Nutrition Research Reviews

cambridge.org/nrr

Manganese in health and disease

Yingchen Wang[1,2,3], Jinyou Li[1,2,3], Jing Zhuang[1,2,3], Yinhang Wu[1,2,3], Jiang Liu[1,2,3] and Shuwen Han[1,2,3,4]

[1]Huzhou Central Hospital, Fifth School of Clinical Medicine of Zhejiang Chinese Medical University, Huzhou, Zhejiang, People's Republic of China; [2]Huzhou Central Hospital, Affiliated Central Hospital Huzhou University, Huzhou, Zhejiang, People's Republic of China; [3]Zhejiang-France United Laboratory of Integrated Traditional Chinese and Modern Medicine in Colorectal Cancer, Huzhou, Zhejiang, People's Republic of China and [4]ASIR (Institute - Association of intelligent systems and robotics), 14B rue Henri Sainte Claire Deville, 92500, Rueil-Malmaison, France

Review Article

Cite this article: Wang Y, Li J, Zhuang J, Wu Y, Liu J, and Han S (2025). Manganese in health and disease. *Nutrition Research Reviews*, page 1 of 11. doi: 10.1017/S0954422425100139

Received: 13 December 2024
Revised: 25 May 2025
Accepted: 30 May 2025

Keywords:
Trace elements; Manganese; Mitochondria; cGAS–STING; Manganese nanomaterials; Cancer

Abbreviations:
Mn, Manganese; MnSOD/SOD2, Manganese superoxide dismutase; NKTs, Natural killer T cells; DMT1, Divalent metal transporters 1; BBB, Blood–brain barrier; CSF, Cerebrospinal fluid; OXPHOS, Oxidative phosphorylation; WHO/FAO, World Health Organization/Food and Agriculture Organization; ROIs, Reactive oxygen intermediates; NRAMP1, Natural resistance-associated macrophage protein 1; *S. aureus*, *Staphylococcus aureus*; HIV, Human immunodeficiency virus; mPTP, Mitochondrial permeability transition pore; iPSC, Induced pluripotent stem cell; mtDNA, Mitochondrial DNA; ROS, Reactive oxygen species; Ras-MAPK, RAS-mitogen-activated protein kinase; H_2O_2, Hydrogen peroxide; PI3K, Phosphatidylinositol 3′-kinase; MRI, Magnetic resonance imaging; dsDNA, Double-stranded DNA; ICIs, Immune checkpoint inhibitors; DCs, Dendritic cells; cGAS-STING, Cyclic GMP-AMP synthase-stimulator of interferon genes; cGAMP, Cyclic guanosine monophosphate; ER, Endoplasmic reticulum; IRF-3, Interferon regulatory factor 3; TBK-1, TANK-binding kinase 1; NF-κB, Nuclear factor kappa B; ISME, Immunosuppressive microenvironment; TME, Tumor microenvironment; PDA, Polydopamine; HA, Hyaluronic acid; NCs, Nanocomplexes; OPDMA, Poly [2 - (N-oxide-N, N-dimethylamino) ethyl methacrylate]

Corresponding author:
Shuwen Han; Email: shuwenhan985@163.com

Abstract

Manganese (Mn) is a crucial trace element that actively participates in a diverse array of physiological processes. Mn is maintained at appropriate levels in the body by absorption and excretion by the body. Dysregulation of Mn homeostasis can lead to a variety of diseases, especially the accumulation of Mn in the brain, resulting in toxic side effects. We reviewed the metabolism and distribution of Mn at multiple levels, including organ, cellular and sub-cell levels. Mitochondria are the main sites of Mn metabolism and energy conversion in cells. Enhanced Mn superoxide dismutase activity reduces mitochondrial oxidative stress and inhibits cancer development. In addition, Mn enhances anti-cancer immune responses through the cGAS–STING pathway. We introduced various delivery vectors for Mn delivery to cancer sites for Mn supplementation and anti-cancer immunity. This review aims to provide new research perspectives for the application of Mn in the prevention and treatment of human diseases, especially by enhancing anti-cancer immune responses to inhibit cancer progression.

Introduction

Manganese (Mn) is the third most abundant transition metal in the Earth's crust[1]. It is widely present in soil (450–4000 mg/kg[2]), where it is involved in the processing and recycling of soil organic carbon[3], and is used as a raw material in industrial fields, including mining, welding and battery manufacturing[4]. For all living organisms, Mn is an essential trace and nutrient element for cellular metabolism[5,6]. Plants need Mn for the synthesis of chlorophyll, the promotion of photosynthesis and maintenance of the normal colour of the blade[7]. Mn widely exists in animals and functions as an enzyme component and activator[8]. As an active cofactor, it participates in a series of biological reactions of a variety of key metalloenzymes, including arginase, pyruvate carboxylase, acetylcholinesterase, glutamine synthetase (GS) and manganese superoxide dismutase (MnSOD/SOD2),[5] to support the normal physiological activities of cells. In the human body, it is involved in fat metabolism, bone growth and the development and normal operation of the nervous system[9–11].

Normal Mn levels range from 4 to 12 μg/l in whole blood, from 1 to 8 μg/l in urine, and from 0·4 to 0·85 μg/l in serum[12]. To maintain the balance of Mn in the human body, the human body absorbs Mn from the environment and diet[13]. The majority of Mn intake comes from water and foods (for example, beans, rice, nuts, whole grains, seafood, seeds, chocolate, tea, *etc.*[14]), with rice (>42%) as the main food source of Mn[15]. Mn intake from environmental exposure or other external sources, such as air pollution or occupational exposure, is relatively rare. Dietary intake of Mn is mainly absorbed in the intestine[16]. Excess Mn is delivered to the liver through the portal vein and excreted with bile through the faeces, while a small amount can be reabsorbed by the intestine. Urinary excretion of Mn is less than 10% of total excretion[17]. In certain populations, such as those with abnormally elevated Mn consumption or gastrointestinal absorption disorders, obtaining sufficient Mn from dietary sources or the environment may be challenging. In such cases, intravenous supplementation of Mn may be necessary to meet the body's requirements. In mice, intravenous administration of Mn has been shown to produce higher concentrations of Mn in most organ tissues compared with inhalation[18]. The disruption of Mn homeostasis leads to a variety of diseases in humans[4]. Mn is needed for the biosynthesis of mucopolysaccharides in bone matrix formation and is a cofactor for enzymes in bone tissue[19]. Long-term dietary Mn deficiency can cause osteoporosis, and its mechanism is related to the increase of serum calcium and phosphorus levels and the decrease of bone calcium levels[20]. Despite its importance for human health (it is a cofactor for normal cellular functioning enzymes), Mn is also toxic to human organs in excess. High levels of Mn are most likely to accumulate in the brain, especially in the basal ganglia, leading to neurotoxicity[21–23]. The main mechanisms of neurotoxicity in the human brain include oxidative stress,

mitochondrial dysfunction, transporter dysregulation, metal imbalances, neuroinflammation and protein trafficking pathway dysregulation[24]. Specifically, Mn destroys DOPA decarboxylase in central nerve cells, resulting in a decrease in L-DOPA content. The balance of L-DOPA and acetylcholine (ACH) is disrupted, and the content of ACH is temporarily increased, resulting in conduction dysfunction in the central nervous system[25]. Excess Mn induces oxidative stress response and causes dopaminergic (DA) neuron degeneration, leading to a series of neuropsychiatric symptoms and signs[26]. The main symptoms are psychological and emotional disturbances, as well as many motor symptoms, including gait disturbance, tremor, stiffness and bradykinesia[27].

In addition, changes in Mn content are one of the characteristic markers of cancer progression and metastasis. Mn increases in a time-dependent manner during the development of carcinoma *in situ* within 3–5 weeks, and a Mn-rich niche is formed in distant metastatic carcinomas[28]. Mn mainly impacts cancer by affecting the body's anti-cancer immune response. Mn can promote the survival and proliferation of immune T cells and effectively promote the cancer killing ability of natural killer T cells (NKT) [29–32]. In summary, Mn plays an important role in anti-cancer immunity in the body. Clarifying the role and mechanism of Mn in cancer is expected to provide new directions for cancer treatment in the future.

As an important nutritional element, appropriate amounts of Mn help to maintain human health and resist diseases, but the imbalance of Mn homeostasis can lead to the development of diseases. Therefore, it is necessary to study its physiological function in human body. We will further review the anti-cancer mechanism of Mn and the precise delivery method of Mn to explore new options for the treatment of tumours.

Pathways of Mn uptake, excretion and distribution

Pathways of Mn uptake

Mn is an important dietary element, and plant foods such as whole grains, nuts and vegetables are rich in Mn, with the most abundant content in tea[33]. Although the content of Mn in animal food (meat, fish and milk) is not high, its absorption and retention are both high, and it is a good source of Mn intake for humans. The efficiency of Mn absorption by the small intestine is affected by many factors, including intestinal pH, divalent metal transporter-1 (DMT1), competition from divalent metals (such as iron, copper, zinc or calcium) and chelators such as phytic acid[34]. Mn is absorbed by intestinal cells in the form of Mn^{3+} through its binding to transferrin. Subsequently, endocytosis internalises the formed complex (Mn^{3+}–transferrin) and facilitates the dissociation of Mn^{3+} into Mn^{2+}[35]. Mn^{2+} is then transported into the cytosol by DMT-1[36]. Mn absorbed from the small intestine enters the blood through small intestinal epithelial cells. Most Mn is bound to Mn-transporting proteins in the plasma for transport, and a small part of the Mn directly enters erythrocytes.

Exposure of the body to the intake of Mn in the occupational environment is the main cause of the toxic side effects of Mn. With the rapid development of modern society, most industrial production involves the metal field, and large amounts of Mn are applied in industrial production. We found that Mn levels were higher in most workers than in the general population,[33,37] and inhalation exposure to airborne Mn was common in welders and smelters[38]. In the occupational environment, humans absorb Mn mainly through the lungs, and only particles with an aerodynamic diameter of less than 5 μm can reach the alveoli. Then, Mn is absorbed in the form of ions.

After people ingest Mn from the external environment, a portion of Mn enters the blood for transport to different tissues[27], and part is transported from the nose to the brain along the olfactory nerve, from which it can bypass the blood-brain barrier (BBB) and enter the central nervous system through the brain[39]. Many ways have been identified for Mn to enter the brain, including the following three main routes: the capillary endothelial cells of the BBB, the choroid plexus of the blood-cerebrospinal fluid barrier, and through the olfactory nerve in the nasal cavity directly to the brain[40]. When the plasma concentration of Mn is within the physiological range (0·076–78 μM), Mn is mainly transported into the brain through saturation of cerebral capillaries. Beyond this range, however, the unsaturated transport of Mn into the brain through cerebrospinal fluid (CSF) occurs more rapidly[41]. The third route is more important because most reports of the toxic side effects of Mn have occurred through inhalation exposure.

Pathways of Mn excretion

The pathways of Mn excretion from the body are as follows: the main pathway is excretion from the liver and gallbladder in the form of faeces, followed by excretion in the form of urine[42]. In addition, a small amount of Mn can be excreted through sweat[43]. Regardless of the level of Mn absorption, adults can maintain the balance of Mn concentrations in tissues by regularly regulating the absorption rate and excretion rate of Mn. In the liver, Mn is separated from the blood and bound to bile before being re-secreted into the intestine. A small fraction of Mn is reabsorbed in the intestine, forming the hepato-enteric circulation. In the brain parenchyma, rapid accumulation of Mn occurs in brain structures such as the amygdala, end grain, hippocampus and pale sphere structure, and Mn has a half-life of approximately 5–7 d. However, Mn has the longest retention time in the periaqueductal grey matter, amygdala and endothelium[43].

Content and distribution of Mn

Mn exists in the human body in the form of a variety of proteins and enzymes such as manganese superoxide dismutase, GS and arginase[44], and acts as a coenzyme in a variety of biological processes such as skeletal system development, energy metabolism, enzyme activation, and functions of the nervous system, immune system and reproductive hormones[6]. Mn is involved in a variety of biological processes such as nutrient metabolism, bone formation, the free radical defence system, ammonia clearance and neurotransmitter synthesis in the brain. Mn is most commonly stored in mitochondria after uptake, and therefore the highest concentration is found in mitochondria-rich organs such as liver, kidney and pancreas[45]. The normal concentration of manganese varies in different human tissues: 1 mg/kg in bone, 1·04 mg/kg in the pancreas[46], 0·98 mg/kg in the renal cortex, 1·2–1·3 mg/kg in the liver and 0·15–0·46 mg/kg in the brain[5] (Fig. 1). We summarise the normal range of Mn content in various organs of the human body in Table 1. Excessive Mn can easily accumulate in the brain, leading to the onset of neuropsychiatric symptoms. In the brain, Mn preferentially accumulates in the caudoputamen, globus pallidus, substantia nigra and subthalamic nucleus[47]. Under normal conditions, intracellular Mn mainly accumulates in mitochondria and participates in the process of oxidative phosphorylation (OXPHOS) in mitochondria. Chronic excessive exposure to Mn has been confirmed to induce mitochondrial

https://doi.org/10.1017/S0954422425100139 Published online by Cambridge University Press

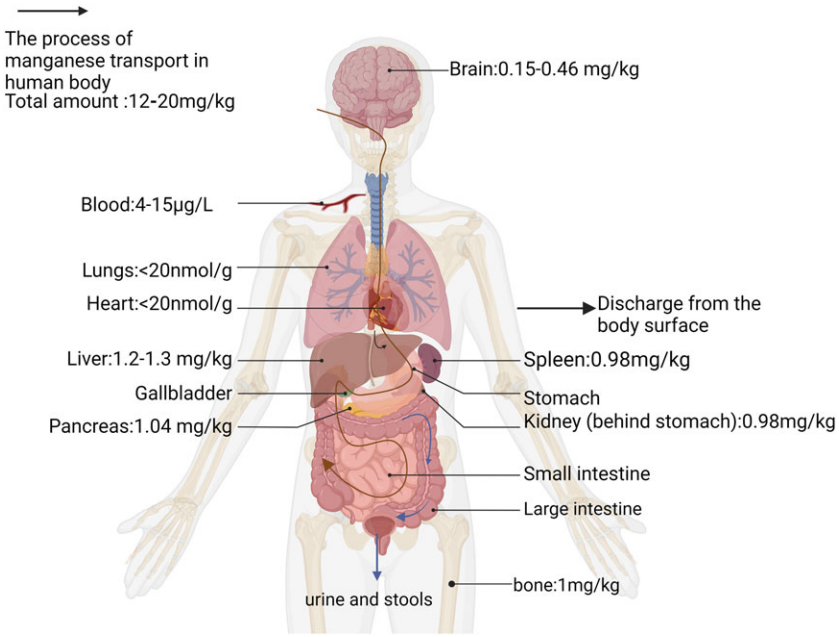

Fig. 1. Mn in the human body. Mn contents in various tissues of the human body and the pathways of Mn intake and excretion.

Table 1. Mn homeostasis. The concentration of Mn in human organs and body tissues ranked from lowest to highest

Organ or body tissue	Concentration	Reference
Urine	0·07–1·703 μg/l	[137]
Blood	4–15 μg/l	[138]
Brain	0·15–0·46 mg/kg	[139]
Spleen	0·98 mg/kg	[140]
Kidney	0·98 mg/kg	[5]
Bone	1 mg/kg	[141]
Pancreas	1·04 mg/kg	[140]
Liver	1·2–1·3 mg/kg	[142]

dysfunction, which is related to oxidative damage[48]. In fact, high concentrations of Mn can cause neurotoxicity and lead to psychiatric diseases[49,50], such as Parkinson's disease and gamma-aminobutyric acid (GABA) system-related diseases[12]. The daily intake of Mn per adult should be approximately 2–6 mg/d[51], and the World Health Organization/Food and Agriculture Organization (WHO/FAO) of the United Nations recommends Mn levels in drinking water <400 μg/l[33].

The effects of Mn homeostasis on microbial survival

The number of bacteria present in the human body is almost equal to the ratio of human cells (1·3:1). The intestinal flora (99%) is the most important group of bacteria in human body, and erythrocytes (84%) are the most important cells[52]. As a metabolic 'organ' in the human body, the interaction between bacterial communities is a key factor affecting human health. Mn is not only an indispensable catalytic centre and structural core for various enzymes but also involved in a variety of biological processes, including OXPHOS, glycosylation and signal transduction. It is also an essential metal element for pathogenic microorganisms to maintain basic biochemical activity and virulence. Hosts can utilise Mn to participate in the process of nutritional immunity to prevent pathogen invasion[53].

Role of Mn in pathogenic microbes

Usually, the survival environment of pathogenic microorganisms in the host body is brutal, and they need the participation of metal ions to maintain survival. The oxidative defence system of human body can kill pathogenic bacteria, but manganese can improve the tolerance of pathogenic bacteria to reactive oxygen intermediates (ROIs). In addition, Mn is involved in the adaptation process of pathogens to the human body by acting as a cofactor for enzymes involved in intermediary metabolism and cell signalling pathways, maintaining the expression of virulence related genes and other pathways[54]. A defence strategy called 'nutritional immunity' is employed by host cells invaded by pathogenic microorganisms. It aims to prevent invading pathogens from acquiring metal ions, such as Mn, from the host[55]. In brief, during an inflammatory episode, Mn binds to calprotectin to compete for or strip the metal from pathogen metalloproteins, inactivating them and weakening their defence against the host immune response. In some cases, pathogens have developed the ability to compete with calprotectin-mediated metal starvation in the gut[56]. In patients with various types of infection, it can be observed that their serum and tissue Mn levels are significantly reduced[57]. A series of experiments have shown that once host cells have phagocytosed pathogens, Mn transporters, including natural resist-associated macrophage protein 1 (NRAMP1) encoded by the human *SLC11A1* gene, and other metal transporters, limit the intracellular utilisation of Mn by pathogens[58,59].

To prevent themselves from being killed, pathogenic microorganisms have evolved a complicated system to obtain metal ions from the host for improved survival[58,60]. Among a variety of pathogens, such as *Staphylococcus aureus*[61], *Staphylococcus pneumoniae*[62], *Salmonella typhimurium*[63,64] and *Yersinia pestis*[65,66], two manganese transport systems have been identified

https://doi.org/10.1017/S0954422425100139 Published online by Cambridge University Press

Table 2. Transport proteins. The functions of different transport proteins in pathogenic microbes/cells

Transport protein	Function	Pathogen microbes/ cell	Reference
BmtA	BmtA transports Mn to fight superoxides contained in cells and to defend the spirochete from the initial host immune response, including the extremely deleterious effects of ROS generated during the innate host immune response to Lyme borreliosis	*Borrelia burgdorferi*	[70]
NRAMP	The metal transporter NRAMP of *Saccharomyces cerevisiae* prevents oxidative damage by transporting manganese into the cell	*Saccharomyces cerevisiae*	[143]
MntH	Competes with the host manganese-binding protein calvin for manganese acquisition, thus enabling the pathogen to proliferate and maintain its SOD activity	*Staphylococcus aureus*	[71]
MntABC			[144]
MntC	MntC maintains SOD activity by binding manganese into the cells, thereby maintaining *S. aureus* virulence		[145]
MntE	*Staphylococcus aureus* uses cationic diffusion accelerator (CDF) family protein MntE to reduce the toxicity of Mn by excreting excess Mn		[73]
MntP	Mn-mediated manganese efflux from the gram-negative pathogen *Salmonella enterica* Typhimurium in response to manganese overload and nitric oxide stress	*Salmonella enterica* serovar Typhimurium	[146]
MntX	In *Neisseria meningitidis*, Mn^{2+} export via MntX regulates the intracellular Mn:Fe ratio and protects against manganese toxicity that is exacerbated in low iron conditions	*Neisseria meningitidis*	[147]

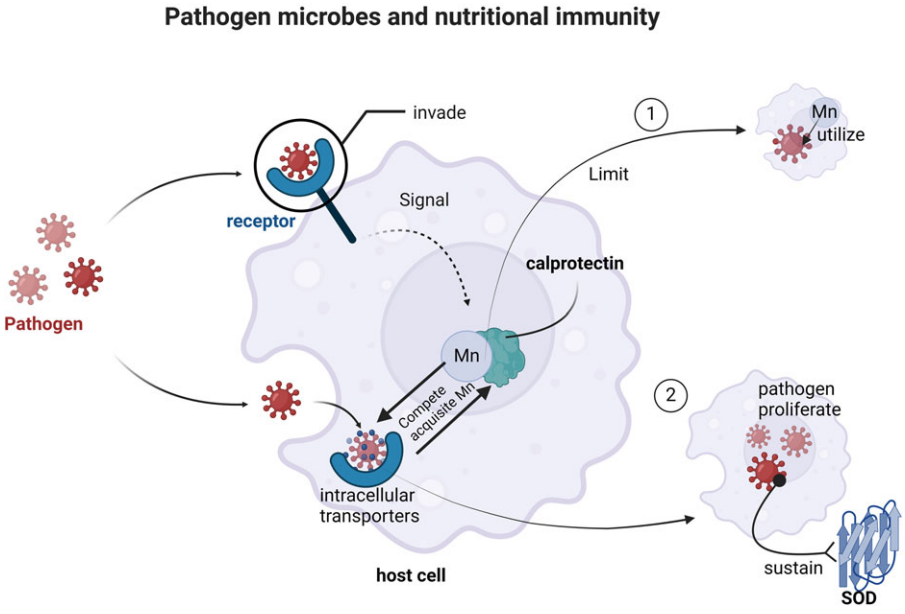

Fig. 2. Pathogen microbes and nutritional immunity. Host cells and pathogenic microorganisms compete for Mn. Calprotectin in host cells compete for the Mn in pathogen metalloproteins, inactivating them and impairing their defence against host immune responses. Pathogenic microorganisms, however, compete with the host calprotectin to obtain Mn, thereby allowing the pathogen to proliferate and maintain its SOD activity.

that are closely related to host pathogenesis and involve intracellular transporters such as MntABC, MntH, NRAMP, BmtA and MntX[67–70]. They control the uptake of Mn and thus the virulence of pathogens. For example, the *S. aureus* proteins MntABC and MntH compete with the host manganese-binding protein calprotectin for Mn acquisition, thereby enabling the pathogen to proliferate and maintain its SOD activity[71] (Fig. 2). The functions of different transport proteins in pathogen microbes/cells are described in Table 2.

Excessive Mn may be harmful to bacteria

Various Mn efflux proteins, such as MntE, MntP and MntX (which have the same names as the proteins listed above but represent different proteins), control the export of excess Mn from bacteria to prevent toxicity caused by excessive Mn[72]. For example, in *Staphylococcus aureus* (*S. aureus*), the Mn export protein MntE is necessary for the pathogen to exert its full virulence during infection, indicating the presence of Mn toxicity in the pathogen, whereas a mutant strain of *S. aureus* lacking the MntE has reduced resistance to oxidative stress and lower oxidative stress levels[73].

In addition, Mn plays a role in regulating the activity of viral enzymes at the host–virus interface, and the most important finding is that Mn contributes to the assembly and integration of human immunodeficiency virus (HIV) [74]. Mn has been shown to increase the number of DNA nucleotide triphosphate errors in pathogens and retroviruses *in vitro*[75]. Thus, in the presence of excess Mn, the mutation rate of HIV increases significantly. In the DNA-based herpes simplex virus, for example, Mn ions seem to act as DNA polymerase super catalysts to promote DNA replication[76].

https://doi.org/10.1017/S0954422425100139 Published online by Cambridge University Press

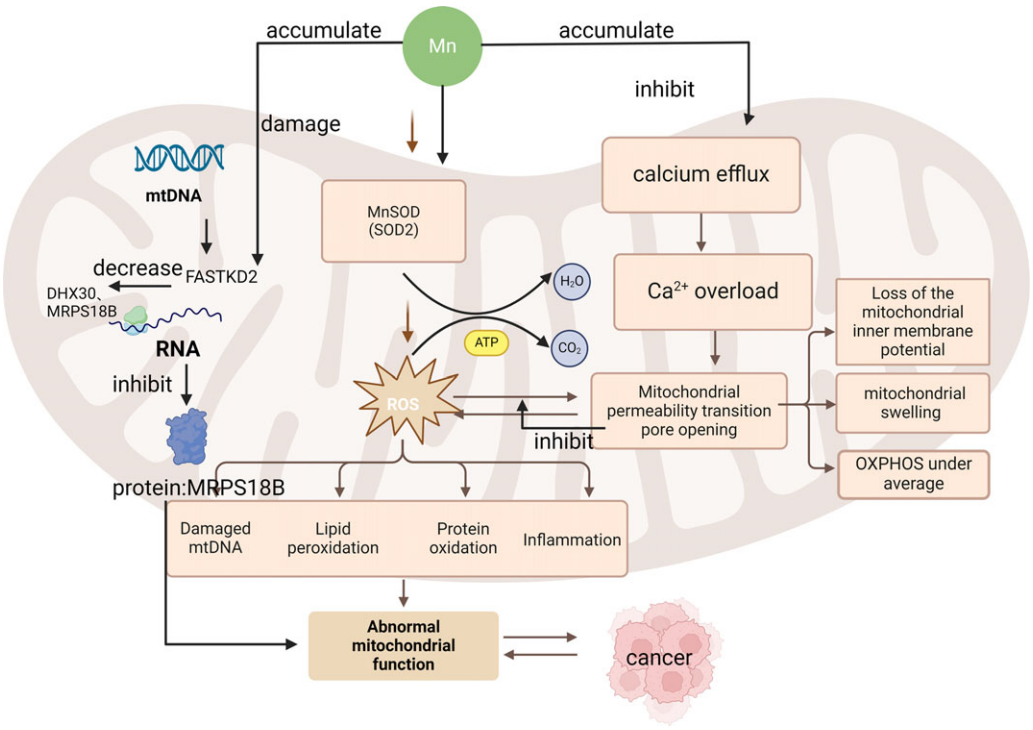

Fig. 3. Role of Mn in mitochondria in human cells. Mn is involved in the regulation of mitochondrial function by regulating SOD2 activity. A disruption of Mn homeostasis in mitochondria impairs the composition and function of mitochondrial RNA particles, leading to a disruption of mitochondrial transcriptional processes that results in impaired assembly and function of the mitochondrial respiratory chain. If Mn accumulates in mitochondria, it inhibits calcium efflux and triggers mitochondrial dysfunction.

In conclusion, pathogens such as bacteria and fungi have robust self-protection systems to regulate Mn homeostasis, thereby maintaining virulence and evading Mn toxicity. Impaired Mn metabolism impairs pathogen proliferation and virulence, and this process could be a potential research target for the prevention of pathogen invasion in the host.

Mn regulates mitochondrial function

At the subcellular level, most of the metabolism of manganese occurs in mitochondria. It enters the mitochondria *via* DMT1 present in the outer mitochondrial membrane, while efflux is very slow[77]. In addition to high storage concentrations, Mn enters mitochondria more rapidly, with intracellular mitochondria increasing Mn at a higher rate than nuclei after chronic Mn treatment[78]. Mitochondria are the site of manganese metabolism and energy conversion in cells. Its main function is OXPHOS to synthesise ATP and supply life activities. In addition to being a key organelle for intracellular energy generation, mitochondria are also involved in metabolic processes such as apoptosis, lipid metabolism and free radical production. The inhibitory effects of excess Mn on the respiratory chain and calcium efflux in cellular mitochondria, and the anti-cancer effects of the antioxidant enzyme MnSOD, are summarised in Fig. 3.

Excessive accumulation of Mn can inhibit calcium efflux

Excess Mn is detrimental to mitochondrial function both *in vivo* and *in vitro*, leading to dysfunction. Mn is involved in the antioxidant system of mitochondria and can interfere with calcium metabolism in mitochondria[79]. Experimental studies have shown that Mn exposure in the brain, especially in the striatum and hypothalamus, leads to Mn accumulation while simultaneously affecting Ca^{2+} metabolism in mitochondria. It inhibits the outflow of Ca^{2+} from mitochondria such that Ca^{2+} gradually accumulates in mitochondria, affecting the transmission of excitation in mitochondria and causing a series of dysfunctions[80]. Elevated calcium levels lead to reactive oxygen species (ROS) production and to the opening of the mitochondrial permeability transition pore (mPTP). This process leads to a loss of the inner membrane potential, mitochondrial swelling, impaired OXPHOS and inhibition of ATP synthesis. All of these processes further generate ROS associated with Mn neurotoxicity and aggravate mitochondrial dysfunction[13].

Dysregulation of Mn homeostasis impairs the assembly and function of the respiratory chain

Mn can be harmful to human health when it is present in excess or deficient in the body. Mn exposure impaired the composition and function of the mitochondrial ribosomal proteins DHX30 and MRPS18B, and the mitochondrial RNA particle FASTKD2, disrupting the mitochondrial transcription process. FASTKD2 is a component of the mitochondrial RNA granule required for the processing of polycistronic mitochondrial RNA, a step necessary for mitochondrial protein synthesis. Notably, genetic disruption of the mitochondrial RNA granule or pharmacological inhibition of mitochondrial transcription–translation in cells is protective against acute Mn exposure *in vitro*[81–83]. FASTKD2 and other mitochondrial RNA binding proteins (including DHX30, GRSF1 and the mitochondrial ribosomal subunit) participate in protein complexes, such as MRPS18B[83,84].

The disruption of Mn homeostasis results in interference with RNA particles within mitochondria. RNA particles are important intermediates for protein synthesis in mitochondria. They are responsible for the transcription of genetic information from DNA into RNA and further direct protein synthesis. The disruption of Mn homeostasis interferes with the formation and stability of RNA particles, thereby affecting protein synthesis within mitochondria.

https://doi.org/10.1017/S0954422425100139 Published online by Cambridge University Press

Werner *et al.* tested whether Mn exposure could induce these RNA granule phenotypes in induced pluripotent stem cell (iPSC)-derived human astrocytes and glutamatergic neurons and reported that iPSC-derived neurons presented reduced levels of DHX30, GRSF1 and MRPS18B when exposed to low Mn concentrations. These results suggested that a disruption of Mn homeostasis could reduce the composition of mitochondrial RNA particles and thus affect mitochondrial protein synthesis[81].

Effect of MnSOD activity on mitochondrial redox balance

Active MnSOD is a mature antioxidant enzyme in mitochondria. MnSOD activity is essential for maintaining the redox balance in mitochondria and can protect cells from oxidative stress damage caused by excessive reactive oxygen species (ROS)[85,86]. In normal cells, MnSOD can maintain mitochondrial integrity and promote cell regeneration. In cancer cells, MnSOD attenuates the deleterious effects of ROS stimulation, including the promotion of cancer development and maintenance.

Specifically, hypoxia and hypermetabolism are the common characteristics of cancer cells, and their daily energy requirements are far higher than normal cells. This means that cancer cells need to produce more mitochondria to meet their energy demand. However, the mitochondria produced by cancer cells often have abnormal phenomena such as wrinkled outer membranes, membrane structural integrity defects, mitochondrial distribution around the nucleus, and hollow mitochondria. An important cause of abnormal mitochondrial structure and morphology is the frequent mutation of mitochondrial DNA (mtDNA) in cancer cells[87]. mtDNA mutations not only cause changes in mitochondrial appearance but also directly cause dysfunction, increase ROS production and redox imbalance in mitochondria, and stimulate the proliferation and invasion of cancer cells[88–90]. During carcinogenesis, tumour cells typically exhibit increased reactive oxygen species (ROS) production[91,92], increased ROS accumulation and dysregulation of antioxidant enzymes[93]. ROS derived from the electron transport chain in mitochondria can activate signalling pathways related to carcinogenesis. For example, H_2O_2 (a form of ROS) can activate receptor tyrosine kinase[94,95], Ras-mitogen-activated protein kinase (Ras-MAPK)[96,97] and phosphatidylinositol 3-kinase (PI3K) pathways[94]. As an antioxidant enzyme, MnSOD can convert superoxide into hydrogen peroxide (H_2O_2) and oxygen, and further convert it into harmless water and oxygen during cancer progression, thereby reducing oxidative damage to cells and playing a protective antioxidant role[98]. Animal experiments have revealed that mice with a monoallelic knockout of MnSOD ($SOD2^{+/-}$) exhibit increased superoxide levels, which leads to the occurrence of cancer[99]. Compared with wild-type control, $SOD2^{+/-}$ mice are more likely to develop cancer and have a shortened lifespan, suggesting that the loss of MnSOD activity promotes carcinogenesis. In addition, an analysis of mitochondrial DNA from patients with breast cancer has shown a common deletion of MnSOD in the blood, resulting in impaired MnSOD activity and increased oxidative damage[93].

In general, enhanced MnSOD activity reduces mitochondrial oxidative stress and inhibits cancer development. Taking advantage of the antioxidant effects of manganese in mitochondria, it has also been used in cancer therapy in some cases. For example, single-atom manganese anchored on carbon dots can effectively concentrate in mitochondria, interfere with their oxidation–reduction balance, and exhibit excellent anti-cancer performance and good magnetic resonance imaging (MRI)

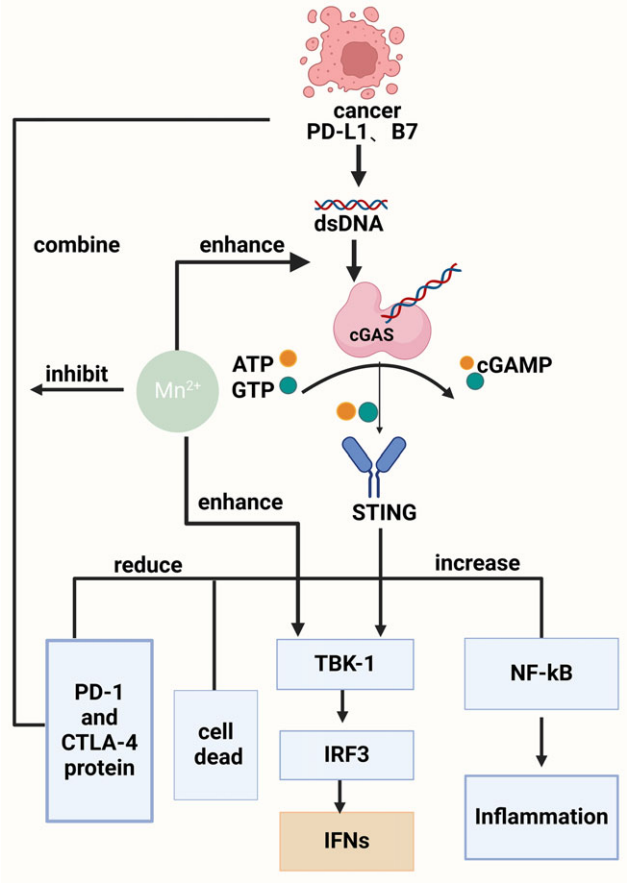

Fig. 4 cGAS-STING signalling pathway. Mn increases the sensitivity of cGAS to dsDNA in cancer cells and regulates the cGAS–STING pathway to promote the anti-cancer immunity of immune cells. Mn binds to cGAS and enhances its anti-cancer effect by inhibiting the binding of immune receptors such as PD-1 and CTLA-4 on the surface of immune cells to ligands such as PDL-1 and BT on the surface of cancer cells. In the STING pathway, Mn stimulates IRF-3 in tumour cells to produce IFN, thereby activating the anti-cancer effect of immune cells such as NKT and CTL.

signal responsiveness under visible light irradiation, showing its application potential in the integration of tumour diagnosis and treatment[100].

Mn enhances anti-tumour immunity through the cGAS–STING pathway

Mn, an indispensable trace element in the human body, is not only an important cornerstone for maintaining health but also plays a non-negligible role in the anti-cancer process. We summarise the key pathways and mechanisms through which Mn exerts its anti-cancer effects by enhancing immune responses (Fig. 4).

Increased dsDNA sensitivity

Further studies showed that Mn-mediated anti-tumour immune responses were dependent on the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS–STING) pathway. Mn can directly interact with cGAS, increase the sensitivity of dsDNA, significantly stimulate the expression of interferon (IFN) regulatory factor (RF3/IRF7) and type I IFN[44], and then stimulate T cells to exert immune function. cGAS activity is affected by a variety of factors, of which the sensitivity of double-stranded DNA (dsDNA)

https://doi.org/10.1017/S0954422425100139 Published online by Cambridge University Press

is a key factor. As an important immune antigen, dsDNA can stimulate the activity of cGAS and trigger a strong immune response. The sensitivity of dsDNA may be insufficient, resulting in a weakened immune response and thus affecting the efficacy of disease treatment. Mn can act on cancer cells, directly bind to cGAS, stabilise cGAS activity, increase its sensitivity to dsDNA[101] and thus stimulate the cGAS–STING pathway to participate in human immune responses. This implies that, in the presence of manganese, even low concentrations of dsDNA are effective in stimulating cGAS activity to elicit a strong immune response.

Inhibition of immunosuppressive molecules

More importantly, Mn could directly bind to cGAS and reduce surface programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) protein concentrations. PD-1 and CTLA-4 are two important immunosuppressive molecules[102], and their elevated expression inhibits T-cell function. By activating the cGAS–STING pathway, manganese ions can reduce the expression of these inhibitory molecules, thereby relieving immunosuppression and enhancing anti-tumour immune responses[102–106]. At present, anti-PD-1/PD-L1 antibodies have been successfully used to treat various types of cancer[107–114]. However, due to individual differences, most patients cannot benefit from this therapy[115,116]. Divalent manganese, as a natural STING agonist, can cooperate with anti-PD-1 /PD-L1 antibodies in cancer immunotherapy[117]. Even in low immunogenic tumour models such as B16, the combination of STING agonists with anti-PD-1/PD-L1 antibody treatment significantly prolonged the survival of mice compared with the corresponding monotherapy[118]. Preliminary clinical evidence suggests that Mn supplementation, when administered as Mn chloride *via* intranasal (0·05–0·1 mg/kg/d) or inhalation (0·1–0·4 mg/kg/d) routes in combination with subsequent intravenous chemotherapy (day 2) and anti-PD-1 antibody (2–4 mg/kg, day 3) on a 3-week cycle, demonstrates promising efficacy in treatment-refractory advanced metastatic solid tumours. The observed objective response rate reached 45·5% with a disease control rate of 90·9% in patients who had failed standard anti-cancer therapies including chemoradiotherapy and prior PD-1 blockade[101]. These findings need further confirmation in randomised controlled trials. In addition, Mn could significantly increase the expression of CD80 and CD86 in Dendritic cells (DCs) by activating the cGAS–STING pathway. CD80 and CD86 are costimulatory molecules that bind to their respective receptors on the surface of T cells and induce T-cell activation, thereby enhancing the adaptive immune response.

Amplify the activities of cGAS and STING

Mn can also amplify the activation of cGAS and STING by increasing cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) production and increasing the binding affinity of cGAMP-STING. STING proteins trigger downstream signals on the endoplasmic reticulum (ER) surface by activating and recruiting interferon regulatory factor 3 (IRF-3), TANK-binding kinase 1 (TBK-1) and nuclear factor kappa B (NF-κB), followed by the expression and secretion of IFNs. Type I IFNs stimulate adaptive and innate immunity to cancer by promoting DC maturation and antigen presentation to stimulate T cells[119]. IFNs can also promote NKT recruitment and CTL infiltration[120] to exert anti-cancer effects. One study showed that STING knockout (Sting gt/gt) mice had a faster growth rate of tumour cells (such as RMA-S lymphoma and B16-BL6 melanoma) than wild-type mice, indicating that STING plays an important role in anti-tumour response. In Rag2 knockout ($Rag2^{-/-}$) mice lacking both T and B cells, when STING was knocked out ($Rag2^{-/-}$ Sting gt/gt), these mice were significantly more sensitive to RMA-S and B16-BL6 tumours. This suggests that STING also plays a key role in NK cell-mediated anti-tumour responses. Knockout of cGAS gene ($Cgas^{-/-}$) in tumour cells by CRISPR/Cas9 technology can reduce the activation of NK cells, further confirming the importance of the cGAS–STING pathway in NKT activation. These experimental results suggest that cGAS in cancer cells recognise their own DNA to produce cGAMP molecules. The cGAMP molecule is recognised by the STING protein of the host cell and activates STING. Activated STING proteins trigger an interferon response and produce cytokines such as IFN-β. These cytokines can activate NK cells to enhance anti-cancer immune responses and improve the ability to recognise and kill cancer cells[121].

On the basis of the mechanism that Mn promotes anti-tumour effects in a cGAS–STING-dependent manner, a bovine serum albumin/ferritin-based nanoagonist incorporating Mn ions (Mn^{2+}) and β-lapachone has been developed. This protein-based cGAS–STING nanoagonist was able to efficiently activate T-cell mediated anti-cancer immune responses in *in vitro* cell experiments and inhibit cancer growth and also showed significant therapeutic effects in animal models[122].

Mn delivery strategies

Mn, as an essential trace element, plays an essential role in anti-cancer immunity under physiological conditions. Studies have demonstrated that the growth of cancer cells and lung metastasis are significantly accelerated in Mn-deficient mice. Exogenous Mn^{2+} effectively activates the cGAS–STING pathway, significantly promotes the ability of host antigen-presenting cells to present cancer antigens, promotes the infiltration of cytotoxic T cells into tumour tissues, and enhances the specific killing of tumour cells[101]. Given these findings, targeted delivery of Mn to cancer sites represents a promising therapeutic strategy for supporting anti-cancer immunity and enhancing the efficacy of cancer treatments. Consequently, the development of efficient Mn delivery systems has become the focus of current research.

Intelligent responsive delivery systems

Due to the immunosuppressive microenvironment (ISME) in cancer tissues[123], the clinical efficacy of cancer immunotherapy often falls short of expectations. As a result, responsive nanocarriers for Mn delivery have emerged, particularly targeting the low pH conditions of the tumour microenvironment (TME). The Warburg effect indicates that cancer cells predominantly rely on aerobic glycolysis for energy, resulting in the accumulation of lactate and creating an acidic environment within cancer tissues[124]. In contrast to the pH of approximately 7·4 in normal tissues, the extracellular environment of cancer cells typically exhibits a pH of 6·8, with even lower pH values in endosomes and lysosomes, around 5·0–5·5[125]. MnO_x nanomaterials remain stable in a neutral environment (pH 7·4)[126] but can effectively catalyse endogenous H_2O_2 to generate O_2 in the acidic TME[127], alleviating cancer hypoxia. The catalytic reaction is as follows: $MnO_2 + 2H^+ \rightarrow Mn^{2+} + 2H_2O + ½O_2$.

MnO_2 nanomaterials are unique TME-responsive nanomaterials that have garnered considerable attention due to their high

https://doi.org/10.1017/S0954422425100139 Published online by Cambridge University Press

biocompatibility, structural stability and easily modifiable surfaces[128]. Nanoshells constructed from MnO_2 can rapidly decompose in acidic TME, releasing Mn^{2+} and the anti-cancer drugs loaded within the shell[129]. Polydopamine (PDA), a novel polymer inspired by mussels, offers natural advantages such as good biocompatibility, adhesion and multiple drug response releases. The PDA shell remains stable at pH 7·4 but ruptures upon reaching the cancer site (pH 6·8) due to acidic conditions[130]. Therefore, coating an additional layer of polydopamine (PDA) on the MnO_2 nanoshell can serve as a 'gate' to control drug release, reducing premature drug release in the bloodstream[131].

Targeted delivery of Mn

In addition to utilising TME characteristics for Mn delivery, targeting the biological characteristics of cancer cells has also become a significant strategy. Hyaluronic acid (HA), recognised for its excellent biocompatibility and CD44 receptor-mediated cancer-targeting capability, has become a widely used delivery vehicle[132,133]. Research indicates that modifying HA on the surface of MnO_2 nanosheets enables successful targeting of Mn^{2+} to cancer sites and its release into the cancer microenvironment[134]. Research also found that decorating MnO_2 surfaces with gene-engineered exosomes carrying CD47 exhibits good cancer-targeting capabilities[120]. Another common targeted delivery strategy involves loading MnO_2 onto nanoparticles coated with the same kind of cancer cell membrane, where the cell membrane coating ensures active cancer targeting, resulting in efficient endocytosis and high accumulation[135]. Furthermore, a study has proposed targeting Mn delivery to the ER, since STING signalling activation and subsequent immune responses are primarily associated with the ER. It reported the design of ER-targeted Mn-based nanocomplexes (NC) by complexing Mn^{2+} with a zwitterionic polymer, poly(2-(*N*-oxide-*N*,*N*-dimethylamino) ethyl methacrylate) (OPDMA). In mouse models of colon and hepatocellular carcinoma, intravenously injected Mn/OPDMA NC delayed cancer growth rates by 2·4–5 times compared with free-Mn^{2+}-treated mice and extended the survival period of the mice[136].

In recent years, a variety of delivery methods have been developed to precisely deliver Mn to cancer sites, including intelligent responsive delivery systems and targeted delivery systems. These strategies are expected to provide novel therapeutic approaches for patients with cancer. By exploiting the low pH properties of the tumour microenvironment and targeted delivery strategies, scientists are designing vectors that can deliver manganese precisely to the cancer site. These innovative delivery systems not only enhance treatment precision but may also lead to new breakthroughs in cancer treatment in future clinical applications.

Conclusions

In conclusion, Mn is an indispensable trace element in the human body, and an imbalance of Mn homeostasis can lead to changes in human physiological states and many diseases. Mn positively regulates host immunity, mitochondria and microbes to exert anti-cancer effects. In recent years, a variety of delivery methods have been developed to precisely supplement manganese nutrition to cancer sites, including intelligent responsive delivery systems and targeted delivery systems. This is expected to provide new therapeutic strategies for cancer patients. However, the specific mechanism of manganese inhibition of tumours is still unclear, and further studies are needed in the future to explore the therapeutic strategies that manganese can be applied to the clinical treatment of cancer. It is hoped that this review can provide new ideas and programmes for scholars to conduct more in-depth research on Mn.

Availability of data and material. Data sharing is not applicable to this article as no new data were created or analysed in this study.

Acknowledgements. Not applicable.

Authors Contributions. Conceived and drafted the manuscript: Han Shuwen and Liu Jiang. Wrote the paper: Zhuang Jing and Wang Yingchen. Reviewed and compiled the literature: Li Jinyou and Wu Yinhang. Designed and drew figures: Li Jinyou. All authors read and approved the paper.

Financial support. This work was supported by Public Welfare Technology Application Research Program of Huzhou (no. 2022GZB04), Zhejiang Medical and Health Technology Project (nos. 2025KY1531 and 2025KY327) and Zhejiang Province Traditional Chinese Medicine Science and Technology Project (no. 2024ZL1018).

Competing Interests. The authors declare that no potential conflicts of interest exist.

Ethical standards. Not applicable.

Consent for publication. Not applicable.

References

1. Wang H S, Lineweaver C H, Ireland T R. (2018) The elemental abundances (with uncertainties) of the most Earth-like planet. *Icarus* **299**, 460–474.
2. Wang X, Wang Q, Zhang D, *et al.* (2024) Fumigation alters the manganese-oxidizing microbial communities to enhance soil manganese availability and increase tomato yield. *Sci Total Environ* **919**, 170882.
3. Zhuang Y, Zhu J, Shi L, *et al.* (2022) Influence mechanisms of iron, aluminum and manganese oxides on the mineralization of organic matter in paddy soil. *J Environ Manage* **301**, 113916.
4. Parmalee N L, Aschner M. (2016) Manganese and aging. *Neurotoxicology* **56**, 262–268.
5. Chen P, Bornhorst J, Aschner M. (2018) Manganese metabolism in humans. *Front Biosci* **23**, 1655–1679.
6. Kawahara M, Kato-negishi M, Tanaka K I. (2023) Dietary trace elements and the pathogenesis of neurodegenerative diseases. *Nutrients* **15**, 2067.
7. Schmidt S B, Jensen P E, Husted S. (2016) Manganese deficiency in plants: the impact on photosystem II. *Trends Plant Sci* **21**, 622–632.
8. Spears J W. (2019) Boron, chromium, manganese, and nickel in agricultural animal production. *Biol Trace Elem Res* **188**, 35–44.
9. Tarnacka B, Jopowicz A, Maślińska M. (2021) Copper, iron, and manganese toxicity in neuropsychiatric conditions. *Int J Mol Sci* **22**, 7820.
10. Viegas M N, Salgado M A, Aguiar C, *et al.* (2021) Effect of dietary manganese and zinc levels on growth and bone status of *Senegalese Sole (Solea senegalensis)* post-larvae. *Biol Trace Elem Res* **199**, 2012–2021.
11. Xia Y, Wang C, Zhang X, *et al.* (2023) Combined effects of lead and manganese on locomotor activity and microbiota in zebrafish. *Ecotoxicol Environ Saf* **263**, 115260.
12. Martins A C, JR., Ruella Oliveira S, Barbosa F, JR., *et al.* (2021) Evaluating the risk of manganese-induced neurotoxicity of parenteral nutrition: review of the current literature. *Expert Opin on Drug Metab & Toxicol* **17**, 581–593.
13. Miah M R, Ijomone O M, Okoh C O A, *et al.* (2020) The effects of manganese overexposure on brain health. *Neurochem Int* **135**, 104688.
14. Peres T V, Schettinger M R, Chen P, *et al.* (2016) Manganese-induced neurotoxicity: a review of its behavioral consequences and neuroprotective strategies. *BMC Pharmacol Toxicol* **17**, 57.

https://doi.org/10.1017/S0954422425100139 Published online by Cambridge University Press

15. Zhou B, Su X, Su D, *et al.* (2016) Dietary intake of manganese and the risk of the metabolic syndrome in a Chinese population. *Br J Nutr* **116**, 853–863.
16. Einhorn V, Haase H, Maares M. (2024) Interaction and competition for intestinal absorption by zinc, iron, copper, and manganese at the intestinal mucus layer. *J Trace Elem Med Biol* **84**, 127459.
17. Myers J E, Thompson M L, Naik I, *et al.* (2003) The utility of biological monitoring for manganese in ferroalloy smelter workers in South Africa. *Neurotoxicology* **24**, 875–883.
18. Wooten A L, Aweda T A, Lewis B C, *et al.* (2017) Biodistribution and PET imaging of pharmacokinetics of manganese in mice using Manganese-52. *PLoS One* **12**, e0174351.
19. Palacios C. (2006) The role of nutrients in bone health, from A to Z. *Crit Rev Food Sci Nutr* **46**, 621–628.
20. Strause L G, Hegenauer J, Saltman P, *et al.* (1986) Effects of long-term dietary manganese and copper deficiency on rat skeleton. *J Nutr***116**, 135–141.
21. Wang X, Li G J, Zheng W. (2006) Upregulation of DMT1 expression in choroidal epithelia of the blood-CSF barrier following manganese exposure *in vitro*. *Brain Res* **1097**, 1–10.
22. Kwakye G F, Paoliello M M, Mukhopadhyay S, *et al.* (2015) Manganese-induced Parkinsonism and Parkinson's disease: shared and distinguishable features. *Int J Environ Res Public Health* **12**, 7519–7540.
23. Dobson A W, Erikson K M, Aschner M. (2004) Manganese neurotoxicity. *Ann N Y Acad Sci* **1012**, 115–128.
24. Harischandra D S, Ghaisas S, Zenitsky G, *et al.* (2019) Manganese-induced neurotoxicity: new insights into the triad of protein misfolding, mitochondrial impairment, and neuroinflammation. *Front Neurosci* **13**, 654.
25. Finkelstein Y, Milatovic D, Aschner M. (2007) Modulation of cholinergic systems by manganese. *Neurotoxicology* **28**, 1003–1014.
26. Santos D, Milatovic D, Andrade V, *et al.* (2012) The inhibitory effect of manganese on acetylcholinesterase activity enhances oxidative stress and neuroinflammation in the rat brain. *Toxicology*, **292**, 90–98.
27. Bouabid S, Tinakoua A, Lakhdar-Ghazal N, *et al.* (2016) Manganese neurotoxicity: behavioral disorders associated with dysfunctions in the basal ganglia and neurochemical transmission. *J Neurochem* **136**, 677–691.
28. Stelling M P, Soares M A, Cardoso S C, *et al.* (2021) Manganese systemic distribution is modulated *in vivo* during tumor progression and affects tumor cell migration and invasion *in vitro*. *Sci Rep* **11**, 15833.
29. Golara A, Kozłowski M, Guzik P, *et al.* (2023) The role of selenium and manganese in the formation, diagnosis and treatment of cervical, endometrial and ovarian cancer. *Int J Mol Sci* **24**, 10887.
30. Sun X, Zhang Y, Li J, *et al.* (2021) Amplifying STING activation by cyclic dinucleotide-manganese particles for local and systemic cancer metalloimmunotherapy. *Nat Nanotechnol* **16**, 1260–1270.
31. Yi M, Niu M, Zhang J, *et al.* (2021) Combine and conquer: manganese synergizing anti-TGF-β/PD-L1 bispecific antibody YM101 to overcome immunotherapy resistance in non-inflamed cancers. *J Hematol Oncol* **14**, 146.
32. Zhang K, Qi C, Cai K. (2023) Manganese-based tumor immunotherapy. *Adv Mater* **35**, e2205409.
33. Martins A C, Krum B N Queirós L, *et al.* (2020) Manganese in the diet: bioaccessibility, adequate intake, and neurotoxicological effects. *J Agric and Food Chem* **68**, 12893–12903.
34. Teeguarden J G, Gearhart J, Clewell H J, 3RD, *et al.* (2007) Pharmacokinetic modeling of manganese. III. Physiological approaches accounting for background and tracer kinetics. *J of Toxicol and Environ Health Part A* **70**, 1515–1526.
35. Gunter T E, Gerstner B, Gunter K K, *et al.* (2013) Manganese transport via the transferrin mechanism. *Neurotoxicology* **34**, 118–127.
36. Gruenheid S, Canonne-Hergaux F, Gauthier S, *et al.* (1999) The iron transport protein NRAMP2 is an integral membrane glycoprotein that colocalizes with transferrin in recycling endosomes. *J Exp Med* **189**, 831–841.
37. Leavens T L, Rao D, Andersen M E, *et al.* (2007) Evaluating transport of manganese from olfactory mucosa to striatum by pharmacokinetic modeling. *Toxicol Sci : an Official J SocToxicol* **97**, 265–278.
38. Bowler R M, Beseler C L, Gocheva V V, *et al.* (2016) Environmental exposure to manganese in air: associations with tremor and motor function. *The Sc Total Environ* **541**, 646–654.
39. Lucchini R G, Dorman D C, Elder A, *et al.* (2012) Neurological impacts from inhalation of pollutants and the nose-brain connection. *Neurotoxicology* **33**, 838–841.
40. Crossgrove J, Zheng W. (2004) Manganese toxicity upon overexposure. *NMR in Biomedicine* **17**, 544–553.
41. Murphy V A, Wadhwani K C, Smith Q R, *et al.* (1991) Saturable transport of manganese(II) across the rat blood-brain barrier. *J Neurochem* **57**, 948–954.
42. Klaassen C D. (1976) Biliary excretion of metals. *Drug Metab Rev* **5**, 165–196.
43. Omokhodion F O, Howard J M. (1994) Trace elements in the sweat of acclimatized persons. *Clinica Chimica Acta; Int J Clin Chem* **231**, 23–28.
44. Wang C, Guan Y, Lv M, *et al.* (2018) Manganese increases the sensitivity of the cGAS-STING pathway for double-stranded DNA and is required for the host defense against DNA viruses. *Immunity* **48**675–687.
45. Aschner M, Erikson K. (2017) Manganese. *Adv Nutr* **8**, 520–521.
46. Barceloux D G. (1999) Manganese. *J toxicol Clin toxicol* **37**, 293–307.
47. Chakraborty S, Aschner M. (2012) Altered manganese homeostasis: implications for BLI-3-dependent dopaminergic neurodegeneration and SKN-1 protection in *C. elegans*. *Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS)* **26**, 183–187.
48. Liu K, Jing M J, Liu C, *et al.* (2019) Effect of trehalose on manganese-induced mitochondrial dysfunction and neuronal cell damage in mice. *Basic Clin Pharmacol Toxicol***125**, 536–547.
49. Khan K, Wasserman G A, Liu X, *et al.* (2012) Manganese exposure from drinking water and children's academic achievement. *Neurotoxicology*, **33**, 91–97.
50. Oulhote Y, Mergler D, Barbeau B, *et al.* (2014) Neurobehavioral function in school-age children exposed to manganese in drinking water. *Environ Health Perspect* **122**, 1343–1350.
51. Freeland-Graves J H, Mousa T Y, KIM S. (2016) International variability in diet and requirements of manganese: causes and consequences. *J Trace Elem Med Biol* **38**, 24–32.
52. Sender R, Fuchs S, Milo R. (2016) Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol* **14**, e1002533.
53. Wu Q, Mu Q, Xia Z, *et al.* (2021) Manganese homeostasis at the host-pathogen interface and in the host immune system. *Semin Cell Dev Biol* **115**, 45–53.
54. Zaharik M L, Finlay B B. (2004) Mn2+ and bacterial pathogenesis. *Front Biosci* **9**, 1035–1042.
55. Hood M I, Skaar E P. (2012) Nutritional immunity: transition metals at the pathogen-host interface. *Nat Rev Microbiol* **10**, 525–537.
56. Zackular J P, Chazin W J, Skaar E P. (2015) Nutritional immunity: S100 proteins at the host–pathogen interface. *J Biol Chem* **290**, 18991–18998.
57. Domej W, Krachler M, Goessler W, *et al.* (2000) Concentrations of copper, zinc, manganese, rubidium, and magnesium in thoracic empyemata and corresponding sera. *Biol Trace Elem Res* **78**, 53–66.
58. Sheldon J R, Skaar E P. (2019) Metals as phagocyte antimicrobial effectors. *Curr Opin Immunol*, **60**, 1–9.
59. Cellier M F, Courville P, Campion C. (2007) Nramp1 phagocyte intracellular metal withdrawal defense. *Microbes Infect* **9**, 1662–1670.
60. Martínez J L, Delgado-Iribarren A, Baquero F. (1990) Mechanisms of iron acquisition and bacterial virulence. *FEMS Microbiol Rev* **6**, 45–56.
61. Horsburgh M J, Wharton S J, Cox A G, *et al.* (2002) MntR modulates expression of the PerR regulon and superoxide resistance in *Staphylococcus aureus* through control of manganese uptake. *Mol Microbiol* **44**, 1269–1286.
62. Marra A, Lawson S, Asundi J S, *et al.* (2002) *In vivo* characterization of the PSA genes from *Streptococcus pneumoniae* in multiple models of infection. *Microbiology (Reading)* **148**, 1483–1491.
63. Kehres D G, Zaharik M L, Finlay B B, *et al.* (2000) The NRAMP proteins of *Salmonella typhimurium* and *Escherichia coli* are selective manganese transporters involved in the response to reactive oxygen. *Mol Microbiol* **36**, 1085–1100.

https://doi.org/10.1017/S0954422425100139 Published online by Cambridge University Press

64. Kehres D G, Janakiraman A, Slauch J M, *et al.* (2002) SitABCD is the alkaline Mn(2+) transporter of *Salmonella enterica* serovar Typhimurium. *J Bacteriol* **184**, 3159–3166.
65. Perry R D, Craig S K, Abney J, *et al.* (2012) Manganese transporters Yfe and MntH are Fur-regulated and important for the virulence of *Yersinia* pestis. *Microbiology (Reading)* **158**, 804–815.
66. Bearden S W, Perry R D. (1999) The Yfe system of *Yersinia pestis* transports iron and manganese and is required for full virulence of plague. *Mol Microbiol* **32**, 403–414.
67. Green R T, Todd J D, Johnston A W. (2013) Manganese uptake in marine bacteria; the novel MntX transporter is widespread in Roseobacters, Vibrios, Alteromonadales and the SAR11 and SAR116 clades. *Isme j* **7**, 581–591.
68. Cellier M F, Bergevin I, Boyer E, *et al.* (2001) Polyphyletic origins of bacterial Nramp transporters. *Trends Genet* **17**, 365–370.
69. Courville P, Chaloupka R, Cellier M F. (2006) Recent progress in structure-function analyses of Nramp proton-dependent metal-ion transporters. *Biochem Cell Biol* **84**, 960–978.
70. Ouyang Z, He M, Oman T, *et al.* (2009) A manganese transporter, BB0219 (BmtA), is required for virulence by the Lyme disease spirochete, *Borrelia burgdorferi*. *Proc Natl Acad Sci U S A* **106**, 3449–3454.
71. Kehl-Fie T E, Zhang Y, Moore J L, *et al.* (2013) MntABC and MntH contribute to systemic *Staphylococcus aureus* infection by competing with calprotectin for nutrient manganese. *Infect Immun* **81**, 3395–3405.
72. Zeinert R, Martinez E, Schmitz J, *et al.* (2018) Structure-function analysis of manganese exporter proteins across bacteria. *J Biol Chem* **293**, 5715–5730.
73. Grunenwald C M, Choby J E, Juttukonda L J, *et al.* (2019) Manganese detoxification by MntE is critical for resistance to oxidative stress and virulence of *Staphylococcus aureus*. *mBio* **10**, e02915-18.
74. Wolfe A L, Felock P J, Hastings J C, *et al.* (1996) The role of manganese in promoting multimerization and assembly of human immunodeficiency virus type 1 integrase as a catalytically active complex on immobilized long terminal repeat substrates. *J Virol* **70**, 1424–1432.
75. Vartanian J P, Sala M, Henry M, *et al.* (1999) Manganese cations increase the mutation rate of human immunodeficiency virus type 1 ex vivo. *J Gen Virol* **80**, 1983–1986.
76. Villani G, Tanguy Le Gac N, Wasungu L, *et al.* (2002) Effect of manganese on *in vitro* replication of damaged DNA catalyzed by the herpes simplex virus type-1 DNA polymerase. *Nucleic Acids Res* **30**, 3323–3332.
77. Wolff N A, Garrick M D, Zhao L, *et al.* (2018) A role for divalent metal transporter (DMT1) in mitochondrial uptake of iron and manganese. *Sci Rep* **8**, 211.
78. Morello M, Canini A, Mattioli P, *et al.* (2008) Sub-cellular localization of manganese in the basal ganglia of normal and manganese-treated rats an electron spectroscopy imaging and electron energy-loss spectroscopy study. *Neurotoxicology***29**, 60–72.
79. Zhang S, Zhou Z, Fu J. (2003) Effect of manganese chloride exposure on liver and brain mitochondria function in rats. *Environ Res* **93**, 149–157.
80. Ijomone O M, Aluko O M, Okoh C O A, *et al.* (2019) Role for calcium signaling in manganese neurotoxicity. *J Trace Elem Med Biol* **56**, 146–155.
81. Werner E, Gokhale A, Ackert M, *et al.* (2022) The mitochondrial RNA granule modulates manganese-dependent cell toxicity. *Mol Biol Cell* **33**, ar108.
82. Popow J, Alleaume A M, Curk T, *et al.* (2015) FASTKD2 is an RNA-binding protein required for mitochondrial RNA processing and translation. *Rna* **21**, 1873–1884.
83. Antonicka H, Shoubridge E A. (2015) Mitochondrial RNA granules are centers for posttranscriptional rna processing and ribosome biogenesis. *Cell Rep* **10**, 920–932.
84. Antonicka H, Lin Z Y, Janer A, *et al.* (2020) A high-density human mitochondrial proximity interaction network. *Cell Metab* **32**, 479–497.
85. Liu Z Q, Liu K, Liu Z F, *et al.* (2021) Manganese-induced alpha-synuclein overexpression aggravates mitochondrial damage by repressing PINK1/Parkin-mediated mitophagy. *Food Chem Toxicol* **152**, 112213.
86. Suski J M, Lebiedzinska M, Bonora M, *et al.* (2012) Relation between mitochondrial membrane potential and ROS formation. *Methods Mol Biol* **810**, 183–205.
87. Cannino G, Ciscato F, Masgras I, *et al.* (2018) Metabolic plasticity of tumor cell mitochondria. *Front Oncol* **8**, 333.
88. Polyak K, Li Y, Zhu H, *et al.* (1998) Somatic mutations of the mitochondrial genome in human colorectal tumours. *Nat Genet* **20**, 291–293.
89. Penta J S, Johnson F M, Wachsman J T, *et al.* (2001) Mitochondrial DNA in human malignancy. *Mutat Res* **488**, 119–133.
90. Hochhauser D. (2000) Relevance of mitochondrial DNA in cancer. *Lancet* **356**, 181–182.
91. HA H C, Thiagalingam A, Nelkin B D, *et al.* (2000) Reactive oxygen species are critical for the growth and differentiation of medullary thyroid carcinoma cells. *Clin Cancer Res* **6**, 3783–3787.
92. Sundaresan M, Yu Z X, Ferrans V J, *et al.* (1996) Regulation of reactive-oxygen-species generation in fibroblasts by Rac1. *Biochem J* **318**, 379–382.
93. Nie H, Chen G, He J, *et al.* (2016) Mitochondrial common deletion is elevated in blood of breast cancer patients mediated by oxidative stress. *Mitochondrion* **26**, 104–112.
94. Kamata H, Hirata H. (1999) Redox regulation of cellular signalling. *Cell Signal* **11**, 1–14.
95. Sundaresan M, Yu Z X, Ferrans V J, *et al.* (1995) Requirement for generation of H2O2 for platelet-derived growth factor signal transduction. *Science* **270**, 296–299.
96. Guyton K Z, Liu Y, Gorospe M, *et al.* (1996) Activation of mitogen-activated protein kinase by H2O2. Role in cell survival following oxidant injury. *J Biol Chem* **271**, 4138–4142.
97. Rao G N. (1996) Hydrogen peroxide induces complex formation of SHC-Grb2-SOS with receptor tyrosine kinase and activates Ras and extracellular signal-regulated protein kinases group of mitogen-activated protein kinases. *Oncogene* **13**, 713–719.
98. Ekoue D N, He C, Diamond A M, *et al.* (2017) Manganese superoxide dismutase and glutathione peroxidase-1 contribute to the rise and fall of mitochondrial reactive oxygen species which drive oncogenesis. *Biochim Biophys Acta Bioenerg* **1858**, 628–632.
99. Zhang Y, Zhang H M, Shi Y, *et al.* (2010) Loss of manganese superoxide dismutase leads to abnormal growth and signal transduction in mouse embryonic fibroblasts. *Free Radic Biol Med* **49**, 1255–1262.
100. Wang S, Ma M, Liang Q, *et al.* (2022) Single-atom manganese anchored on carbon dots for promoting mitochondrial targeting and photodynamic effect in cancer treatment. *ACS Applied Nano Materials* **5**, 6679–6690.
101. Lv M, Chen M, Zhang R, *et al.* (2020) Manganese is critical for antitumor immune responses via cGAS-STING and improves the efficacy of clinical immunotherapy. *Cell Res* **30**, 966–979.
102. Yang M, Li J, Gu P, *et al.* (2021) The application of nanoparticles in cancer immunotherapy: targeting tumor microenvironment. *Bioact Mater* **6**, 1973–1987.
103. Han Y, Liu D, Li L. (2020) PD-1/PD-L1 pathway: current researches in cancer. *Am J Cancer Res* **10**, 727–742.
104. Salmaninejad A, Valilou S F, Shabgah A G, *et al.* (2019) PD-1/PD-L1 pathway: basic biology and role in cancer immunotherapy. *J Cell Physiol* **234**, 16824–16837.
105. Shen X, Zhang L, Li J, *et al.* (2019) Recent findings in the regulation of programmed death Ligand 1 expression. *Front Immunol* **10**, 1337.
106. Buchbinder E I, Desai A. (2016) CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am J Clin Oncol***39**, 98–106.
107. Herbst R S, Giaccone G, De Marinis F, *et al.* (2020) Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med* **383**, 1328–1339.
108. Motzer R J, Penkov K, Haanen J, *et al.* (2019) Avelumab plus Axitinib versus Sunitinib for advanced Renal-Cell Carcinoma. *N Engl J Med* **380**, 1103–1115.
109. Salik B, Smyth M J, Nakamura K. (2020) Targeting immune checkpoints in hematological malignancies. *J Hematol Oncol* **13**, 111.
110. Chen R, Manochakian R, James L, *et al.* (2020) Emerging therapeutic agents for advanced non-small cell lung cancer. *J Hematol Oncol* **13**, 58.
111. Zhu X D, Sun H C. (2019) Emerging agents and regimens for hepatocellular carcinoma. *J Hematol Oncol* **12**, 110.

https://doi.org/10.1017/S0954422425100139 Published online by Cambridge University Press

112. Robert C, Schachter J, Long G V, *et al.* (2015) Pembrolizumab versus Ipilimumab in advanced Melanoma. *N Engl J Med* **372**, 2521–2532.
113. Tang B, Yan X, Sheng X, *et al.* (2019) Safety and clinical activity with an anti-PD-1 antibody JS001 in advanced melanoma or urologic cancer patients. *J Hematol Oncol* **12**, 7.
114. Qiu Z, Chen Z, Zhang C, *et al.* (2019) Achievements and futures of immune checkpoint inhibitors in non-small cell lung cancer. *Exp Hematol Oncol* **8**, 19.
115. Yi M, Jiao D, Xu H, *et al.* (2018) Biomarkers for predicting efficacy of PD-1/PD-L1 inhibitors. *Mol Cancer* **17**, 129.
116. Niu M, Yi M, Li N, *et al.* (2021) Predictive biomarkers of anti-PD-1/PD-L1 therapy in NSCLC [J]. *Exp Hematol Oncol* **10**, 18.
117. Ghaffari A, Peterson N, Khalaj K, *et al.* (2018) STING agonist therapy in combination with PD-1 immune checkpoint blockade enhances response to carboplatin chemotherapy in high-grade serous ovarian cancer. *Br J Cancer* **119**, 440–449.
118. Pan B S, Perera S A, Piesvaux J A, *et al.* (2020) An orally available non-nucleotide STING agonist with antitumor activity. *Science* **369**, eaba6098.
119. Li C, Li T, Niu K, *et al.* (2022) Mild phototherapy mediated by manganese dioxide-loaded mesoporous polydopamine enhances immunotherapy against colorectal cancer. *Biomater Sci* **10**, 3647–3656.
120. Cheng L, Zhang P, Liu Y, *et al.* (2023) Multifunctional hybrid exosomes enhanced cancer chemo-immunotherapy by activating the STING pathway. *Biomaterials* **301**, 122259.
121. Marcus A, Mao A J, Lensink-Vasan M, *et al.* (2018) Tumor-derived cGAMP triggers a STING-mediated interferon response in non-tumor cells to activate the NK cell response. *Immunity* **49**, 754–763.
122. Wang X, Liu Y, Xue C, *et al.* (2022) A protein-based cGAS-STING nanoagonist enhances T cell-mediated anti-tumor immune responses. *Nat Commun* **13**, 5685.
123. Hayes C, Donohoe C L, Davern M, *et al.* (2021) The oncogenic and clinical implications of lactate induced immunosuppression in the tumour microenvironment. *Cancer Lett* **500**, 75–86.
124. Ippolito L, Morandi A, Giannoni E, *et al.* (2019) Lactate: a metabolic driver in the tumour landscape. *Trends Biochem Sci* **44**, 153–166.
125. Lee E S, Gao Z, Bae Y H. (2008) Recent progress in tumor pH targeting nanotechnology. *J Control Release* **132**, 164–170.
126. Zhang J, Xu M, Mu Y, *et al.* (2019) Reasonably retard O(2) consumption through a photoactivity conversion nanocomposite for oxygenated photodynamic therapy. *Biomaterials* **218**, 119312.
127. Luo S, Yang Y, Chen L, *et al.* (2024) Outer membrane vesicle-wrapped manganese nanoreactor for augmenting cancer metalloimmunotherapy through hypoxia attenuation and immune stimulation. *Acta Biomater* **181**, 402–414.
128. Ning Z, Yang L, Yan X, *et al.* (2022) Effect and mechanism of the Lenvatinib@H-MnO(2)-FA drug delivery system in targeting intrahepatic cholangiocarcinoma. *Curr Pharm Des* **28**, 743–750.
129. Zhou Z H, Liang S Y, Zhao T C, *et al.* (2021) Overcoming chemotherapy resistance using pH-sensitive hollow MnO(2) nanoshells that target the hypoxic tumor microenvironment of metastasized oral squamous cell carcinoma. *J Nanobiotechnology* **19**, 157.
130. Zheng X, Zhang J, Wang J, *et al.* (2015) Polydopamine coatings in confined nanopore space: toward improved retention and release of hydrophilic cargo. *J Phys Chem C* **119**, 24512–24521.
131. Liu J, Guo C, Li C, *et al.* (2023) Redox/pH-responsive hollow manganese dioxide nanoparticles for thyroid cancer treatment. *Front Chem* **11**, 1249472.
132. Wang B, Wang T, Jiang T, *et al.* (2024) Circulating immunotherapy strategy based on pyroptosis and STING pathway: Mn-loaded paclitaxel prodrug nanoplatform against tumor progression and metastasis. *Biomaterials* **306**, 122472.
133. Catania G, Rodella G, Vanvarenberg K, *et al.* (2023) Combination of hyaluronic acid conjugates with immunogenic cell death inducer and CpG for glioblastoma local chemo-immunotherapy elicits an immune response and induces long-term survival. *Biomaterials* **294**, 122006.
134. Liang X, Wang D, Zhao Y, *et al.* (2024) Tumor microenvironment-responsive manganese-based nano-modulator activate the cGAS-STING pathway to enhance innate immune system response. *J Nanobiotechnology* **22**, 535.
135. Luo G, Li X, Lin J, *et al.* (2023) Multifunctional calcium-manganese nanomodulator provides antitumor treatment and improved immunotherapy via reprogramming of the tumor microenvironment. *ACS Nano* **17**, 15449–15465.
136. Zhu H, Xu C, Geng Y, *et al.* (2025) Endoplasmic reticulum-targeted polymer-manganese nanocomplexes for tumor immunotherapy. *ACS Nano* **19**, 4959–4972.
137. Tuakashikila Y M, Mata H M, Kabamba M M, *et al.* (2023) Reference intervals for Cd, Hg, Mn and Pb in the general children population (3-14 years) of Kinshasa, Democratic Republic of Congo (DRC) between June 2019 and June 2020. *Arch Public Health* **81**, 40.
138. Williams M, Todd G D, Roney N, *et al.* (2012) Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles [M]. *Toxicological Profile for Manganese*. Atlanta (GA); Agency for Toxic Substances and Disease Registry (US).
139. O'neal S L, Zheng W. (2015) Manganese toxicity upon overexposure: a decade in review. *Curr Environ Health Rep* **2**, 315–328.
140. Rahil-Khazen R, Bolann B J, Myking A, *et al.* (2002) Multi-element analysis of trace element levels in human autopsy tissues by using inductively coupled atomic emission spectrometry technique (ICP-AES). *J Trace Elem Med Biol* **16**, 15–25.
141. Liu Y, Byrne P, Wang H, *et al.* (2014) A compact DD neutron generator-based NAA system to quantify manganese (Mn) in bone *in vivo*. *Physiol Meas***35**, 1899–1911.
142. Morton J, Tan E, Leese E, *et al.* (2014) Determination of 61 elements in urine samples collected from a non-occupationally exposed UK adult population. *Toxicol Lett* **231**, 179–193.
143. Luk E E, Culotta V C. (2001) Manganese superoxide dismutase in *Saccharomyces cerevisiae* acquires its metal co-factor through a pathway involving the Nramp metal transporter, Smf2p. *J Biol Chem* **276**, 47556–47562.
144. Radin J N, Zhu J, Brazel E B, *et al.* (2019) Synergy between nutritional immunity and independent host defenses contributes to the importance of the MntABC manganese transporter during *Staphylococcus aureus* infection. *Infect Immun* **87**, e00642-18.
145. Handke L D, Gribenko A V, Timofeyeva Y, *et al.* (2018) MntC-dependent manganese transport is essential for *Staphylococcus aureus* oxidative stress resistance and virulence. *mSphere* **3**, e00336-18.
146. Ouyang A, Gasner K M, Neville S L, *et al.* (2022) MntP and YiiP contribute to manganese efflux in *Salmonella enterica Serovar Typhimurium* under conditions of manganese overload and nitrosative stress. *Microbiol Spectr* **10**, e0131621.
147. Veyrier F J, Boneca I G, Cellier M F, *et al.* (2011) A novel metal transporter mediating manganese export (MntX) regulates the Mn to Fe intracellular ratio and *Neisseria* meningitidis virulence. *PLoS Pathog* **7**, e1002261.

https://doi.org/10.1017/S0954422425100139 Published online by Cambridge University Press