years, nanomaterials have made significant progress and development in drug delivery, diagnosis and imaging, treatment, vaccines, and other fields (Wang G. et al., 2023). Various metal ion-regulated nanomaterials have also made great progress in tumor treatment research. They not only optimize the metal ion-based antitumor treatment system but also provide the possibility for the combination of metal ion treatment with other treatment strategies. These characteristics make metal-based nanomaterials show great potential for tumar treatment.

This article will comprehensively summarize the diverse types, intricate mechanisms, and the latest research advancements in the field of metal-based antitumor nanomaterials and offer insights into

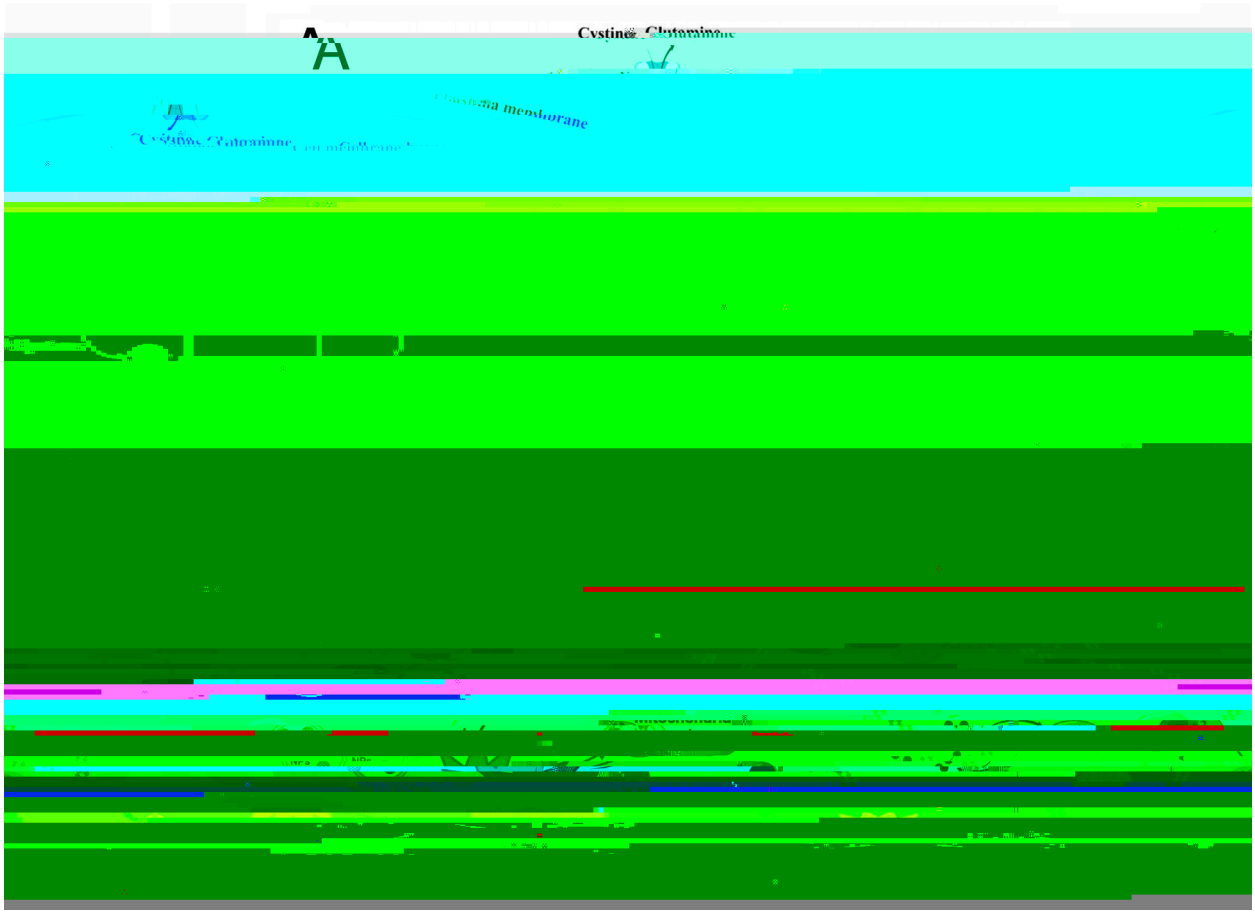

FIGURE 1
(A) ; (B) 53. (, 2023); (C) 4.0. 2023

enhancing the antitumor effects (Wang et al., 2023d; Yao et al., 2021).

Another method to increase the level of free Fe^{2+} within cells is to target iron-related proteins, among which ferritin degradation is considered an effective approach. A ferritin-hijacking nanoparticle (Ce6-PEG-HKN_{15}) is fabricated, by conjugating the ferritin-homing peptide HKN15 with the photosensitizer chlorin e6 (Ce6) for endogenous ferroptosis without introducing Fenton-reactive metals (Zhu et al., 2022). Since the HKN15 peptide can target ferritin, the photosensitizer chlorin e6 (Ce6) can specifically aggregate around ferritin. Under laser irradiation, the activated Ce6 in these nanoparticles synergizes with the generated ROS to effectively destroy ferritin and release Fe^{2+}. In turn, the released iron partially interacts with intracellular excess H_2O_2 to produce O_2, thereby enhancing photodynamic therapy and further amplifying oxidative stress. Xiong et al. prepared a nano-activator (DAR) which was assembled by doxorubicin (DOX), tannic-acid (TA) and IR820 as a photosensitizer to make full use of endogenous iron stored in endo-lysosome, realizing ferroptosis and its related oxidative stress through artificially intracellular positive feedback loop, providing an innovative solution for the development of antitumor treatment based on ferroptosis-immunotherapy (Xiong et al., 2021).

Calcium (symbol: Ca) is a chemical element with an atomic number of 20, and its ionic form is Ca^{2+}. Calcium is the most abundant metal element in the human body and is crucial for the formation of bones and teeth. In the body, calcium exists in three main forms: free calcium, complex calcium, and protein-bound calcium, which can convert into each other. Among them, free calcium is the only physiologically active form. As an indispensable second messenger in cells, calcium ions (Ca^{2+}) participate in the regulation of almost all physiological processes by activating specific target proteins. Due to the importance of Ca^{2+}, its concentration is strictly controlled (Berridge et al., 2000; Carafoli, 2002; Liu et al., 2020; Marchi et al., 2020; Monteith et al., 2017). The concentration of free calcium within cells is only 100 nM, much lower than the extracellular calcium concentration (Bagur and Hajnoczky, 2017). Fluctuations in Ca^{2+} concentration will affect normal calcium signal transmission and thus affect cellular physiological functions. The homeostasis of intracellular Ca^{2+} mainly relies on the orderly cooperation of various Ca^{2+} channels in the cell membrane and organelles (such as the endoplasmic reticulum, mitochondria, and

lysosomes) (Berridge, 2016; Clapham, 2007; Huang et al., 2022).

Manganese (element symbol: Mn) is a transition element with an atomic number of 25, having various valence states, including Mn^{2+}, Mn^{3+}, Mn^{4+}, Mn^{6+}, and Mn^{7+}. The most common form of manganese found in living tissues is Mn^{2+} and Mn^{3+}. Manganese plays an important role in various physiological processes, including development, energy metabolism, antioxidant defense, and immune function. Manganese acts as a cofactor for various enzymes in the body, such as arginase, manganese superoxide dismutase (MnSOD), and cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS), etc. (Liu et al., 2022; Zhu et al., 2019). Among them, the cGAS protein is an important DNA sensor that activates the host immune response, and the cGAS-STING signaling pathway plays a crucial role in innate immune responses (Wang et al., 2018). Therefore, manganese is an important immune activator and the level of manganese in cells also needs precise regulation. Manganese efflux pumps and metal transporters ZIP8, ZIP14, and ZnT10 play a key role in this process (Xin et al., 2017). Due to the chemical properties of strong redox capabilities that similarity to iron, manganese can also produce ·OH through a Fenton-like reaction, increasing oxidative stress and producing cytotoxic effects (Ju et al., 2022).

Numerous epidemiological investigations have found a significant positive correlation between low manganese and tumor occurrence (Kim, 2010; Tu et al., 2010). The purpose of antitumor manganese nanodrugs is to increase the concentration of intracellular free Mn^{2+}. After nanoparticles are internalized by cells, the release of Mn^{2+} depletes intracellular glutathione (GSH), enabe the sufficient generation of reactive oxygen species (ROS) and effectively kill tumor cells. In addition, Mn^{2+} can also catalyze conversion of cellular H_2O_2 to ·OH through a Fenton-like reaction. It also promotes the decomposition of H_2O_2 to O_2 and continuously catalyzes the conversion of O_2 to cytotoxic $\cdot O^{2-}$ via oxidase-like activity that enhance the therapeutic effects of radiotherapy and starvation therapy (Zhu et al., 2021).

immunotherapies such as tumor vaccines, immune checkpoint blockade therapy, adoptive cell therapy, manganese-based tumor immunotherapy has signifi

and size can easier to be controled and adjusted. These advantages make them widely used in tumor imaging and combined tumor therapy (Zhong et al., 2022). Zhang et al. utilized hollow mesoporous organosilica nanoparticles to integrate ultrasmall photothermal CuS particles onto the surface of the organosilica and the molecular drug Disulfiram (DSF) inside the mesopores and hollow interiors. The ultrasmall CuS acted as both photothermal agent under near-infrared (NIR) irradiation for photonic tumor hyperthermia and Cu^{2+} self-supplier in an acidic tumor microenvironment to activate the nontoxic DSF drug into a highly toxic diethyldithiocarbamate (DTC)-copper complex for enhanced DSF chemotherapy (as shown in Figure 6), which effectively achieved a remarkable synergistic in-situ anticancer outcome with minimal side effects (Zhang et al., 2021).

Chen et al. constructed CuS-pgh NMs by encapsulating copper sulfide nanoparticles using polylysine/glucose oxidase/hyaluronic acid shells (Chen et al., 2020), Liu et al. constructed a hybrid nanosystem composed of DNAzyme and Cu^{2+} (Liu et al., 2021), in which copper can mediate Fenton-like reactions to generate highly toxic hydroxyl radicals, enhancing thestarvation and chemodynamic tumor suppression effects. Cui et al. developed a safe, mitochondria-targeted copper-depleting nanoparticles. These nanoparticles can reduce the oxygen consumption and oxidative phosphorylation of triple-negative breast cancer (TNBC), promote glycolysis metabolism, reduce ATP production, cause mitochondrial membrane potential damage and increased oxidative stress, thereby induce the apoptosis of TNBC (Cui et al., 2021). A kind of nanochelator, Imi-OSi, were reported that can inhibit tumor angiogenesis through copper consumption, and form secondary particles through the phosphate/Cu^{2+} reaction polymerization to block blood vessels (Yang et al., 2019). For starvation-augmented cuproptosis and photodynamic synergistic therapy, a glucose oxidase (GOx)-engineered nonporous copper coordination nanomaterial GOx@[Cu(tz)] was developed. It inhibited 92.4% of tumor growth in athymic mice with bladder tumors, and the systemic toxicity produced was extremely low (Xu WJ. et al., 2022). Chang et al. designed a Ce6@AT-PEG-MSN-Pt (CAPMP) nanomotor, consisting of a janus platinum-mesoporous silica core, with acyl thiourea groups (copper chelators) conjugated with polyethylene glycol on the surface, and chlorin e6 (photosensitizer) in the pores, which can spontaneously

of many proteins, playing the role of a “life gear” in the process of transporting substances and exchanging energy (Kambe et al., 2015). In mammalian cells, there are two forms of zinc: protein-bound zinc and free zinc. The former is used to maintain the catalytic activity and structural stability of metalloenzymes and transcription factors, while the latter acts as a signaling ion to regulate signal transduction (Maret, 2013). Therefore, zinc plays a significant role in many biological processes, including cell division, metabolic regulation, and immune responses. To maintain normal physiological functions, cellular zinc homeostasis is subtly coordinated by a set of zinc homeostasis regulatory proteins, including the Zrt-, Irt-like protein (ZIP) family for zinc influx, the zinc transporter (ZnT) family for zinc efflux, metallothioneins (MTs) for zinc intracellular storage, and metal-response-element-binding transcription factor (MTF)-1 for zinc cytosolic sensing (Colvin et al., 2010).

It has been confirmed that the imbalance of zinc homeostasis is related to the development, invasion, and metastasis of various tumors (Bendellaa et al., 2024; Wang et al., 2020). Increasing evidence suggests that the elevation of intracellular zinc levels is mainly due to the overexpression of zinc transporters (ZIPs), which may promote the progression of certain specific cancers such as breast and pancreatic cancer. For example, ZIP6, ZIP7, and ZIP10 are highly expressed in breast cancer. Additionally, although zinc itself does not have redox activity, it can indirectly participate in the regulation of redox metabolism by acting as a catalytic or structural cofactor for proteins such as metallothioneins (MTs), copper/zinc superoxide dismutase (Cu/Zn-SOD), and the tumor suppressor protein p53. The balance of zinc homeostasis successfully activates antioxidant defenses, while zinc deficiency can disrupt protein structures and impair protein function, ultimately leading to oxidative stress and causing cell death. Accordingly, zinc chelation therapy mediated by zinc chelators can be used to treat certain types of cancer. Similar to zinc deficiency, zinc overload also has pro-oxidant properties. Excessive intracellular zinc can enter the mitochondria through the mitochondrial Ca^{2+} uniporter (MCU) (Medvedeva and Weiss, 2014), then irreversibly inhibit components of the electron transport chain (ETC.), which may stimulate the production of mitochondrial superoxide anions ($\cdot O_2$

TABLE 1 (***Continued***) Typical metal ions-based nanomaterial for tumor therapy in recent years.

Immunotherapy	Mn^{2+}	MnO@mSiO-iRGD NPS	132 ± 7	iRGD	pH	Mn^{2+}-induced cGAS-STING pathway-activated immunotherapy	(Sun et al., 2022)
		amorphous porous Mn_2P (APMP) NPs	~180	Lipid layer	pH	The same as above	Hou et al. (2020)
		Mn-cGAMP nanovaccine	168 ± 20	-	-	The same as above	Chen et al. (2021)
		PLGA-MnO_2NPs	116	PLGA	-	Reducing hypoxia and abundance of immunosuppressive metabolites, increasing NK cell activity	Murphy et al. (2021)
Cuproptosis	Cu^{2+}	Perflourocarbon-/Ce6-loaded Cu@ZIF-8 (SonoCu)	~100	Macrophage membrane	pH, ultrasound	Binding to FDX1, inducing oligomerization of lipoylated DLAT	Chen et al. (2023)
		Elesclomol/Cu coencapsulated polymer nanoparticles	62.8	An amphiphilic biodegradable polymer (PHPM)	ROS	The same as above	Guo et al. (2023)
		H-ferritin-Cu-regorafenib Nanoplatform	15.5	H-ferritin	pH	Inducing cuproptosis, resulting in a synergistical effect with regorafenib-mediated lethal autophagy	Jia et al. (2023)
		CuET-CuO@BSA	40.38 ± 0.17	BSA	ROS	Triggering ROS generation through Fenton-like reaction, inducing cuproptosis, enhancing the therapeutic effect of CuET	Wu et al. (2024a)
		ES@Cu(II)-MOF NPs	152.7	PEG	pH	Generating toxic ·OH and consuming endogenous GSH, triggering cuproptosis, triggering robust ICD, combing with an anti-PD-L1, achieving excellent antitumor effects	Lu et al. (2024a)
	Cu^{+}	GOx@[Cu(tz)]	234	-	-	Binding to FDX1, inducing oligomerization of lipoylated DLAT	Xu et al. (2022a)
Zinc overload	Zn^{2+}	BSArGO@ZIF-8 NSs	~800	BSA	808-nm NIR light	increase of reactive oxygen species (ROS), initiating mitochondrial apoptotic, mediated ion-interference and photothermal combined therapy	Lv et al. (2022)
		^{F127}ZIF-8_{CCCP}	180	Pluronic F127	NIR irradiation	leading to increased intracellular osmotic pressure and production of reactive oxygen species (ROS)	Ding et al. (2023a)
		ZnS@BSA	≈100	BSA	-	activating cGAS/STING signals, leading to an improved immunotherapy efficacy	Cen et al. (2021)
		Zn-LDH	10	-	-	triggering a strong metal immunotherapy against solid tumors	Zhang et al. (2022)

(Continued on following page)

the solubility, stability, and biocompatibility of metal ions through their surface modification and functionalization, further optimizing the application of metal ion therapy. Additionally, the nanoplatform is capable of delivering multiple components simultaneously, achieving synergistic effects of different therapeutic mechanisms. Metal ions in combination with other treatment strategies can be used to design new synergistic anti-tumor regimens, improving tumor treatment outcomes, and reducing the potential toxicity of drugs to normal tissues. Additionally, strategies that modulate the homeostasis of multiple metals have shown promising anti-tumor effects. Recently, there has been considerable research on regulating the homeostasis of various metals for cancer treatment. For instance, Shen et al. reported a pH-responsive nanoplatform (CaO_2@ZIF-Fe/Ce6@PEG) that simultaneously causes overload of iron and calcium within tumor cells, providing a robust self-supplied ROS pathway to further enhance the efficacy of CDT/PDT (cacyiormacopper/-225.532egulmix46.2318meostllow.8o1n 83272sti3705.836530.1Tref7407.509272sti3705.03@830.1Tref74ns2997272sti3705.03acy30.1Tref749.606643rch59.18405.03

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activat ing the innate immune response

tumors. In conclusion, combining the advantages of nanotechnology, metal ions have emerged as a new strategy for anticancer therapy.

Metal-based nanomaterials have been proven to have tremendous potential as targeted drug delivery systems, imaging agents, and therapeutics. Due to their unique advantages, metal nanomaterials have broad application prospects and significant research value in numerous fields. Compared to other types of nanomaterials, metal-based antitumor nanomaterials have the following advantages. First and foremost, metal-based nanomaterials can release a large amount of specific metal ions in the tumor microenvironment, thereby disrupting the metal ion balance required for cellular function. Therefore, metal-based nanomaterials hold great promise for enhancing the imbalance of metal homeostasis in cancer cells. Currently, metal-based nanomaterials under study either through metal chelation or metal overload lead to the disruption of metal homeostasis in cancer cells, ultimately resulting in cell death through various means such as apoptosis, pyroptosis, ferroptosis, cuproptosis, et al. Secondly, due to their small size and high surface area-to-volume ratio, metal nanomaterials exhibit unique physical, chemical, and optical properties, such as strong near-infrared absorption, magnetothermal effects, and the ability to easily accumulate, separate, or undergo targeted movement and localization. These properties enable metal nanomaterials to play a unique role in tumor diagnosis and treatment. For example, gold nanomaterials can rapidly heat up under laser irradiation through the photothermal conversion effect, thereby killing tumor cells and achieving photothermal therapy (Khoobchandani et al., 2020). Magnetic nanomaterials, on the other hand, can indirectly kill tumor cells through the magnetothermal effect, showing good antitumor effects. Furthermore, metal nanomaterials have a high surface area and abundant active sites, which can serve as carriers for anticancer drugs, enhancing the uptake of drugs by cancer cells and improving the efficacy of cancer treatment while reducing the dosage of antitumor drugs. Surface modification of metal nanomaterials can also further enhance their biocompatibility and safety, reducing their potential systemic side effects. Additionally, metal nanomaterials have shown great potential in tumor immunotherapy. For instance, by preparing ultra-small metal-organic nanomaterials, it is possible to achieve sufficient accumulation at the tumor site and rapid renal clearance, enhancing treatment efficacy and greatly reducing long-term tumor shncer handTJ/F81Tf10.1(in3(FTD()Tj/F61Tf0.53110TD[(cacy))Tj694.730nd)-196-10.62byimprovag-543.114ducisolu antin

therapeutic efficacy in treating breast and other forms of human cancers.

Although metal nanomaterials show great potential for tumor treatment at present, they still have many limitations. Firstly, although many anti-tumor mechanisms of metal ion based nanodrugs have been reported, but most of them have only been validated in cell lines. Therefore, further research on these mechanisms in more organoid and animal models is necessary to deeply elucidate the anti-tumor mechanisms and effects of metal ion-based nanodrugs. However, the lack of animal models that can accurately simulate human tumor conditions is one of the recognized deficiencies in the field, leading to a weak correlation between preclinical studies and clinical trial results. For this reason, researchers are trying to establish organoids from patients, which are innovative screening devices as close as possible to the *in vivo* environment. The established platform takes into account tumor angiogenesis and the 3D microenvironment, so as to select the human

intracellular ion imbalances but can also enhance the effects of other anti-tumor therapies such as chemotherapy, radiotherapy, photothermal therapy, and photodynamic therapy. They play a role in comprehensive tumor treatment and achieve synergistic effects of different treatment mechanisms, and demonstrate significant potential. However, many obstacles need to be addressed in various aspects such as the selection of model

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