the signaling and energy metabolism of immune cells by regulating calcium ion (Ca^{2+}) signaling pathways and intracellular ATP stability [55]. Through these multiple regulatory functions, magnesium ions significantly increase the efficacy of cancer immunotherapy, provide new therapeutic strategies and ideas, and improve the therapeutic prognosis of patients.

Manganese ions (Mn^{2+})

Manganese ions (Mn^{2+}) play important roles in biology and are involved in several physiological processes and cellular functions. As a trace element, manganese plays an indispensable role in the maintenance of normal physiological functions in living organisms. In addition, manganese ions are important in immune cell activation and function, which are essential for the normal function of the immune system. First, manganese ions are involved in regulating the activation and proliferation of T cells [60]. During the T-cell receptor (TCR) signaling process, manganese ions participate as cofactors in the regulation of the activity of a variety of enzymes, such as protein kinase C (PKC) and phosphatase, thereby promoting the activation and proliferation of T cells and enhancing their ability to respond to antigens. Second, manganese ions affect the activity and function of macrophages [60]. Macrophages are important antigen-presenting and phagocytic cells in the immune system, and the activity of intracellular enzymes such as superoxide dismutase (SOD) is regulated by manganese ions, which increase the antioxidant capacity and phagocytosis of pathogens in macrophages, thereby improving the antibacterial and antiviral capacity of the immune system. In addition, manganese ions regulate the production of active oxidative enzymes and cytokines in NK cells and the resulting cytotoxicity and cytokine secretion [60], which enhances the killing effect of NK cells on tumor cells. Overall, manganese ions play important roles in immune cell activation and function, enhancing the ability of the immune system to fight against pathogens and tumor cells by regulating the activity and function of T cells, macrophages, and NK cells and maintaining the immune balance and healthy state of the body.

Although the relevant studies are still in the preliminary stage, some studies have suggested that manganese ions may play a regulatory role in cancer immunotherapy. First, manganese ions are involved in regulating the activation and function of T cells, which may contribute to the enhancement of T-cell recognition and killing of tumor cells [60]. By regulating the T-cell receptor (TCR) signaling pathway and the activity of related signaling molecules, manganese ions can influence the degree of T-cell activation and antitumor effects. Second, manganese ions may enhance the killing effect of macrophages, which are important antitumor cells in the immune system, by increasing their phagocytosis and cytokine production, thus enhancing the ability of the immune system to attack tumors [61]. Third, manganese regulates the antioxidant capacity of immune cells by serving as a cofactor of the antioxidant enzyme superoxide dismutase (SOD) [62], which can increase the antioxidant capacity of immune cells, protect immune cells from oxidative stress damage, and maintain their normal function. Fourth, manganese ions participate in regulating the signaling pathway of immune cells, affecting the production and release of cytokines and thus the ability of immune cells to recognize and kill tumor cells. Fifth, manganese ions may enhance immune surveillance and clearance of tumors by the immune system by influencing the activity and proliferation of immune cells, thus increasing the effectiveness of immunotherapy [63].

Manganese ions can effectively activate the cGAS-STING signaling pathway in immune cells [60, 64]. Within the tumor microenvironment, intracellular cGAS detects DNA fragments released by tumor cells, generating the signaling molecule cGAMP, which subsequently triggers downstream signaling through the STING

protein. Manganese ions enhance this process, promoting a more efficient activation of the cGAS-STING pathway. Activation of this pathway leads to the production of type I interferons (such as IFN-α and IFN-β) and various pro-inflammatory factors, enhancing the immune surveillance and cytotoxicity of NK cells and macrophages. This, in turn, strengthens the innate immune system's ability to recognize and attack tumor cells.

In summary, manganese ions in cancer immunotherapy may enhance the ability of the immune system to attack tumors and improve the effectiveness of immunotherapy by regulating the activity and function of T cells, macrophages and other immune cells. However, further studies and explorations of the specific mechanisms of manganese ions in cancer immunotherapy are needed.

The role of metal ions in cancer immunotherapy

Zinc ions in cancer immunotherapy

The role of zinc ions in immune cell function is an important direction in cancer immunotherapy research. Studies have shown that zinc ions regulate T-cell activity and function through multiple pathways. For example, zinc ions increase the proliferation and cytotoxic activity of T cells by regulating signaling pathways within T cells [65], especially the NF-κB and MAPK pathways [66]. Zinc ions were found to significantly improve the efficacy of CAR-T-cell therapy by increasing T-cell activation and persistence [67]. In addition, zinc ions play important roles in regulating the functions of natural killer (NK) cells and macrophages. Zinc ions can enhance the ability of NK cells to kill tumor cells by increasing their cytotoxic activity and IFN-γ secretion [66]. Another study demonstrated that zinc ions could regulate the polarization state of macrophages, promoting their transformation to antitumor M1-type macrophages, thereby inhibiting tumor growth [39, 66]. These findings reveal the potential of zinc ions to enhance innate immune responses.

The regulatory role of zinc ions in the tumor microenvironment should not be overlooked. The tumor microenvironment usually has complex immunosuppressive properties that hinder effective immune responses. Studies have shown that zinc ions can regulate the tumor microenvironment and enhance the function of immune cells through various mechanisms [39]. For example, zinc ions can attenuate the immunosuppressive effects in the tumor microenvironment by inhibiting the function of immunosuppressive cells, thereby enhancing antitumor immune responses [39]. In addition, zinc ions can directly inhibit the growth and survival of tumor cells by regulating their metabolic and apoptotic pathways [66].

The use of zinc supplements has also shown potential benefits. Several clinical studies have shown that zinc supplementation can improve immune function and therapeutic outcomes in cancer patients. For example, a study in patients with advanced tumors revealed that zinc supplementation significantly increased T-cell activity and the immune response in patients, leading to improved clinical prognosis [66]. In addition, zinc ions play an important role in the development of cancer vaccines. Zinc ions can act as adjuvants [68, 69] to increase the immunogenicity of cancer vaccines and improve antitumor immune responses. These studies indicate that zinc ions have broad application prospects for improving the immune function of patients and increasing the efficacy of cancer vaccines.

Zinc ions have also been recognized as promising cofactors in comprehensive tumor therapy regimens. Several studies have shown that zinc can enhance the effects of conventional therapies through a variety of mechanisms. For example, zinc can enhance the antitumor effects of radiotherapy by increasing radiosensitivity. A study on the combined application of zinc and radiotherapy revealed that zinc significantly inhibited tumor growth by promoting the oxidative stress response of tumor cells and increasing the efficacy of radiation therapy [37]. Zinc ions can also inhibit tumor development by regulating the autophagy process in tumor cells [70]. Autophagy is an intracellular degradation pathway that plays an important role in the survival and growth of tumor cells. Zinc can inhibit tumor growth by regulating the expression of autophagy-related genes and promoting autophagic apoptosis in tumor cells [71]. This mechanism provides a new idea for the application of zinc in tumor therapy.

In summary, the application of zinc ions in cancer immunotherapy has important potential and broad prospects. Recent studies have shown that zinc ions can regulate immune cell function, the tumor microenvironment and tumor cell metabolism through multiple mechanisms, thus enhancing antitumor immune responses. Clinical applications of zinc supplements have also shown significant therapeutic effects. However, the safety and optimal use strategy of zinc ions still need further research. In the future, with a deeper understanding of the mechanisms of action of zinc ions and the development of novel therapeutic technologies, the application of zinc ions in cancer immunotherapy will have broader prospects.

Copper ions in cancer immunotherapy

The application of copper ions in tumor immunotherapy is an emerging topic of high interest in the field of tumor research. In recent years, studies have shown that copper ions play multiple important roles in the tumor microenvironment and the immune system, with significant effects on the regulation of tumor growth, metastasis and immune responses [29, 72]. Copper is an essential trace element involved in many biological processes, such as

angiogenesis, oxidative stress, apoptosis and immune regulation [44, 73]. Abnormal copper metabolism is closely associated with the onset and progression of many diseases, especially tumors. Understanding and exploiting the properties of copper ions has the potential to provide new strategies and tools for tumor immunotherapy.

First, the role of copper ions in the tumor microenvironment has a profound impact on tumor progression and immune escape. Copper ions can influence tumor growth and spread by promoting angiogenesis [42]. Angiogenesis is necessary for tumor growth and metastasis, and copper ions, as angiogenic factors, can activate vascular endothelial cells and promote neovascularization. This process not only provides tumor cells with necessary nutrients and oxygen but also provides a pathway for tumor cell metastasis. In addition, copper ions can regulate the level of oxidative stress in the tumor microenvironment [49, 74]. Oxidative stress refers to abnormally elevated levels of reactive oxygen species (ROS), which can cause cellular damage and DNA mutations, thereby promoting tumorigenesis and development. Copper ions regulate the generation and removal of ROS by influencing redox reactions, and the effects on oxidative stress, in turn, influence the growth and survival of tumor cells.

Second, the role of copper ions in tumor immunomodulation provides new ideas for tumor immunotherapy. Immune escape is a key step in the process of tumor development, and tumor cells escape the surveillance and attack of the immune system through a variety of mechanisms. Copper ions can regulate the function of immune cells and enhance antitumor immune responses. For example, copper ions can influence the immunosuppressive effects of tumor cells on T cells by regulating the expression of programmed death ligand 1 (PD-L1) [75], an important immune checkpoint molecule that binds to programmed death receptor 1 (PD-1) on the surface of T cells and inhibits T-cell activation and function. By regulating the expression of PD-L1, copper ions can increase T-cell activity and improve the therapeutic effect of immune checkpoint inhibitors [22, 29]. In addition, copper ions can enhance antigen presentation and immune activation by regulating the function of macrophages and dendritic cells [48], thereby increasing the immunogenicity and therapeutic efficacy of tumor vaccines.

The application of copper ions in tumor immunotherapy has great potential but faces many challenges. First, copper ions are cytotoxic at high concentrations and can cause nonspecific cellular damage. Therefore, in tumor immunotherapy, the dose and distribution of copper ions need to be precisely controlled to ensure their specific accumulation at the tumor site. The next issue is the delivery and release of copper ions. How to effectively deliver copper ions to the tumor microenvironment and release them within a specific time and space range is the key to achieving their therapeutic effects. To this end, researchers have developed a variety of nanocarriers and drug delivery systems, such as copper-based nanoparticles [76], copper ion chelators [49], and copper ion release control systems [77], to improve the therapeutic efficacy and safety of copper ions. In addition, the mechanism of action of copper ions in different tumor types may differ, and in-depth studies on their specific effects and regulatory mechanisms in different tumors are needed to achieve personalized and precise tumor immunotherapy.

In conclusion, the application of copper ions in tumor immunotherapy is promising, and by regulating the tumor microenvironment and immune response, copper ions are expected to become an important means of tumor therapy. However, many technical and safety challenges still need to be overcome in practical applications, and the therapeutic strategies and methods of copper ions need to be optimized continuously through multidisciplinary cooperation and technological innovation to achieve broad application in the clinic. In the future, with an in-depth understanding of the mechanism of copper ions and the development of new drug delivery systems, the application of copper ions in tumor immunotherapy will be further expanded and perfected, which will lead to more effective therapeutic solutions and better survival prognoses for patients with tumors.

Magnesium ions in cancer immunotherapy

The application of magnesium ions in tumor immunotherapy is a relatively new area of research, but there is already evidence that magnesium ions play an important role in regulating the immune system and tumor microenvironment [31]. Magnesium is an essential trace element involved in a variety of biological processes, such as cell metabolism, protein synthesis, and DNA replication and repair [53, 78]. In tumor immunotherapy, the application of magnesium ions focuses on the regulation of immune cell function, modification of the tumor microenvironment, and potential role of magnesium ions in immune checkpoint inhibitor therapy.

First, magnesium ions enhance the antitumor immune response by regulating the function of immune cells. Studies have shown that magnesium ions can affect the activation and function of T cells, which are the core cells of the body's antitumor immune response, and that magnesium ions can enhance the activation and proliferation of T cells by regulating the T-cell receptor (TCR) signaling pathway [31]. In addition, magnesium ions can regulate the receptor expression and function of natural killer (NK) cells and increase their ability to kill tumor cells [79, 80]. Therefore, by supplementing with magnesium ions or regulating the magnesium metabolism, the antitumor

ability of T cells and NK cells can be effectively improved, and the antitumor immune response of the body can be enhanced (Fig. 2).

Second, magnesium ions play an important role in modifying the tumor microenvironment. The tumor microenvironment refers to the complex system composed of tumor cells and their surrounding stromal cells, blood vessels, immune cells and extracellular matrix. The tumor microenvironment plays a key role in the process of tumorigenesis, development and metastasis [81]. Magnesium ions can affect tumor growth and spread by regulating intercellular interactions, the composition of the extracellular matrix and the balance of metabolites in the tumor microenvironment. For example, magnesium ions can influence matrix degradation and remodeling by regulating the activity of extracellular matrix metalloproteinases (MMPs) [82], which in turn inhibits tumor cell invasion and metastasis. In addition, magnesium ions reduce the levels of proinflammatory factors in the tumor microenvironment by regulating oxidative stress [83], decreasing inflammatory responses, improving the tumor microenvironment, and inhibiting tumor growth and proliferation. Therefore, magnesium ions have important application potential in the modification of the tumor microenvironment.

Third, the potential role of magnesium ions in immune checkpoint inhibitor therapy is also an area of interest. Currently, PD-1/PD-L1 and CTLA-4 are the most common immune checkpoint inhibitor targets. However, not all patients respond well to immune checkpoint inhibitor therapy, and studies have shown that magnesium ions may play a regulatory role in this process. For example, magnesium ions can enhance the response of T cells to immune checkpoint inhibitors by regulating their metabolism and improving their persistence and function [31]. In addition, magnesium ions can enhance the therapeutic effect of immune checkpoint inhibitors by regulating immune cell infiltration in the tumor microenvironment [84]. Therefore, magnesium ions, as an adjuvant therapy, are expected to increase the therapeutic effect of immune checkpoint inhibitors and improve the prognosis of patients.

Finally, the application of magnesium ions in tumor immunotherapy faces some challenges. Although magnesium ions show great potential in regulating immune cell function and modifying the tumor microenvironment,

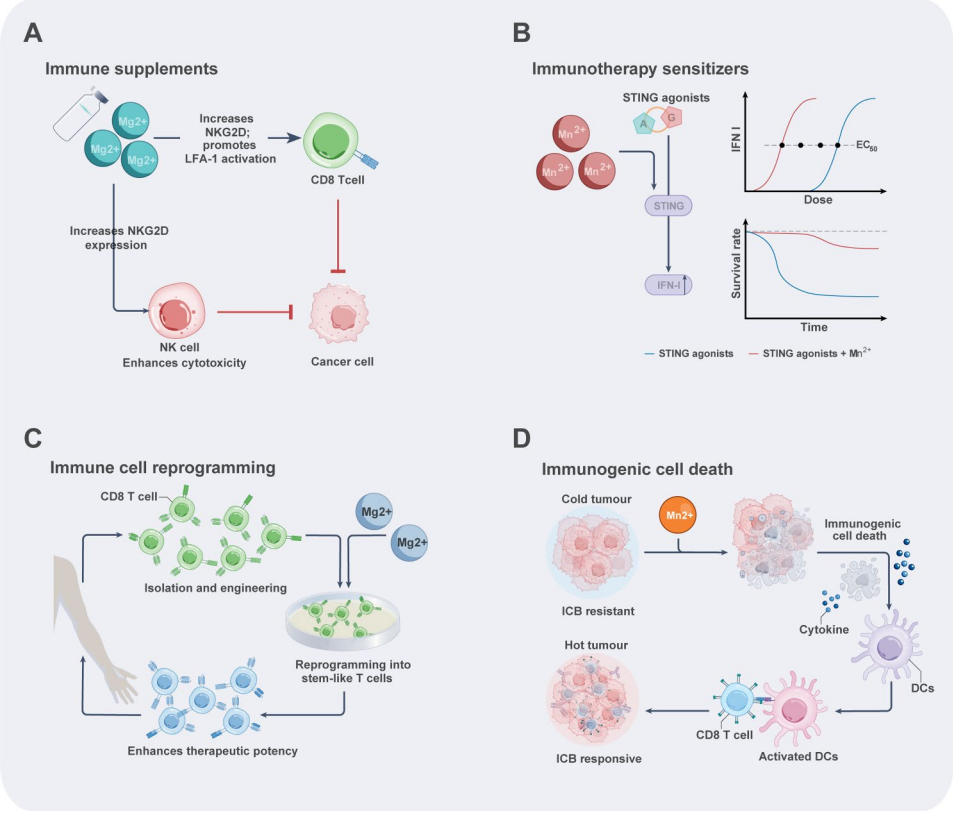

Fig. 2 Metalloimmunotherapies in cancer. **(A)** Metal-ion-based immune supplements. For example, Mg^{2+} supplements enhance anticancer immune responses by augmenting the cytotoxicity of CD8 T cells and NK cells [31, 161]. **(B)** Metal-ion-based immunotherapy sensitizers [63]. For example, Mn^{2+} amplifies the activation of STING and enhances the therapeutic efficacy of immunotherapies. **(C)** Metal-ion-mediated immune-cell reprogramming [162]. For example, Mg^{2+} can reprogramme CD8 T cells ex vivo by increasing their stemness to enhance the potency of adoptive cell transfer. **(D)** Immunogenic cell death induced by metal complexes or metal ions [63]. For example, Mn^{2+} induce immunogenic cell death in cancer cells

their safety and efficacy in clinical applications still need to be further verified. Excessive amounts of magnesium ions may lead to toxic reactions, so precise control of their dosage and usage is needed. In addition, differences between different tumor types and individual patients need to be considered when personalizing treatment. Future studies should explore the mechanism of action of magnesium ions more deeply and pursue the development of novel magnesium ion delivery systems and combination therapeutic regimens to improve the effectiveness of their application in tumor immunotherapy. In conclusion, the application of magnesium ions in tumor immunotherapy has broad prospects, and through multidisciplinary cooperation and technological innovation, magnesium ions are expected to become an important means of tumor treatment with improved therapeutic effects and quality of life for patients.

Manganese ions in cancer immunotherapy

In recent years, tumor immunotherapy, as a new frontier in cancer treatment, has achieved remarkable clinical results and improved survival in countless patients. Manganese is an essential trace element, second only to iron in the human body. Manganese ions have shown marked effects in maintaining nerve [85], heart and muscle functions [86]; improving immunity [87]; and improving the hematopoietic system.

The cGAS-STING pathway is an important natural immune activation pathway discovered in recent years that recognizes DNA in the cytoplasm and triggers a strong immune response [88]. Studies have shown that manganese ions can significantly increase the sensitivity of cGAS to DNA (Fig. 2), promote its synthesis of the second messenger cGAMP, and increase the affinity of STING proteins for cGAMP, thereby activating the downstream immune response [64, 89]. This process not only enhances the recognition and clearance of tumor cells by host cells but also promotes the activation and proliferation of tumor-specific T cells. In addition, manganese ions can enhance the tumor immune response by modulating the function of antigen-presenting cells, such as dendritic cells (DCs) and macrophages (Mϕs) [64, 90]. These cells play a key role in the uptake, processing and delivery of tumor antigens to T cells. Manganese ions can increase the expression of costimulatory molecules on the surface of antigen-presenting cells and improve their uptake and processing of antigens, which in turn promotes the activation and differentiation of T cells [60]. Manganese ions can also increase the infiltration and survival ability of T cells in the tumor microenvironment, making them to exert antitumor effects more effectively. Studies have shown that manganese ions can significantly increase the killing activity of NK cells and promote their secretion of cytokines such as IFN-γ [91]. These cytokines not only directly inhibit the growth and metastasis of tumor cells but also further activate and recruit other immune cells to participate in the antitumor immune response [92–94].

Although the study of manganese ions in tumor immunotherapy is still in its infancy, some preliminary clinical trials have shown their potential application value. With a deeper understanding of the mechanism of manganese ions in tumor immunotherapy, an increasing number of studies have explored their application value in clinical practice. For example, researchers have developed novel immunomodulators or vaccine adjuvants based on manganese ions with the aim of enhancing tumor therapeutic efficacy by increasing the antitumor activity of the immune system [95, 96]. In addition, manganese ions have been used in combination with other immune checkpoint inhibitors (e.g., PD-1 antibodies) to achieve synergistic therapeutic effects [97]. Studies have shown that manganese ions can effectively synergize with immune checkpoint inhibitors across multiple tumor models, significantly reducing the required dosage of PD-1 antibodies. In this phase I clinical study, 22 evaluable patients were enrolled, most of whom had manganese ion levels below the normal range in peripheral blood at baseline. Patients received varying concentrations of manganese ions combined with PD-1 antibodies and chemotherapy (referred to as "Mn-immunotherapy"). After a median follow-up of 12 months, the Mn-immunotherapy protocol was found to have manageable side effects and demonstrated substantial efficacy across various tumors, achieving a disease control rate of 90.9%, with particularly noteworthy outcomes in ovarian, breast, and pancreatic cancers [60].

In conclusion, the application of manganese ions in tumor immunotherapy presents new opportunities and challenges for research in this field. We expect that more studies will reveal the mysteries of manganese ions in tumor immunotherapy and promote their wide application in clinical practice, thus increasing the benefits for patients with tumors.

Metal ion derivatives in cancer immunotherapy

Metallic nanomaterials in cancer immunotherapy

Nanotechnology holds great promise for improving immunotherapy outcomes for patients with metastatic cancer. Unlike traditional cancer immunotherapy, rationally designed nanomaterials can trigger specific tumor-killing effects, thereby improving immune cell exposure to major metastatic sites such as bone, lung, and lymph nodes; optimizing antigen presentation; and inducing durable immune responses. Specifically, these materials can directly reverse the immune status of the primary tumor, harness the potential of peripheral immune cells to prevent the formation of premetastatic ecological

niches, and inhibit tumor recurrence through postoperative immunotherapy [98].

Metallic nanomaterials, especially the nanomorphic forms of zinc, magnesium, manganese, and copper, have demonstrated unique advantages and broad application prospects in cancer immunotherapy [99]. Owing to their unique physicochemical properties, these nanomaterials can play a variety of roles in the tumor microenvironment, including enhancing the activity of immune cells [100–102], promoting the apoptosis of tumor cells [103–105], and regulating the tumor microenvironment [106, 107], thus achieving effective treatment of cancer [108].

Zinc nanomaterials in cancer immunotherapy

The application of zinc nanomaterials in cancer immunotherapy is rapidly expanding, and their potential in tumor therapy is receiving increasing attention [36]. As an essential trace element, zinc is involved in a variety of biochemical reactions, including enzyme catalysis and the regulation of gene expression. These biological properties of zinc are further amplified at the nanoscale, and zinc nanomaterials have become important in cancer therapeutic research because of their unique physicochemical properties. In recent years, through a series of in vivo and ex vivo experiments, researchers have revealed the multiple roles of zinc nanomaterials in regulating the tumor immune microenvironment, enhancing the effects of immunotherapy and reducing the side effects of conventional treatments.

First, the application of zinc nanomaterials in cancer immunotherapy reflects their powerful immunomodulatory ability. First, zinc-based nanoparticles can induce tumor cells to undergo autophagy, a process of self-digestion and degradation, through which a large amount of zinc ions can be released, which in turn triggers oxidative stress and apoptosis [109, 110]. This mechanism not only kills tumor cells directly but also promotes the immunogenic death of tumor cells, releases tumor-associated antigens, and enhances the antitumor response of the immune system. Second, zinc-based nanoparticles can activate immune cells such as macrophages and dendritic cells, increase their phagocytosis and antigen-presenting ability, and subsequently promote the activation and proliferation of T cells [14, 111]. This regulatory effect on immune cells helps disrupt the immunosuppressive state of tumors and restore the antitumor function of the immune system.

Zinc nanomaterials also have unique advantages as drug carriers in cancer immunotherapy. How to effectively deliver antitumor drugs to the tumor site and reduce their damage to normal tissues is a difficult problem that needs to be solved. Studies have shown that zinc nanomaterials can be precisely targeted to tumor tissues through surface modification or complexation with other functional molecules and can release drugs under specific microenvironmental conditions (e.g., acidic or reducing environments). In addition, zinc nanomaterials, when used in combination with chemotherapy, radiotherapy, or other treatments [112, 113], can enhance the combined therapeutic effect and achieve effective control of multidrug-resistant tumors. Zinc-based nanoparticles can be used as carriers of chemotherapeutic drugs [114] to achieve the targeted delivery and controlled release of drugs through their nanosize effect and surface modification, thus increasing the bioavailability of chemotherapeutic drugs and the sensitivity of tumor cells. Moreover, zinc nanoparticles can enhance the killing effect of chemotherapeutic drugs on tumor cells through mechanisms such as inducing autophagy [115].

Finally, the application of zinc nanomaterials in cancer immunotherapy has shown great potential in combination with photothermal therapy (PTT) or photodynamic therapy (PDT) [116, 117]. PTT and PDT, rapidly developing tumor therapies in recent years, rely on the heat or reactive oxygen species generated by photosensitizers or photothermal agents under light irradiation at specific wavelengths to kill tumor cells [118, 119]. Zinc nanomaterials are ideal carriers for photosensitizers or photothermal agents because of their good optical properties and biocompatibility. For example, researchers have developed zinc-based nanoparticles that can effectively absorb near-infrared (NIR) light and generate localized high temperatures in tumor tissues, thereby directly killing tumor cells [120]. In addition, zinc nanomaterials can combine with PDT to induce apoptosis in tumor cells by generating reactive oxygen species (e.g., single-linear oxygen or hydroxyl radicals) [121]. More importantly, zinc nanomaterials can to further activate the immune system by releasing zinc ions or other drugs after photothermal or photodynamic therapy, thus achieving complete tumor clearance. This multimodal treatment strategy not only effectively inhibits tumor growth and metastasis but also prevents tumor recurrence by inducing a strong immune memory effect.

In summary, the application of zinc nanomaterials in cancer immunotherapy has multiple advantages, ranging from enhancement of the immune response and precise drug delivery to the facilitation of photothermal/photodynamic therapy. With the continuous development of nanotechnology and immunotherapy techniques, zinc nanomaterials are expected to play even more important roles in future cancer treatment as multifunctional, low-toxicity and innovative therapies. Further research in this area will help reveal the mechanism of zinc nanomaterials in tumor immunotherapy and promote their translation into clinical applications.

Magnesium nanomaterials in cancer immunotherapy

Magnesium nanomaterials, emerging as an important type of nanotechnology material, have gradually gained attention in recent years for their application in cancer immunotherapy. As the second largest cation in the human body, magnesium has excellent biocompatibility and biodegradability. These properties make magnesium nanomaterials promising in the field of cancer therapy. In combination with immunotherapy, magnesium nanomaterials can effectively enhance antitumor immune responses, improve therapeutic effects, and significantly reduce the side effects of conventional therapy.

First, the application of magnesium nanomaterials in cancer immunotherapy reflects their unique immunomodulatory function. Studies have shown that magnesium nanomaterials can enhance the antitumor immune response of the body by modulating the activity of immune cells. As important intracellular second messengers, magnesium ions are involved in a variety of signaling pathways, especially in the activation of T cells and NK cells. For example, magnesium nanomaterials can promote T-cell proliferation and cytokine secretion, thereby enhancing T-cell-mediated tumor cell killing [122]. In addition, magnesium nanomaterials can attenuate tumor escape from the immune system by inhibiting immunosuppressive factors in the tumor microenvironment, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [123]. Because of this multilayered immunomodulatory effect, magnesium nanomaterials exhibit unique advantages in cancer immunotherapy. Magnesium nanomaterials also ameliorate the tumor microenvironment by promoting tumor angiogenesis and extracellular matrix remodeling, making it easier for immune cells to infiltrate tumor tissues. This effect helps to enhance the ability of immune cells to recognize and attack tumor cells [122].

Second, magnesium nanomaterials can be used as drug carriers to significantly improve the delivery efficiency and therapeutic effect of antitumor drugs. Traditional chemotherapy and radiotherapy often cause excessive damage to normal tissues because of the lack of targeting, whereas magnesium nanomaterials are ideal drug carriers because of their controlled degradability and good biocompatibility [124]. By the surface modification of magnesium nanomaterials, researchers have enabled them to carry a variety of antitumor drugs or immunomodulators and deliver them precisely to the tumor site. For example, magnesium nanomaterials can be loaded with immune checkpoint inhibitors (e.g., PD-1 or CTLA-4 inhibitors) [99, 125], which are slowly released in specific tumor microenvironments, thereby effectively inhibiting the growth and metastasis of tumor cells. In addition, the gradual degradation of magnesium nanomaterials in vivo releases magnesium ions, which further enhance the local antitumor immune response and reduce the toxicity of the drug to normal tissues. This highly efficient and low-toxicity drug delivery system opens a new path for cancer treatment.

Third, magnesium nanomaterials have the potential for combination with other therapeutic agents in cancer immunotherapy, especially in combined photothermal therapy (PTT) and photodynamic therapy (PDT) [126]. Magnesium nanomaterials can serve as ideal carriers for photosensitizing or photothermal agents because of their excellent physicochemical properties [127]. For example, magnesium-based nanoparticles can bind to photosensitizers through surface modification [121], and these photosensitizers then generate heat or reactive oxygen species in response to light at specific wavelengths and thereby directly killing tumor cells. In addition, magnesium nanomaterials can further activate the body's immune response through the gradual release of magnesium ions after photothermal or photodynamic therapy, thus increasing the antitumor effect. This multimodal therapeutic strategy not only effectively inhibits tumor growth and metastasis but also reduces the risk of tumor recurrence by inducing a long-lasting immune memory effect.

In conclusion, the application of magnesium nanomaterials in cancer immunotherapy is promising, and with the continuous development of nanotechnology and immunotherapy technology, magnesium nanomaterials are expected to play an even more important role in future cancer therapy. The existing research has focused mainly on the preparation of magnesium nanomaterials and their biological effects in vitro and in vivo, and future studies will further explore their mechanisms of action and potential for clinical application. For example, the distribution and drug release properties of magnesium nanomaterials in vivo can be optimized by adjusting their physicochemical properties (e.g., particle size, surface charge, functionalized modifications) [128], thus improving the targeting and safety of therapy. In addition, the combined application of magnesium nanomaterials with other immunotherapeutic treatments (e.g., CAR-T-cell therapy, oncolytic virus therapy) is worth further exploration. Overall, magnesium nanomaterials, as novel and multifunctional materials for cancer immunotherapy, have significant application potential and research value and will lead to new breakthroughs in the field of cancer therapy.

Manganese nanomaterials in cancer immunotherapy

The application of manganese nanomaterials (MnNPs) in cancer immunotherapy is becoming a topic of intense research interest [129]. Owing to their unique chemical and physical properties, such as magnetism, redox properties, photoresponsiveness, and good biocompatibility,

manganese nanomaterials show great potential for modulating the tumor microenvironment, enhancing immune responses, and achieving multifunctional synergistic therapies. These properties enable manganese nanomaterials not only to act directly on tumor cells but also to enhance anticancer effects by modulating the host immune system [130].

First, the magnetic properties of manganese nanomaterials make them important tools in cancer immunotherapy. The magnetic properties of manganese enable the precise localization of MnNPs to the tumor site under the guidance of an applied magnetic field, which improves drug targeting and therapeutic effectiveness [131]. In immunotherapy, magnetic MnNPs can be directed by a magnetic field to aggregate in the tumor region and interact with immune cells such as macrophages and dendritic cells, thereby increasing their ability to capture and present tumor antigens. This enhanced antigen presentation can activate T cells more effectively to initiate a strong antitumor immune response. In addition, magnetic MnNPs can be used in magnetothermal therapy to directly kill tumor cells by inducing a local thermal effect through an alternating magnetic field [132]. This thermal damage not only leads to the necrosis of tumor cells but also releases tumor-associated antigens, further enhancing the immune response. The combination of magnetothermal therapy and immunotherapy results in dual effects on the tumor and significantly improves the therapeutic effect by increasing the release of antigens and promoting the activation of immune cells [132].

Second, the redox properties of manganese nanomaterials play an important role in regulating the tumor microenvironment. The tumor microenvironment usually has immunosuppressive properties, such as low oxygen, an acidic environment and the presence of immunosuppressive cytokines, which together inhibit the activity of immune cells and limit the effect of immunotherapy. Owing to their multivalent properties (e.g., the presence of both Mn (II) and Mn (III)) and ability to undergo redox reactions in the TME, manganese nanomaterials can significantly alter the local chemical environment. For example, MnNPs can catalyze the decomposition of hydrogen peroxide (H_2O_2) via Fenton-like reactions [133] to generate highly reactive oxygen species (ROS) [134, 135], such as hydroxyl radicals (-OH), which can trigger oxidative stress and apoptosis in tumor cells. In addition, the redox reaction of MnNPs can regulate the pH in the TME, reducing the survival advantage of tumor cells while enhancing the function of immune cells [129]. More importantly, by inhibiting the action of immunosuppressive molecules, such as programmed death ligand-1 (PD-L1), manganese nanomaterials can reverse immunosuppression and reactivate suppressed immune cells, thus significantly increasing the effect of immunotherapy [135].

Third, the photoresponsiveness of manganese nanomaterials provides additional therapeutic options for cancer immunotherapy. Mn nanomaterials perform well in photothermal therapy (PTT) and photodynamic therapy (PDT). In photothermal therapy, manganese nanomaterials can generate local high temperatures under near-infrared light (NIR) irradiation, which directly induces the apoptosis of tumor cells while releasing tumor antigens and promoting tumor recognition and attack by the immune system [136]. In photodynamic therapy, MnNPs act as photosensitizers and generate reactive oxygen species (e.g., singlet oxygen $^1O_2$) under light irradiation at specific wavelengths, and these species are capable of inducing oxidative stress and apoptosis in tumor cells [136]. In addition, the combination of these photoresponsive therapies with immunotherapy can increase antigen release from tumor cells and thus immune cell activation, creating a synergistic effect that can further improve therapeutic efficacy. The photoresponsiveness of manganese nanomaterials not only expands the available strategies for cancer immunotherapy but also provides a more effective therapeutic approach through multimodal synergy.

Finally, owing to their biocompatibility and multifunctionality, manganese nanomaterials have a wide range of application prospects in cancer immunotherapy. Manganese, as an essential trace element, is harmless to the human body when present in appropriate amounts, which provides a strong expectation of biocompatibility for the clinical application of manganese nanomaterials. In addition, manganese nanomaterials can be metabolized and degraded into harmless ionic forms that can be absorbed or excreted by the body, and this characteristic greatly reduces the risk of toxicity caused by long-term retention of the material in the body. In terms of application, manganese nanomaterials can not only be used as drug carriers to help deliver chemotherapeutic drugs, gene therapy factors, or immunomodulators but also can be functionalized through surface modification and thus individually designed for different tumor types and therapeutic needs (Fig. 3). For example, manganese nanomaterials can be surface modified with tumor-specific antibodies or immunomodulatory molecules to improve targeting and immune activation or combined with other therapeutic treatments (e.g., radiotherapy and chemotherapy) to achieve synergistic multimodal therapy [135]. Owing to these properties, manganese nanomaterials show great potential for application in cancer immunotherapy and are expected to provide more effective treatment options for cancer patients through comprehensive and multifunctional therapeutic strategies.

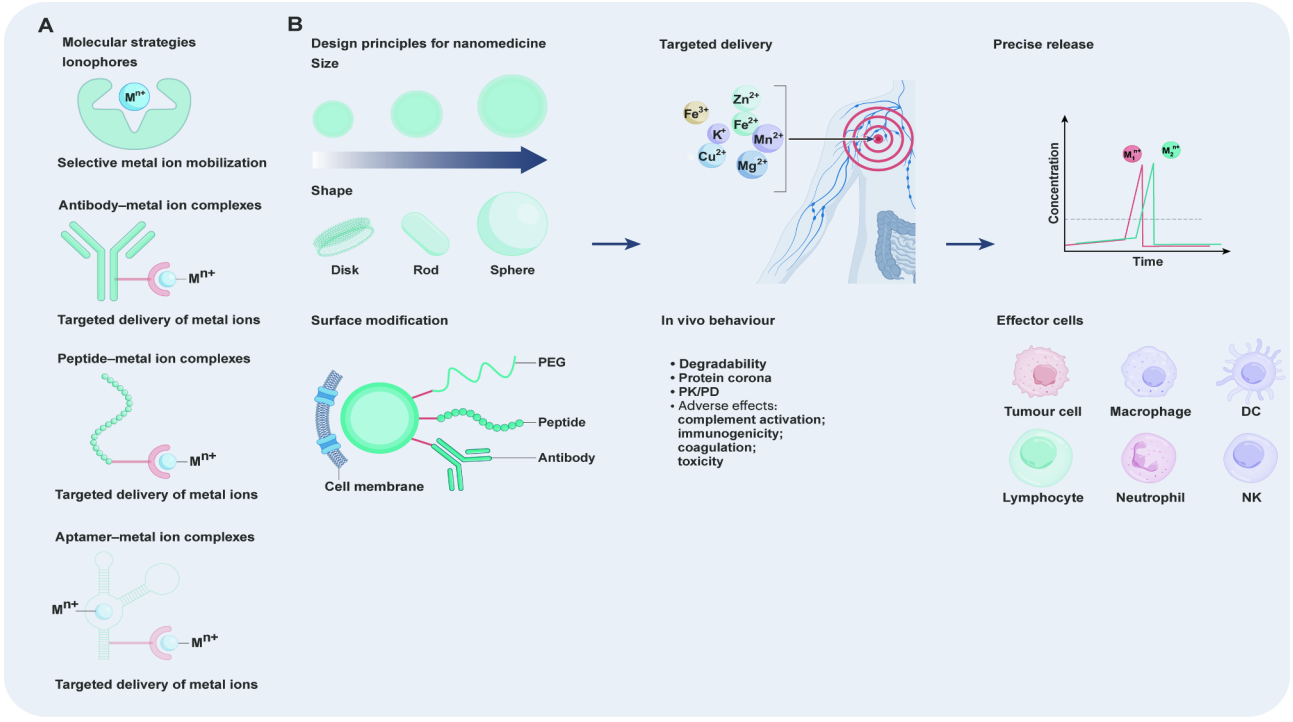

Fig. 3 Precision metalloimmunotherapy in cancer. **(A)** Molecular engineering of ionophores and metal-ion-containing drug conjugates for the precise modulation of metal ions in vivo. **(B)** Design principles for precision metalloimmunotherapy that may allow for targeted delivery across physiological barriers and for the controlled release of metal ions in the cancer tissue at the appropriate time. M^{n+}, a metal ion with a positive charge of 'n'; PK, pharmacokinetic; PD, pharmacodynamic

In conclusion, the application of manganese nanomaterials in cancer immunotherapy relies on their unique magnetic properties, redox properties, photoresponsiveness, and high biocompatibility. Because of these unique chemical and physical properties, manganese nanomaterials can effectively modulate the tumor microenvironment, enhance the antitumor response of the immune system, and synergize with other therapeutic methods in a comprehensive multimodal therapeutic strategy. With the continual development of nanotechnology and cancer immunotherapy, the application of manganese nanomaterials in the field of cancer therapy will become more promising, and new breakthroughs for increasing the effectiveness of cancer treatment and the survival rate of patients are expected.

Copper nanomaterials in cancer immunotherapy

The application of copper nanomaterials in cancer immunotherapy is gradually becoming a research hotspot, and their unique physicochemical properties provide a solid foundation for their application in this field. Copper nanomaterials (CuNPs) have excellent biocompatibility and present a wide range of application prospects due to their redox capacity, tunable chemical reaction activity, and maneuverability in both ex vivo and in vivo environments.

First, the unique redox properties of copper nanomaterials play an important role in cancer immunotherapy. Copper can participate in a Fenton-like reaction in vivo, which enables CuNPs to catalyze the generation of highly reactive hydroxyl radicals (-OH) from hydrogen peroxide (H_2O_2) in the tumor microenvironment [34]. Hydroxyl radicals have an extremely strong oxidative capacity and can trigger oxidative stress in tumor cells, which in turn leads to the apoptosis and necrosis of tumor cells. In addition, this redox property can produce an immune-enhancing effect at the tumor site by destroying tumor cells, releasing tumor antigens, and further activating dendritic cells and macrophages in the immune system. This immune-activating effect can enhance the T-cell-mediated antitumor immune response, creating multiple strikes against the tumor. This application of redox reactions based on copper nanomaterials represents a unique tumor therapeutic mechanism by which CuNPs exhibit significant advantages in cancer immunotherapy. Copper nanoparticles can accumulate in tumor cells and release copper ions to trigger cuproptosis (copper death), a novel mode of programmed cell death [75, 137, 138]. By inducing cuproptosis, Cu nanoparticles can directly kill tumor cells and release tumor-associated antigens and damage-associated molecular patterns (DAMPs) to enhance the antitumor response of the immune system. Copper nanoparticle-induced cuproptosis also promotes immune

cell infiltration and activation [16, 139, 140]. This action helps disrupt the immunosuppressive state of the tumor and restore the antitumor function of the immune system, thereby enabling cancer immunotherapy.

Second, copper nanomaterials have tunable surface chemistry, which makes their applications in cancer immunotherapy more flexible and diverse. The surface of CuNPs can be chemically modified or functionalized to confer targeting properties or increase their biological activity. This flexibility in surface chemistry allows copper nanomaterials to be designed for different therapeutic needs, resulting in a wide range of applications. Copper nanoparticles can also be used in combination with other therapeutic means, such as chemotherapy and radiotherapy, to achieve synergistic treatment of cancer through multiple pathways and multitargeted effects on tumor cells and the tumor microenvironment [141, 142].

Third, copper nanomaterials have excellent photothermal effects, providing an additional therapeutic avenue for cancer immunotherapy. Copper nanomaterials can effectively absorb near-infrared (NIR) light and convert it into thermal energy [143]. This photothermal effect can generate high temperatures locally in the tumor and directly induce thermal damage and necrosis in tumor cells. Moreover, the heat stress response can increase the permeability of the tumor cell membrane, allowing the release of more tumor antigens into the tumor microenvironment, thus promoting the activation of antigen-presenting cells to stimulate a potent antitumor immune response. In addition, photothermal therapy can also increase the infiltration and activity of immune cells by increasing the temperature of the tumor site, further strengthening the effect of immunotherapy. This combination of photothermal effects and immunotherapy based on copper nanomaterials provides a new integrated therapeutic strategy for tumor treatment.

Finally, the multifunctionality of copper nanomaterials gives them potential for a wide range of applications in cancer immunotherapy. In addition to their redox properties, surface chemical tunability, and photothermal effects, copper nanomaterials can enhance therapeutic effects through combination with immunomodulators, chemotherapeutic drugs, or gene therapy vectors. For example, CuNPs can be used as drug delivery carriers [144] to target chemotherapeutic drugs or immunomodulators to the tumor site, achieving the dual effects of efficient tumor cell killing and immune system regulation. In addition, copper nanomaterials can be combined with gene therapy to deliver specific genes to tumor cells or immune cells as nanocarriers, thereby synchronizing gene regulation and antitumor effects. Owing to their multifunctionality, CuNPs have great flexibility and application value in the field of cancer therapy.

Copper nanomaterials have promising applications in cancer immunotherapy. Owing to their unique redox properties, surface chemical tunability, photothermal effects, and multifunctionality, these materials have unique advantages in antitumor therapy. With the development of nanotechnology and immunotherapy, copper nanomaterials are expected to play an increasingly important role in future cancer therapy, providing new hope for improving therapeutic effects and patient survival.

In conclusion, the above studies demonstrate the promise of metallic nanomaterials in cancer immunotherapy. Zinc, magnesium, manganese and copper nanomaterials enhance antitumor immune responses through various mechanisms, including the modulation of immune cell function, the regulation of the tumor microenvironment, the induction of apoptosis in tumor cells, and the ability to act as drug carriers. These metallic nanomaterials can be used not only alone but also in combination with other therapeutic agents to increase the effectiveness of antitumor therapy. However, the clinical application of metallic nanomaterials still faces some challenges, such as control of toxicity and side effects, optimization of drug delivery systems, and development of individualized treatment protocols (Fig. 3). Future studies should continue to focus on the mechanism of action of metallic nanomaterials, develop safer and more effective drug delivery systems, and explore combination therapy strategies to promote their clinical translation and application in cancer immunotherapy. Overall, metallic nanomaterials provide a new direction and hope for cancer immunotherapy and are expected to become an important tool for cancer treatment.

Metal alloys in cancer immunotherapy

Cancer immunotherapy, which recognizes and destroys tumor cells by mobilizing the body's own immune system, has made remarkable progress in recent years. However, traditional cancer immunotherapies, such as immune checkpoint inhibitors and cancer vaccines, still face some challenges, such as limited therapeutic efficacy and severe side effects. In recent years, metal alloy materials have shown great potential for application in cancer immunotherapy because of their unique physicochemical properties, such as excellent mechanical strength, controlled degradation rate and good biocompatibility. Metal alloy materials, with zinc, magnesium, manganese and copper as the main components, can participate in and modulate immune responses more effectively because of the important physiological functions of these metals in organisms. In this section, the possible applications of zinc, magnesium, manganese and copper alloy materials in cancer immunotherapy and their mechanisms of action are discussed in detail.

Zinc alloy materials in cancer immunotherapy

Zinc alloys, owing to their excellent mechanical properties and corrosion resistance, play an important role in several industrial sectors. Zinc is an essential trace element in living organisms and is involved in a variety of physiological processes, including the maintenance of immune function. This property makes it possible that zinc alloys may have indirect or revelatory roles in medicine, especially in treatments related to the immune system. Although there is no direct evidence that zinc alloys can be used directly in cancer immunotherapy, the function of elemental zinc in living organisms provides us with ideas for exploring its new applications in cancer therapy.

By shifting the focus from zinc alloys to the element zinc itself, we can see the potential role of zinc in cancer immunotherapy. Studies have shown that zinc ions can exert antitumor effects by influencing the signaling, proliferation and apoptosis of tumor cells [37]. In addition, zinc is necessary to maintain the normal function of the immune system, and moderate supplementation with zinc can enhance the body's immune response [65] and improve its anticancer function. Therefore, in cancer immunotherapy, zinc can play various roles, for example, as an adjuvant therapy to enhance the immunotherapeutic effect or as part of a drug carrier to facilitate the targeted delivery of anticancer drugs. These potential applications provide directions for further research on the use of zinc in cancer immunotherapy.

Although the direct application of zinc alloy materials in cancer immunotherapy is still immature, with the continuous development of science and technology and deep interdisciplinary integration, more innovative applications are expected in the future. For example, by optimizing the composition, surface treatment techniques, and degradation rates of zinc alloys, it is possible to develop materials that are more suitable for medical applications. These materials could serve not only as medical implants to provide support, repair, or therapeutic functions in cancer treatment but also as drug carriers, tissue engineering scaffolds, and other tools comprehensive cancer therapies. Therefore, while the application of zinc alloy materials in cancer immunotherapy is still in its early stages, their future development prospects are promising.

Magnesium alloy materials in cancer immunotherapy

As a green engineering material, magnesium alloys have excellent properties, such as low density, high strength, good thermal conductivity, and significant vibration damping effects. In the medical field, magnesium alloys have attracted attention because of their good biodegradability and biocompatibility [145, 146]. In contrast to traditional stainless steel, titanium alloy and other implant materials, magnesium alloy materials can gradually degrade after implantation without the need for a second surgery for removal, thus reducing patient pain and medical costs. This property gives magnesium alloy material a unique advantage in cancer immunotherapy, where it can be used as a local implant material to inhibit tumor growth and promote tissue repair through the action of its degradation products.

The application of magnesium alloys in cancer immunotherapy is based mainly on the antitumor effects of their degradation products. First, magnesium hydroxide produced by the degradation of magnesium alloys can continuously alkalinize the tumor microenvironment, inhibit the proliferation of tumor cells and activate antitumor immunity [147]. Second, hydrogen, another important product of magnesium alloy degradation, has significant anti-inflammatory and antioxidant effects and can effectively inhibit oxidative stress and increase sensitivity to conventional antitumor drugs [147]. In addition, magnesium ions play important roles in biological processes such as energy metabolism, macromolecule synthesis and genetic information transfer, and increasing their concentration can remodel the local tumor microenvironment and further inhibit the growth and metastasis of tumor cells. Together, these mechanisms indicate that magnesium alloys have good application prospects in cancer immunotherapy.

In practical applications, magnesium alloys can be used as novel antitumor implant materials, such as magnesium alloy particles and stents [147]. When these implants locally degrade in the tumor, their degradation products can act directly on tumor cells and the tumor microenvironment to inhibit tumor growth and promote tissue repair. In addition, magnesium alloys can be used in combination with immunotherapeutic drugs, and their degradation products can synergistically enhance the immunotherapeutic effect [83]. However, the application of magnesium alloys in cancer immunotherapy also faces some challenges, such as the precise control of the degradation rate and the validation of long-term safety and efficacy [83]. In the future, with the continuous development of materials science, biomedical engineering, and cancer immunology, the application of magnesium alloys in cancer immunotherapy will be extended. By optimizing the composition, structure and surface treatment technology of magnesium alloys, their antitumor effect and biocompatibility can be further improved to provide safer and more effective therapeutic options for cancer patients.

Manganese alloy materials in cancer immunotherapy

Owing to the composition and nature of manganese alloys, they are not directly used as therapeutic agents in cancer immunotherapy; rather, the element manganese (especially Mn^{2+} ions) plays the key role. Nevertheless, we

can explore the potential role of manganese alloy materials, the specific role of manganese ions in immunotherapy, and possible future directions for their application.

The potential role of manganese alloy materials in cancer immunotherapy is mainly as sources or carriers of elemental manganese. The stable release or controlled extraction of elemental manganese may be achieved by controlling the conditions during the preparation process of manganese alloys and thus the unique physical and chemical properties of the alloys. Thus, in the context of cancer immunotherapy, manganese alloy materials can be considered "reservoirs" or "slow-release systems" that provide a continuous, stable supply of Mn^{2+} ions to the body. Although this is not a direct therapeutic application of manganese alloy materials per se, it offers the possibility of the effective utilization of Mn^{2+} ions in immunotherapy.

The central role of Mn^{2+} ions in cancer immunotherapy have been extensively studied and validated. Manganese promotes the maturation and activation of antigen-presenting cells mainly through the activation of the cGAS-STING pathway, which in turn triggers a strong antitumor immune response. Mn^{2+} ions can significantly increase the sensitivity of cGAS for the detection of cytoplasmic DNA, promote its synthesis of the second messenger cGAMP, and increase the binding ability of STING to cGAMP, thereby dramatically increasing the cellular responsiveness to tumor-associated DNA [148]. This activation state not only promotes the recognition and presentation of tumor antigens by antigen-presenting cells but also enhances the infiltration and killing ability of cytotoxic T cells, which provides a new strategy and hope for cancer therapy.

Although manganese alloy materials have not yet been directly applied to cancer immunotherapy, on the basis of their potential value in the supply of manganese ions, possible future development directions include developing manganese alloy materials with increased biocompatibility and stability for the precise release and targeted delivery of Mn^{2+} ions; exploring the combined application of manganese alloy materials with other therapeutic methods, such as the use of manganese alloy materials with immune checkpoint inhibitors, to further improve the therapeutic effects; and conducting in-depth research on the specific mechanisms of action and long-term safety of manganese ions in cancer immunotherapy to provide a more solid theoretical basis for clinical application. These efforts are expected to promote the innovative application of manganese alloy materials in the field of cancer immunotherapy to provide new treatment options and hope for cancer patients.

Copper alloy materials in cancer immunotherapy

Although copper alloy materials are not directly involved in cancer immunotherapy in alloy form, the element copper and its properties offer new perspectives and possibilities for research in this field.

The main potential contribution of copper alloy materials in cancer immunotherapy is in their role as a stable source of copper. Copper is an essential trace element involved in a variety of biological processes, including energy metabolism and antioxidant defense. In cancer immunotherapy, copper may regulate the function of immune cells and promote the apoptosis of tumor cells through its unique biological activity [149]. Copper alloy materials, owing to their good processability and stability, can be used as carriers of copper in medical applications to ensure the sustained and stable release of copper in the body, thus exerting potential anticancer effects.

Copper ions play a direct and important role in cancer immunotherapy. Copper ions can induce oxidative stress in tumor cells, disrupting the intracellular redox balance and thus triggering apoptotic programs [150]. In addition, copper ions can combine with certain anticancer drugs to form complexes with increased activity, enhancing the antitumor effects of the drugs [151]. Moreover, copper ions can regulate the functions of immune cells, such as activating macrophages and promoting T-cell activation [152], thus enhancing the body's antitumor immune response. These mechanisms of action indicate that copper ions have important potential for application in cancer immunotherapy.

With the ongoing development of materials science and biomedical engineering, the innovative application of copper alloy materials in cancer immunotherapy is promising. In the future, the precise release and targeted delivery of copper ions at the tumor site can be achieved by designing copper alloy materials with specific surface properties and release characteristics. This targeted delivery strategy can not only improve the therapeutic efficiency of copper ions but also reduce damage to normal tissues. In addition, copper alloy materials can be combined with other therapeutic tools, such as immune checkpoint inhibitors and gene therapy, to improve the efficacy and safety of cancer immunotherapy through the synergistic effects of multiple pathways and targets. These innovative applications will lead to new therapeutic options and hope for cancer patients.

Overall, metal alloy materials have promising applications in cancer immunotherapy. Zinc, magnesium, manganese and copper alloy materials may enhance antitumor immune responses through a variety of mechanisms, including the modulation of immune cell function, the modulation of the tumor microenvironment, the induction of apoptosis in tumor cells, and the delivery of therapeutic materials as drug carriers. These metal

alloy materials can be used not only alone but also in combination with other therapeutic methods to increase the effectiveness of antitumor therapy. However, the clinical application of metal alloy materials still faces some challenges, and there are yet no substantial applications of these materials in the field of cancer immunotherapy. Future studies should continue to focus on the synthesis of metal alloy materials and their mechanisms of action, develop better biocompatible alloy materials, and explore application strategies in combination therapy to promote the clinical translation and application of these materials in cancer immunotherapy. Overall, metal alloy materials provide a new direction and hope for cancer immunotherapy and are expected to become an important tool for cancer treatment.

Safety and targeted delivery systems of biometallic ions and derivatives

The safety of biometallic ions and derivatives in cancer immunotherapy

Biometallic ions and derivatives exhibit promising therapeutic potential in cancer immunotherapy, yet their safety remains a critical issue that must be addressed before clinical application. Primarily, the toxicity of biometal ions could adversely affect immune cells and other healthy cells. For instance, ions such as copper, iron, and manganese at high concentrations readily induce oxidative stress, producing excessive reactive oxygen species (ROS) that lead to intracellular oxidative damage and inflammatory responses [34, 153, 154]. In cancer immunotherapy, where high doses of metal ions or their derivatives are often required to activate immune responses, there is an increased risk of harm to healthy cells. To address this concern, current research focuses on optimizing dosage ranges and investigating the minimum effective and maximum safe doses in vivo to minimize adverse effects.

Secondly, the biodistribution and accumulation of biometallic ions in the body significantly impact their safety profile. Many metal ions and their nano-derivatives, once introduced into the body, may accumulate in non-target organs such as the liver and kidneys, potentially leading to chronic toxicity and organ damage. For example, excessive iron accumulation in the liver can impair liver function [155, 156], while long-term manganese accumulation may result in neurotoxicity [157, 158]. To address this, researchers are developing targeted delivery systems, such as nanoparticles or biodegradable carriers encapsulating bio-metal ions, to reduce accumulation in non-target tissues and achieve efficient release at the tumor site. Additionally, strategies are being explored to regulate metal ion excretion pathways to minimize accumulation in non-target organs. Optimizing the biodistribution of bio-metals in the body can enhance their safety and clinical potential in cancer immunotherapy.

Lastly, the long-term safety of metal ions within the body requires further evaluation, particularly critical for sustaining therapeutic efficacy in cancer treatment. Since cancer immunotherapy often involves repeated dosing, the long-term safety of bio-metal ions directly influences their clinical applicability. Prolonged exposure to certain metal ions may result in chronic toxicity, immune system disruptions, or endocrine imbalances. Therefore, future research must focus on systematically studying the chronic toxicity of metal ions, especially through extended in vivo studies or in animal models, to assess their long-term biocompatibility. Additionally, as personalized cancer immunotherapy becomes more prevalent, tailoring metal ion therapy to accommodate patient-specific factors (such as age and baseline health) is essential for ensuring safety. Through these ongoing optimizations, the safety of bio-metals and their derivatives in cancer immunotherapy can be effectively enhanced, facilitating their successful clinical translation.

Specific delivery systems for biometallic ions and derivatives

Controlled release strategies and the development of specific delivery systems for metal ions play a critical role in advancing bio-metal ions as emerging solutions in cancer immunotherapy [105, 159, 160]. Traditional metal ion therapies face challenges such as dose control issues, high toxicity, and poor targeting, which limit their capacity for precise in vivo release and optimal therapeutic effects. Controlled release strategies enable the gradual release of metal ions, effectively inhibiting tumors while reducing adverse effects. For instance, metal ions encapsulated in nanoparticles, polymer capsules, or liposomes are gradually released upon reaching specific targets, ensuring a sustained local high concentration at the lesion site or in target cells or tissues, while minimizing accumulation in non-target tissues. This approach not only helps reduce unnecessary toxic load but also enhances the immune-activating efficiency of metal ions, thereby strengthening their anti-cancer potential. By optimizing controlled release technology, researchers can better regulate the release rate of metal ions, extend their therapeutic activity, and enhance their practicality in cancer treatment.

To enable bio-metal ions to act more precisely within the tumor microenvironment, the design and development of specific delivery platforms is particularly critical. Unlike general carrier delivery systems, metal ion-specific delivery platforms are capable of recognizing particular markers or physiological conditions within the tumor microenvironment, allowing for "targeted release" at the lesion site. For example, by conjugating metal ions to specific antibodies, peptide chains, or other tumor

microenvironment targets, the ions can be directed precisely to the tumor region, thereby enhancing immune cell recognition and cancer cell-killing capabilities at the molecular level [23]. Additionally, tumor tissues typically exhibit characteristics such as acidic pH, hypoxia, or high reductive conditions, which can be leveraged to develop responsive carriers that activate or release metal ions under these environmental triggers, further increasing the specificity and efficiency of delivery. This targeted delivery platform not only ensures that bio-metal ions effectively reach the tumor site but also enables their release under specific conditions to maximize cytotoxicity against cancer cells and immune activation potential.

Table 4 Comparison of biometallic ion immunotherapy and conventional cancer immunotherapy [63, 171–180]

Comparison items	Characterization	Bio-metal ion immunotherapy	Conventional cancer immunotherapy
Specific	Targeting	Improved targeting through interactions with specific molecules in the tumor microenvironment	Dependent on tumor-specific antigens
	Delivery systems	Nanoparticles, carrier materials enable targeted delivery	Usually administered intravenously with no specific targeted delivery
	Cellular/Molecular Targets	Direct interaction with tumor-associated molecules	Mainly activates immune cells such as T cells and NK cells
	Sensitivity to immune escape	Reduction of tumor immune escape capacity	Limited by tumor cell escape mechanisms
therapeutic effect	Efficiency of immune activation	Enhancement of local anti-tumor response through ion signaling	Activation of T cells, natural killer cells
	sustainability	Longer duration of action due to metal ion stability	Repeated dosing is required to maintain the therapeutic effect
	Regulation of the tumor microenvironment	Modulation of autophagy and oxidative stress to enhance immune response	Acts on the systemic immune system with less impact on TME
	Role in drug resistance	Multi-targeted action, may reduce drug resistance	Prone to drug resistance
side-effects	systemic toxicity	Higher doses may cause organ toxicity such as liver and kidney damage	May trigger systemic immune response
	Immune side effects	Localized toxicity predominates, with fewer immune side effects	May cause autoimmune side effects
	Pharmacokinetic control	Precision delivery needed to minimize off-target toxicity	Difficult to accurately control concentration in specific tissues
	cumulative effect	Potential metal ion accumulation problems	Usually, no long-term cumulative problems

The combined application of controlled release and specific delivery strategies greatly enhances the clinical translatability and immunotherapeutic potential of bio-metal ions. These advanced techniques ensure that metal ions achieve maximum therapeutic efficacy with minimal toxicity in cancer immunotherapy, thereby overcoming many of the limitations seen in traditional treatments. Current studies have demonstrated the positive effects of metal ions—such as copper, zinc, iron, magnesium, and manganese—in activating immune cells, promoting cytokine secretion, and enhancing anti-tumor immune responses [39, 48, 60]. Looking ahead, as nanotechnology, bioengineering, and immunology continue to converge, ongoing innovations in controlled release and specific delivery platforms will significantly improve the stability, safety, and efficacy of bio-metal ions in clinical applications. This multifaceted and multi-dimensional approach to delivery and control not only introduces new solutions for cancer immunotherapy but also opens extensive avenues for the research and application of bio-metal ions.

Conclusions and perspectives

Although cancer metal immunotherapy shows great potential compared with conventional cancer immunotherapy (Table 4), it still faces multiple challenges in clinical application. Firstly, the toxicity and safety issues associated with bio-metal ions continue to be significant obstacles to clinical translation. Many metal ions, when reaching certain concentrations, can induce cytotoxicity, oxidative stress, and inflammatory responses, which may even harm normal tissues. Even trace accumulation over time can lead to cumulative toxicity. Therefore, achieving precise controlled release of bio-metals within the tumor microenvironment while preventing accumulation in non-target tissues is a critical challenge to address. Additionally, different tissues in the body exhibit varying affinities and metabolic characteristics for metal ions, which can lead to uneven biodistribution and increase toxicity risks to non-target tissues. These issues restrict the therapeutic scope of bio-metals in immunotherapy, raising safety concerns for their use in cancer immunotherapy.

Secondly, the delivery and stability of bio-metal ions within the tumor microenvironment present additional challenges. Metal ions readily interact with proteins and other molecules in vivo, and this non-specific binding can lead to a loss of activity during delivery or unwanted distribution to non-target sites. Furthermore, the tumor

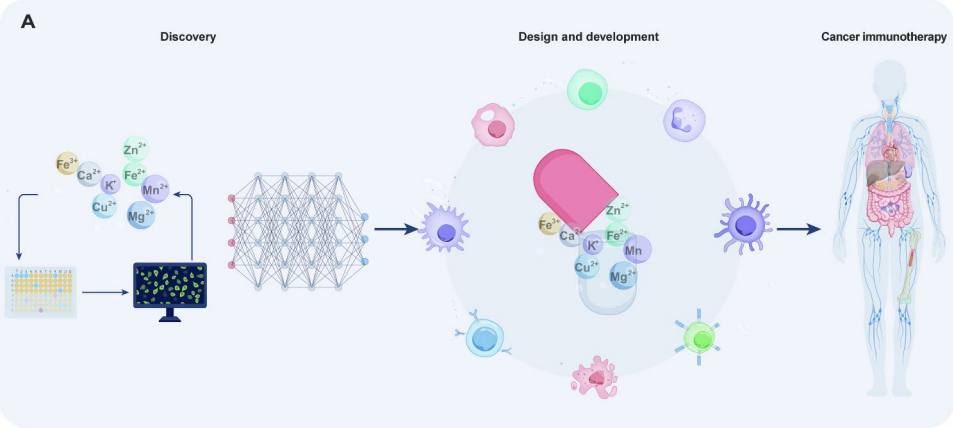

Fig. 4 Future research directions in metalloimmunotherapy in cancer. **A.** left: the discovery of metalloimmunological processes and mechanisms via metallomics (that is, the use of -omics tools to understand how metal or metalloid elements interact with immune processes) and metallomics-integrated multi-omics. Centre: the design of suitable strategies for the development of metalloimmunotherapies, and the leveraging of molecular engineering and nanobiotechnology to develop precision metalloimmunotherapies. Right: metalloimmunotherapies may be tested and optimized for the treatment of cancer

microenvironment is often highly heterogeneous, with variations in pH, redox states, and biochemical conditions across different tumor types and within specific regions of a single tumor. This heterogeneity complicates the design of delivery carriers tailored for specific environments. Developing a bio-metal delivery platform that enables stable, precise, and controlled release under various microenvironmental conditions is therefore a key research focus. For instance, investigating intelligent nanocarriers or responsive polymer materials that release bio-metals upon triggers such as pH or oxygen level changes could enhance their application in cancer immunotherapy. Additionally, delivery platforms must maintain high in vivo stability to prevent premature release in non-target regions, which is crucial for enhancing the selectivity and efficacy of the treatment.

In the future, to advance the application of bio-metal ions in cancer immunotherapy, research should focus on enhancing their specificity and biocompatibility. With advancements in targeting technology, the design of more selective metal ion delivery systems, combined with strategies for immune system modulation, can enable these ions to activate immune cells while maintaining tumor-specific cytotoxicity. For example, integrating metal ion delivery with CAR-T cell therapy or immune checkpoint inhibitors may yield synergistic anti-cancer effects. Additionally, fundamental research must further elucidate the mechanisms of various metal ions, identifying their specific targets and pathways within cellular immune responses, to provide theoretical support and experimental data for clinical applications. By continuously optimizing delivery strategies and deepening mechanistic understanding, bio-metals hold promises to play a unique role in cancer immunotherapy, offering patients safer and more effective treatment options (Fig. 4).

Author contributions

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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