*Journal of Science and Technology*
*ISSN: 2456-5660 Volume 8, Issue 02 (Feb -2023)*
*www.jst.org.in* *DOI:https://doi.org/10.46243/jst.2023.v8.i02.pp26- 63*

# From Zine Balance to Disense Progression: Decoding the Puzzle of Neurodegeneration

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***To Cite this Article***
N. Danamurthy, T. Sujatha, K. Ravindranadh, M. Sushma, "**From Zine Balance to Disense Progression: Decoding the Puzzle of Neurodegeneration**" *Journal of Science and Technology, Vol. 08, Issue 02- Feb 2023, pp26-63*

***Article Info***
*Received: 29-01-2023 Revised: 05-02-2023 Accepted: 15-02-2023 Published: 26-02-2023*

ABSTRACT

A vital trace element in the human body, zinc is involved in many physiological functions, including DNA repair, neurotransmission, oxidative stress, and protein synthesis. Intracellular zinc is exported by members of the zinc transporters (ZnTs) family, while extracellular zinc is imported by Zrt-and-Irt-like proteins (ZIPs). The preservation of cellular zinc homeostasis depends on these mechanisms. Neurodegenerative disorders have been associated with imbalances in zinc metabolism. Through processes like ferroptosis, protein phase separation, oxidative stress, neuroinflammation, and cell death control, zinc level disruptions may affect the survival and function of neurons and consequently contribute to the development of neurodegenerative disorders. Our knowledge of the pathophysiology of these illnesses may thus be improved by doing a thorough analysis of the regulatory network of zinc and looking into the connection between neurodegenerative disorders and zinc dysmetabolism. Furthermore, it could provide new perspectives and methods for treating neurodegenerative illnesses.

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## 1. Introduction

Zinci is the most common trace element in the brain and has a role in maintaining protein homeostasis, neuronal growth, neurotransmission, and DNA repair. It is noteworthy that over 2800 human proteins, or 10% of the human proteome, are zinc-binding proteins [1]. Zinc shortage and zinc excess may both cause cell malfunction, which can exacerbate immunological dysregulation [2] and neurodegeneration [3]. The zinc transporters (ZnTs) family members or Zrt-and-Irt-like proteins (ZIPs) are primarily responsible for cellular zinc homeostasis. By importing external zinc or exporting internal zinc, these proteins, which are mostly expressed in the plasma membrane, control the amount of zinc in cells [4]. Thus, focusing on ZnTs or ZIPs may be a useful tactic to treat illnesses linked to zinc dysmetabolism. Patients with neurodegenerative diseases have abnormally high zinc levels in their brains. For example, individuals with Alzheimer's disease (AD) and those with Parkinson's disease (PD) have considerably higher zinc levels in their brain tissue [5,6]. Zincoverload promotes the production of β-amyloid protein (Aβ) and the accumulation of Aβ and α-synuclein [7–9], indicating that zinc reduction may be beneficial during neurodegeneration. In this review, we systematically summarized the zinc regulatory network and emphasized the role of zinc dysmetabolism in the development of neurodegenerative diseases, such as Huntington's disease (HD), AD, PD, ALS, Parkinson's disease, epilepsy, and stroke. Additionally, by controlling the amount of zinc in the brain, a number of zinc chelators have been discovered or created to slow the

course of neurodegenerative illnesses. In an attempt to identify a possible treatment for neurodegenerative illnesses, we compiled the roles of zinc chelators in these conditions.

## 2. Theregulatorynetworkofzinc:ZNTs,ZIPsandotherproteins

Thehomeostasisandintracellulardistributionofzincaretightly regulatedtoensurethebalanceofintracellularzincconcentration. The stable state of Zn2+within cells is predominantly maintained by the coordinated activities of zinc-regulated transporters ZIPs and zinc trans- porters ZnTs. ZIPs are responsible for transporting Zn2+from the extracellular environment or intracellular vesicles into the cytoplasm [10],whileZnTstransportZn2+fromthecytoplasmtotheextracellular environment or intracellular vesicles[11]. This complementary inter- action guarantees the equilibrium and stability of intracellular Zn2+concen- tration [12]. ZnTfamilyproteins

ZnTs belong to a family of transmembrane proteins thatregulate intracellular Zn2+homeostasis primarily by transferring accumulated Zn2+fromthecytoplasmtotheextracellularspace[13]. Thereareten subtypes of ZnTs, called ZnT1 to ZnT10, which are involved in regu- lating Zn2+transport in diverse tissues and cell types (Table 1). ZnT1 ZnT1, one of the first recognized subtypes among ZnTfamily proteins,iswidelypresentinvariouscells,primarilylocalizedtothecell membraneandendoplasmicreticulum(ER). Itregulatesthebalanceand metabolismofintracellularandextracellularZn2+byextrudingZn2+ outofthecell[14,15]. expressionandactivityofZnT1areinflu- enced by transcription factors, post-translational modifications,and protein interaction. The promoter region of the ZnT1 gene has many transcription factor binding sites, including cAMP-response element binding protein (CREB)[16], metal regulatory transcription factor1(MTF-1)[17],andspecificityprotein1(Sp1)[18]. Thebinding of these factors to the ZnT1 promoter region may enhance ZnT1 tran- scription and raise its expression levels. Additionally, the nuclear factor-κB(NF-κB)andhypoxia-induciblefactor-1(HIF-1)signaling pathways may impact the transcription and expression of theZnT1 gene[19,20]. The phosphatidylinositol 3 kinase/protein Kinase B (PI3K/Akt) signaling pathway may change the phosphorylation and sta- bility of ZnT1 protein, consequently regulating its transport activity and function[21]. Furthermore, the ubiquitination of ZnT1 may also degrade it [22]. Due to its crucial involvement in regulating cellular zinc homeostasis, the ZnT1playsasignificantroleinvariousdiseaseprocess Maternal zinc deficiency may decrease ZnT1 expression in neonatal rats' brains [23]. Furthermore, the onset and progression of metabolic disorders are closely linked to aberrant ZnT1 protein expression. ZnT1 has a strong correlation with clinical indicators of changes in glucose metabolism and is elevated in obesity [24]. The development and spread of tumors are also impacted by aberrant ZnT1 protein expression. ZnT1 increases the invasion and proliferation of BIU87 bladder cancer cells and is overexpressed in bladder cancer [25]. Furthermore, individuals with hepatocellular carcinoma have a much greater expression level of ZnT1 protein in their livers, three times higher than those of patients with liver cirrhosis. This might potentially aid in the growth of liver cancer and contribute to a bad prognosis [26]. Using the TCGA database to analyze the expression levels of ZnT1 in various tumor types, a research found that high ZnT1 expression was linked to a poor prognosis in esophageal cancer, pancreatic cancer, colonrecta adenocarcinoma, gastric adenocarcinoma, and thymic carcinoma [27]. Furthermore, the emergence and progression of neurodegenerative illnesses are intimately linked to mutations and aberrant expression of the ZnT1 gene. When comparing postmortem brain slices of AD patients to normal corticaltissue, researchers found greater levels of ZnT1, which rose as the illness progressed [28]. In contrast, ZnT1 levels were markedly elevated in the periphery. blood and brains of people with epilepsy [29]. These results highlight the importance of ZnT1asa.

**Table 1**
Locations and functions of ZnT family proteins.

| Subtype | Tissues | Cell types in brain | Localizations | Functions | Modulating factors | References |
|---|---|---|---|---|---|---|
| ZnT1 | low tissue specificity | astrocytes, microglia | cell membrane, intracellular vesicles | transports $Zn^{2+}$ out of cell; transports $Zn^{2+}$ into intracellular vesicles | $Zn^{2+}$, CREB, MTF-1, Sp1, PI3K/Akt, NF-κB, HIF-1 | [14–22] |
| ZnT2 | pancreas, kidneys | excitatory neurons, inhibitory neurons | intracellular vesicles, zymogen granules, endosomes, mitochondria, cell membrane | transports $Zn^{2+}$ into endosomes, zymogen granules, mitochondria and secretory vesicles; transports $Zn^{2+}$ out of cells | $Zn^{2+}$, MTF-1, Sp1, TNFα | [30–37] |
| ZnT3 | cerebral cortex, testis, epididymis | excitatory neurons, inhibitory neurons | presynaptic membrane | transports $Zn^{2+}$ from cytoplasm into synaptic vesicles | $Zn^{2+}$, neurotrophic factor, oxidants, toxins | [46–51, 650] |
| ZnT4 | prostate, basal neurons, intestine | low cell specificity | endosome membrane, late endosomal membrane, lysosomal membrane | transports $Zn^{2+}$ from cytoplasm into endosomes or lysosomes | $Zn^{2+}$, MTF-1, oxidants | [16,56–58] |
| ZnT5 | liver, pancreas, kidney, islet B cells | low cell specificity | ER, Golgi apparatus, intracellular vesicles, cell membrane | transports $Zn^{2+}$ from cytoplasm into organelles; regulates activation and folding of alkaline phosphatase | $Zn^{2+}$, MTF-1, XBP1, PI3K/Akt, NF-κB | [63–74,81, 82] |
| ZnT6 | brain, islet B cells, colon, eye, lung | excitatory neurons, inhibitory neurons, oligodendrocytes, oligodendrocyte precursor cells | Golgi apparatus | transports $Zn^{2+}$ from cytosol into the organelle; regulates the activation and folding of alkaline phosphatase | $Zn^{2+}$, MTF-1, Nrf2 | [68–70, 79–84] |
| ZnT7 | duodenum, small intestine, colon, placenta | excitatory neurons, inhibitory neurons, oligodendrocytes, oligodendrocyte precursor cells, microglia | Golgi apparatus | transports $Zn^{2+}$ from cell membrane into the Golgi apparatus; regulates alkaline phosphatase activation and folding | $Zn^{2+}$, MTF-1 | [66,68, 87–89,651] |
| ZnT8 | pancreas | low cell specificity, low expression level | cell membrane, intracellular vesicles | transports $Zn^{2+}$ from cytoplasm into secretory vesicles | $Zn^{2+}$, MafA, NeuroD1, Nkx6.1, PDX-1, ERK/HIF-1α | [94–101, 652] |
| ZnT9 | low tissue specificity | excitatory neurons, inhibitory neurons, oligodendrocytes, oligodendrocyte precursor cells | mitochondria, ER, nucleus | transports $Zn^{2+}$ from mitochondria to cytosol | $Zn^{2+}$, ATF2, PARK2, ATF9 | [113–118] |
| ZnT10 | intestine, liver, brain | neurons, astrocytes | cell membrane, Golgi apparatus, endosome | transports $Mn^{2+}$ and $Zn^{2+}$ out of cell | $Zn^{2+}$, chromium, $Mn^{2+}$; angiotensin 2; β-naphthoflavone; vitamin D3 | [79, 121–129] |

possible target for treatment in the treatment of a number of pathological diseases. ZnT2 Primarily expressed in the kidney and pancreas [30, 31], the ZnT2 protein is found in a variety of structures, including the mitochondrial membrane [34], endosomal membrane [32], zymogen granule membrane [33], and cell membrane. Numerous molecular processes may control the ZnT2 protein's expression and function. Transcription factors including MTF-1 and Sp1 stimulate ZnT2 transcription and expression by attaching to the promoter region of the ZnT2 gene [30, 35]. The ZnT2 protein's expression and function are also influenced by post-translational changes. The ZnT2 protein has been phosphorylated. shown to impact its location from late endosomes to lysosomes, which in turn impacts lysosomal biogenesis and Zn2+ levels in lysosomes [36,37]. The incidence and prognosis of a number of malignancies are strongly correlated with the ZnT2 protein's expression level. Research has shown a notable rise in the ZnT2 protein's expression level in the breast. cancer [38]. Nevertheless, prolactin receptors may decrease the invasiveness of MDA-MB-453 breast cancer cells by causing intracellular redistribution of Zn2+ via ZnT2 [39]. ZnT2 protein mutations may result in zinc deficiency by impairing zinc transport and absorption. Lower levels of Zn2+ in breastmilk are seen in female carriers of ZnT2 mutations, which may result in severe zinc insufficiency in neonates [40]. In neonates, a heterozygous G87R ZnT2 mutation results in decreased intracellular Zn2+transport, which eventually produces a temporary zinc shortage [41]. Additionally, aberrant expression and ZnT2 protein malfunctioning in the neural system are intimately linked to the onset and progression of neurological disorders. According to a previous research, the autophagy/lysosome pathway was promptly triggered by recurrent epileptic convulsions, and the cerebral cortex showed elevated ZnT1 and ZnT2 expressions [42]. This suggests that the intracellular zinc level may play a role in the control of autophagy. By triggering the connection between V-type proton ATPase catalytic subunit A (ATP6V1A) and signal transducer and activator of transcription 3 (STAT3), zinc has been shown to enhance autophagic flow [43]. By promoting transcription factor EB (TFEB)-dependent cathepsin B and cathepsin D expressions and V-ATPase assembly, zinc also improves autophagic flux and lysosomal function [44]. Notably, zinc shortage also increases adenosine 5'-monophosphate-activated protein

kinase (AMPK) activation and LC3II expression in HT-22 cells, which induce autophagy [45]. According to these research, autophagic activation may be encouraged by zinc imbalance and lead to neurodegeneration.

ZnT3

The ZnT3 protein is mostly expressed in the nervous system and is involved in processes like synaptic plasticity, signal transmission, and neuronal development [46–48]. Because of its N-terminal neuron-specific signal sequence, the ZnT3 protein is primarily localized to the presynaptic membrane in the nervous system [48]. Numerous molecular processes control the ZnT3 protein's production and function, and neurotrophic factors may inhibit the ZnT3 protein's expression, which raises the amount of Zn2+ in neurons and affects synaptic plasticity and neural development [49]. The ZnT3 protein's activity is also impacted by external variables like oxidants and toxins, which cause changes in intracellular Zn2+ levels and subsequently impact neuronal function [50,51]. More research is necessary to have a better understanding of knowledge of the ZnT3 gulatory network, which is presently little understood. Significant cognitive deficits seen in children with ZnT3 deletion at or above 6 months of age [52] provide evidence that abnormal expression of the ZnT3 protein has been connected to cognitive impairments. Recent research have shown a tight relationship between the ZnT3 protein and the development of neurological illnesses. Additionally, research has shown that ZnT3 knockout mice perform abnormally in trace fear training and fear extinction, suggesting that ZnT3 is involved in associative fear memory and extinction but not intrinsic fear [53]. According to these research findings, ZnT3 is essential for controlling cognitive function, and abnormal ZnT3 protein expression is also strongly associated with the development and progression of mental illnesses. reported a notable drop in the concentration of zinc in the serum. Depression is associated with a tendency of lower ZnT3 protein expression levels [54]. Additionally, ZnT3 mutant mice have shown greater vulnerability to seizures brought on by kainic acid [55].ZnT4

The ZnT4 protein, which is mostly found in the late endosomal and lysosomal membranes and aids in the transfer of cytoplasmic Zn2+, is significantly expressed in the prostate, basal neurons, and small intestine. lysosomes or endosomes [56]. Transcription factors like ZnT4 protein expression is regulated by CREB and MTF-1, which in turn affect intracellular Zn2+ levels [16,57]. Moreover, oxidative stress may modify intracellular Zn2+ levels by influencing the ZnT4 protein's expression and function [58]. ZnT4 protein dysregulation is directly linked to the onset and progression of progression of many illnesses. ZnT4 expression has been shown to be downregulated by more than three times in whole blood samples from patients with systemic inflammatory response syndrome [59]. Furthermore, type II diabetes patients' peripheral blood mononuclear cells have been shown to express less ZnT4 protein, which may be a factor in the disease's development [60]. Furthermore, a poor prognosis is linked to the ZnT4 protein, which is significantly expressed in prostate cancer [61]. On the other hand, in a mouse model of acute inflammation, ZnT4 expression was decreased, indicating a connection between immune system disorders and aberrant ZnT4 expression [62].ZnT5 The liver, pancreas, kidney, and pancreatic isletβ cells are the main organs that express the ZnT5 protein [63,64]. It is found in the plasma membrane [67], cellular vesicles [66], the ER [65], and the golgi apparatus [63]. ZnT5 mediates the distribution of Zn2+ throughout cellular organelles by forming a Zn2+counter-transport heterodimer with ZnT6 [68]. ZnT5 also stimulates early Zn2+ secretion and controls the activation and folding of of alkaline phosphatase and other enzymes [69, 70]. Through regulating intracellular Zn2+ levels, ZnT5 contributes to a number of physiological functions, such as immunological response [71], insulin storage [63], and cell growth [64]. Transcription factors MTF-1 and X-boxbinding protein 1 (XBP1) directly control the ZnT5 protein's expression level, which impacts intracellular Zn2+ levels [69,71]. Additionally, the activation The overexpression of the PI3K/Akt signaling pathway is linked to of ZnT5[72], whereas ZnT5-mediated delayed hypersensitivity reactions are mediated by the NF-κB signaling pathway[73]. Additionally, factors like metalions, such as Zn2+, and oxidants can affect both the ZnT5 protein's expression and activity [71,74]. In individuals with type II diabetes, aberrant ZnT5 expression was linked to the generation of interleukin 6 (IL-6) according to a previous research [75]. ZnT5 is also significantly expressed in high-grade gliomas [76] and colon cancer [77], although its expression is decreased in pancreatic cancer [78]. The important significance of the ZnT5 protein in the development of osteoblasts and cardiac conduction system cells has also been shown by research. Male ZnT5-deficient mice show particular cardiogenic abrupt death and have reduced bone mass [64].ZnT6 ZnT6isprimarilyfoundinthebrain,particularlyinthecerebellum, hippocampus, parahippocampal gyrus, temporal gyrus, andcingulate gyrus,anditisalsoexpressedinBcells,colon,eyes,andlungs[79,80]. ZnT6localizestotheGolgiapparatus[81],andformsaheterodimer with ZnT5, facilitating the entry of Zn2+into cellularcompartments alongthesecretorypathway[68,82].ZnT6isinvolvedinregulatingthe activationandfoldingofenzymessuchasalkalinephosphatase[69,70].

ZnT6 expression is increased upon activation of the nuclearfactor erythroid2-related factor2/antioxidant response elements (Nrf2/ARE) signaling pathway [83]. In addition, the—825/—839bplocuson the ZnT6 MTF-1 binding sites were functional, and the promoter had a metal-responsive component (MRE). By encouraging MTF-1 to bind to the MRE, a high quantity of Zn2+ (80 μM) may increase ZnT6 expression [84]. ZnT6 levels in plasma have been shown to be significantly correlated with the severity score of systemic inflammatory response syndrome in a prior research [59]. A worse prognosis has been linked to increased ZnT6 expression in colorectal and pancreatic cancers [85]. Knockdown of ZnT6 decreases cell growth in Capan-1 cells by suppressing the extracellular regulated protein kinases 1/2 (ERK1/2), mitogen-activated protein kinase (MAPK), and NF-kB signaling pathways [86]. As will be addressed later, ZnT6 was shown to be upregulated in colorectal cancer [85], and its abnormal expression is also

intimately linked to the onset and progression of neurological diseases.

ZnT7

ZnT7 protein is extensively expressed in diverse tissues, withhigh expression reported in the duodenum, small intestine, colon, and placenta,primarilylocalizedtotheGolgiapparatus[66].ZnT7mediates he entrance of Zn2+from the cytoplasm into the Golgi apparatus via the secretorypathway[66,68], andby promotingZn2+balance inthe early secretory route, which controls the folding and activation of enzymes such alkaline phosphatase [66]. Since MTF-1 is often linked to elevated ZnT7 expression, it is possible that MTF-1 plays a role in controlling ZnT7 expression [87]. ZnT7 may prevent oxidative stress-induced apoptosis in MC3T1-E3 cells by lowering the aggregation of intracellular free zinc and PI3K/Akt and ERK signaling activation routes [88]. In skeletal muscle cells, ZnT7 overexpression may also encourage the phosphorylation of Akt and Irs2 [89]. Mice that have the ZnT7 gene deleted exhibit stunted development, decreased adiposity, and decreased dietary zinc absorption, suggesting that ZnT7 plays a role in controlling body fat and dietary zinc absorption [90]. Furthermore, food-induced insulin resistance and glucose intolerance are more common in male ZnT7 mutant mice given a high-fat diet [89]. These results highlight the complex function of ZnT7 in metabolic balance, body fat management, and dietary zinc regulation. While ZnT7 expression inhibition may enhance tumor growth and invasion in fruit flies via the c-Jun N-terminal kinase (JNK) signaling pathway [92], ZnT7 is abundantly expressed in colorectal and pancreatic cancer [77,78], and its loss may accelerate early prostate tumor development [91]. Furthermore, scientists have shown bone marrow failure, testicular hypoplasia, and growth retardation in male twins with ZnT7 mutations, underscoring the critical function of ZnT7 in human development [93].

ZnT8

ZnT8 is located on the cell membrane and cytoplasmic vesicle membranes and is highly expressed in the pancreatic beta cells that produce insulin. It is in charge of moving free zinc from the cytoplasm into the secretory vesicles of the beta cells, which helps them produce and secrete insulin [94–96]. Zn2+ is transported by the ZnT8 protein's homodimerin-dependent subunit. in a pH-dependent way. At lower pH levels within the organelles, the two histidine residues in the zinc-binding site of the ZnT8 protein become protonated, causing the transport of Zn2+ into the musculoaponeurotic fibrosarcoma oncogene family A [97]. Two transcription factors that are highly expressed in pancreatic beta cells, MafA and Neurogenic Differentiation Factor 1 (NeuroD1), directly interact with the ZnT8 gene's promoter region to increase ZnT8 expression, which raises the levels of Zn2+ inside the beta cell vesicles and encourages the production and release of insulin [98,99]. Furthermore, by either directly or indirectly controlling the expression of the ZnT8 gene, NK6 homeobox 1 (Nkx6.1) and pancreatic and duodenal homeobox 1 (PDX-1) may similarly influence insulin production [100,101]. The development of diabetes is linked to zinc dysmetabolism. Animals with zinc deficiency were shown to have reduced insulin granules in their pancreatic beta cells and impaired glucose-stimulated insulin production [102]. Additionally, compared to women who take adequate amounts of zinc, those who consume low amounts of zinc may have a 17% higher risk of developing diabetes [103]. Another study found a connection between ZnT8 dysfunction and lower plasma zinc concentrations that control glucose tolerance and diabetes [104], and ZnT8 mutations were strongly linked to an increased risk of type II diabetes [105], indicating that ZnT8-mediated zinc transporting is essential for the development of diabetes. In fact, mice with ZnT8 deletion showed slightly reduced glucose tolerance [106], but mice with human ZnT8 overexpression showed increased glucose tolerance [107]. These findings indicated that ZnT8 may be a promising target for diabetes treatment. Apart from diabetes, ZnT8 has been shown to block the NF-κB pathway in diabetic kidney disease and stimulate the production of tumor necrosis factorαinduced protein 3 (TNFAIP3), which prevents apoptosis in renal tubular epithelial cells [108]. In a diabetic nephropathy mouse model, ZnT8 also inhibits the transforming growth factor-beta/Smads (TGF-β/Smads) signaling pathway, which reduces renal tubulointerstitial fibrosis and epithelial-mesenchymal transition [109]. ZnT8 protein levels were shown to be correlated with thyroid peroxidase and glutamic acid decarboxylase in non-obese persons with autoimmune thyroiditis linked to diabetes, suggesting a possible role of ZnT8 in raising the risk of autoimmune thyroiditis [110]. ZnT8 may be a new thyroid autoantigen, since it has been demonstrated to be strongly expressed in immune-related thyroid illnesses relative to non-immune-related thyroid diseases [111]. Furthermore, research shows that single nucleotide variations in the ZnT8 gene are linked to low levels of low-density lipoprotein cholesterol and can lower the risk of cardiovascular disease in postmenopausal women [112].ZnT9 Widely expressed in many different tissues, ZnT9 is mainly found in the nucleus, ER membrane, and mitochondrial membrane [113–115]. It helps preserve mitochondrial structural integrity and facilitates the outflow of Zn2+ from mitochondria [116]. At the moment, nothing is known about how ZnT9 protein expression and activity. Activating transcription factor 2 (ATF2), PARK2, and activating transcription factor 9 (ATF9) have been identified as putative transcription factors involved in controlling the expression of the ZnT9 protein by examination of transcription factor-centered regulatory networks [117,118].

According to recent research, the development and progression of a number of diseases are linked to aberrant ZnT9 protein expression and dysfunction. In a zinc-deficient zebrafish model, reduced ZnT9 expression has a major impact on embryonic development.

Similar to this, in a C.elegans model, ZnT9 knockout results in elevated mitochondrial Zn2+ levels, mitochondrial structural damage,

reduced longevity and poor animal development [120]. The expression of ZnT9 in the spinous layer of postmenopausal women was significantly lower when comparing the levels of zinc transport proteins in premenopausal and postmenopausal human vaginal

tissue [113]. Additionally, transcriptionomic analysis revealed changes in ZnT9 expression in the brain tissues of patients with AD and PD [117,118].ZnT10 The ZnT10 protein is expressed specifically in the liver, small intestine, and brain neurons [79,121]. It is found in the endosomal membrane, golgi apparatus membrane, and cell membrane [122, 123], which mediates the intracellular outflow of Mn2+ and Zn2+, therefore controlling mitochondrial activity and cellular oxidative stress [123,124]. The expression and function of the ZnT10 protein are controlled by many variables. The expression of ZnT10 is downregulated by Zn2+, angiotensin2, β-naphthoflavone, and chromium [122,125–127], while Mn2+ increases the manifestation of it [121]. There are possible vitaminD responsive elements (VDREs) in the 5'-flanking region of the ZnT10 promoter, vitamin D3 might enhance ZnT10 protein in a vitamin D re- ceptor (VDR)-dependent way [128]. Additionally, either HIF-1 or HIF-2 is essential for starting the transcription of ZnT10 by attaching to The hypoxic elements in its gene promoter. A high concentration of Mn2+ potentially provide a protective response to Mn2+ poisoning by activating HIF1 and HIF2 to upregulate ZnT10 [129]. DuetoitscrucialroleinMn2+transport,mutationsorknockoutof the ZnT10 protein might cause to hypermanganesemia accompaniedby muscular tone disorders[130]. ZnT10 expression is downregulated in high-grade glioma tissues, which might impact the tumor's negative prognosis [131]. On the other hand, ZnT10 overexpression can reduce the expression of NADPH oxidase 1 (NOX1), which inhibits NF-κB activation and the production of reactive oxygen species (ROS) and reduces smooth muscle cell aging [50]. ZnT10 is found to colocalize with transferrin receptor and Rab5-positive endosomes and form cova-lent hetero-and oligomers with ZnT2, ZnT3, and ZnT4. The interaction between ZnT10 and ZnT3 blocks ZnT10 from entering synaptic vesic vesic vesic vesic vesic vesic vesic vesic vesic vesic vesi-cles, but the ZnT3/ZnT10 heterocomplex regulates the signaling via raising MEK and ERK1/2 phosphorylation of the epidermal growth factor receptor (EGFR) [123].

ZIP family proteins

The zinc transporters Zrt1p and Irt1p in brewer's yeast have structural similarities with the ZIP family of proteins, a class of transmembrane proteins having eight transmembrane domains [12]. There are now 14 distinct ZIP family protein types (ZIP1 through ZIP14) known to exist (Table 2). These proteins are found in many cellular components and membranes, and they are in charge of the Intracellular Zn2+ sorption, transport, and distribution [132].ZIP Family proteins are essential regulators of cellular functions such immunological response, growth, division, and death [133,134]. The relevance of ZIP family proteins in conditions like diabetes [133] and cancer [135] has drawn a lot of interest recently; thus, a thorough examination of the roles of ZIP family proteins will assist uncover the Zn2+ regulation in cells and its function in illnesses. ZIP Code 1 Without notable tissue specialization, ZIP1 is expressed uniformly in a variety of tissues [136]. It mostly localizes to the ER and cell membranes, allowing Zn2+ to be transported from the extracellular space through its transmembrane into the intracellular environment structure[137]. An essential component is the extracellular zinc content.

**Table 2**
Locations and functions of ZIP family proteins.

| Subtype | Tissues | Cell types in brain | Localizations | Functions | Modulating factors | References |
|---|---|---|---|---|---|---|
| ZIP1 | low tissue specificity | neurons, oligodendrocytes, astrocytes, oligodendrocyte precursor cells, microglia | cell membrane, ER | transports $Zn^{2+}$ into cells, | IL-6, TNF-α, $Zn^{2+}$, melatonin, growth hormone | [137, 139–143] |
| ZIP2 | prostate, uterine epithelial cells | muller glia | cell membrane | transports $Zn^{2+}$ into cells | STAT3, IL-6, TNF-α, pH, growth hormone | [142, 152–155, 158] |
| ZIP3 | testis | low cell specificity, low expression level | cell membrane | transports $Zn^{2+}$ into cells | MTF-1, CREB, $Zn^{2+}$ chelator, RREB-1 | [160–163] |
| ZIP4 | kidney, intestine, stomach, colon, jejunum, duodenum | muller glia | cell membrane, endosome | transports $Zn^{2+}$ into cells | $Zn^{2+}$, gut flora | [152, 170–173] |
| ZIP5 | liver, kidney, pancreas, intestine, colon, spleen | cone photoreceptor cells | cell membrane | transports $Zn^{2+}$ into cells | $Zn^{2+}$, miRNA, alcohol, $Fe^{2+}$ | [181–188] |
| ZIP6 | breast, prostate, placenta, kidney, pituitary, corpus callosum | neurons, oligodendrocytes, oligodendrocyte precursor cells | cell membrane | transports $Zn^{2+}$ into cells | STAT3, $Zn^{2+}$, $Fe^{2+}$, cadmium, insulin, ZAP70 | [190–195, 653] |
| ZIP7 | low tissue specificity | muller glia, cone/ rod photoreceptor cells, bipolar cells, horizontal cells | ER, Golgi apparatus | transports $Zn^{2+}$ from ER/ Golgi to cytoplasm | miR-139-5p, CK2, glucose, cadmium | [74, 201–206] |
| ZIP8 | pancreas | microglia | cell membrane, lysosome | transports $Zn^{2+}$, $Fe^{2+}$ and $Mn^{2+}$ into cells, transports $Zn^{2+}$ from lysosome to cytoplasm | $Zn^{2+}$, $Fe^{2+}$, $Mn^{2+}$, cadmium, lead, MTF-1, sp1, RREB1, HIF-2, TNF-α, bacterial infection | [162, 215–228, 654] |
| ZIP9 | pancreas, testis, pituitary, kidney, liver, uterus, heart, prostate, brain | neurons, astrocytes, oligodendrocyte precursor cells, oligodendrocytes, microglia | cell membrane, Golgi apparatus, mitochondria, nucleus | transports $Zn^{2+}$ into cells; transports $Zn^{2+}$ from Golgi/ mitochondria to cytoplasm | sp1, STAT3, Notch, $Zn^{2+}$, testosterone, prochloraz, eneximin, epicatechin, catechin, radiation, hypoxia | [237–246, 248] |
| ZIP10 | thyroid gland | microglia, excitatory neurons, inhibitory neurons | cell membrane | transports $Zn^{2+}$ into cells | MTF-1, JAK/STAT, thyroid hormone, erythropoietin, $Zn^{2+}$, cadmium, $Zn^{2+}$ chelator | [251–256, 265] |
| ZIP11 | low tissue specificity | excitatory neurons, inhibitory neurons, astrocytes, oligodendrocyte precursor cells, oligodendrocytes, microglia | cell membrane, Golgi apparatus, nucleus | transports $Zn^{2+}$ into cells | MTF-1, $Zn^{2+}$, $Zn^{2+}$ chelator | [262–266] |
| ZIP12 | brain, eye | astrocytes, muller glia | cell membrane | transports $Zn^{2+}$ into cells | $Zn^{2+}$, HIF-1α, oxidative stress | [269–273] |
| ZIP13 | low tissue specificity | low cell specificity, low expression level | Golgi apparatus, ER | transports $Zn^{2+}$ from Golgi to cytoplasm | $Zn^{2+}$, TGF-β, vitamin D3 | [277–280] |
| ZIP14 | liver, pancreas | neurons | cell membrane, endosome, lysosome | transports $Zn^{2+}$, $Fe^{2+}$ and $Mn^{2+}$ into cells | ATF4, ATF6α, $Fe^{2+}$, p53, LPS, IL-1β, IL-6, hemochromatosis proteins | [191, 285–292, 655] |

ZIP1 expression modulator. While zinc deficiency increased the plasma membrane level of ZIP1 by decreasing its rate of endocytosis[139], high zinc treatment significantly inhibited the protein expression of ZIP1 in a transcription-independent manner[138]. This suggests that the post-transcriptional regulations are primarily responsible for the zinc concentration-regulated ZIP1 expression. Nonetheless, further research is necessary to fully understand ZIP1's post-transcriptional regulatory network. Notably, a number of other variables also play a role in ZIP1 regulation. It has been shown that oxidative stress increases zinc uptake activity by increasing ZIP1 expression in astrocytes [140]. Additionally, it has been shown that inflammatory agents including IL-6 and tumor necrosis factor α (TNF-α) increase ZIP1 expression [141]. Furthermore, melatonin can activate the ERK pathway by upregulating the expression of ZIP1 in hypoxia-induced N2a cells [143], indicating that the hormones may also be involved in ZIP1 regulation. Regretfully, the mechanisms underlying oxidative stress, inflammation, and hormone regulation of ZIP1 expression remain unknown. Additionally, ZIP1 mRNA expression in children showed a positive correlation with growth hormone levels [142]. Robust oxidative stress may result from cells experiencing chronic inflammatory stress [144]. Therefore, by inducing oxidative stress in cells, inflammation may increase ZIP1 expression. Additionally, zinc deficiency may cause oxidative stress by reducing Nrf2 nuclear translocation [145], so oxidative stress may be the cause of the zinc deficiency-induced upregulation of ZIP1. When combined, the relationships between inflammation, oxidative stress, and environmental zinc content may help uncover the regulatory mechanism pertaining to ZIP1 expression.

Prior research showed that ZIP1 expression was decreased in breast and prostate cancer tissues, which was linked to a drop in cellular Zn2+ content. This occurrence might result in
an equilibrium between apoptosis and cell proliferation, thus promoting
promoting the growth of tumors and a poor prognosis [146,147]. Numerous inherited and acquired zinc metabolism problems are also linked to the ZIP1 protein. A lack of ZIP1 protein may result in inadequate

uptake of Zn2+ inside cells, which can cause signs of zinc deficiency, including growth retardation, decreased immunological function, and skindam-
[62,148,149] years old. On the other hand, increased intracellular Zn2+ concentrations brought on by ZIP1 protein overexpression may result in zinc poisoning [150]. ZIP1 in immune cells controls the function of the immune
system[13]. ZIP1 was found in the cytoplasm and plasmam membrane of macrophages, and macrophages lacking ZIP1 exhibited significantly reduced intracellular zinc and phagocytic capacity[151]. This suggests that ZIP1-mediated zinc homeostasis may play a role in the macrophages' removal of immunogenic substances like pathogens.

ZIP code two
Zn2+ is transported inward from the extracellular environment by the ZIP2 protein, which is specifically expressed in prostate and uterine epithelial cells and mostly localized to the cell membrane.
[152]. A prior investigation showed that the overexpression of the STAT3
may increase the expression level of ZIP2 [153]. Furthermore, ZIP2's activity is increased in acidic pH environments, mostly due to extracellular pH, and is not significantly affected by extracellular HCO3- levels [154]. It is noteworthy that ZIP2 overexpression results in increased Nrf2 activity and glutamate-cysteineligase expression, which facilitate glutathione synthesis. Growth hormone supplementation was found to induce ZIP2 expression in a cohort of 15 children with short stature, showing a positive correlation with growth hormone levels [142]. This finding suggests a potential regulatory role of growth hormone in ZIP2 expression.
[155], suggesting that Zn2+ influx mediated by ZIP2 may control oxidative
tension.
The expression level of ZIP2 and the genetic variation of the ZIP2 gene are linked to the development and course of a number of inflammatory and infectious disorders [156,157]. According to another research, the expression level of ZIP2 is markedly elevated in inflammatory and infectious circumstances, which encourages immune cells to absorb zinc in order to sustain immune function [158]. ZIP2 also plays a critical function in mouse cardiac ischemia/reperfusion damage and is engaged in cardiac protection [153]. Additionally, malignancies such breast, liver, and gastrointestinal cancers showed abnormal expression levels of ZIP2, which may be linked to tumor cell proliferation, metastasis, and treatment resistance.
[159] All things considered, these results highlight ZIP2's significance in a variety of physiological processes and disease settings.

ZIP 3.
In intesticular tissue, the ZIP3 protein is abundantly expressed and mostly found on the cell membrane, where it facilitates the transfer of Zn2+ from the extracellular space into the cytoplasm [160].
Several transcription factors as well as epigenetic alterations control the function of the ZIP3 protein. The unique Ras-responsive transcription element known as human Ras-responsive element-binding protein 1 (RREB1),
may suppress ZIP3 expression when downregulated, which lowers Zn2+ levels in cancer and precancerous cells [161]. Furthermore, the transcription factors MTF-1 and CREB1 increase the expression of ZIP3.
By binding to the ZIP3 promoter region [162], a Zn2+ chelator reduces ZIP3 expression in Caco-2 cells, indicating that Zn2+ concentration regulates ZIP3 [163].
Tumor cells usually have low levels of ZIP3 protein expression. For instance, the expression of ZIP3 protein is considerably reduced in a number of malignancies, including prostate, pancreatic, and liver tumors. Tumor cells' increased capacity for proliferation and invasion may be linked to this deficit [159,161]. Three days of stimulating PBMCs with plantlectins led to a drop in the expression levels of ZIP3 protein and a rise in inflammatory markers [164], indicating a strong association between ZIP3 protein and the development and course of chronic inflammatory disorders. The ZIP3 protein may be involved in diabetes and metabolic diseases. Stem cells isolated from human exfoliated deciduous teeth (SHED) show increased ZIP3 expression after differentiating into insulin-secreting SHEDβcells, but ZIP3 mutant cells show decreased ZIP3 expression.
Zn2+ cellular levels and concurrently reduced insulin secretion in

SHEDβcells [165]. According to some reports, ZIP3 has no role in obtaining Zn2+ from the mother's circulation to secrete into milk. Rather, it mostly aids in the mammary gland's cellular retention and absorption of Zn2+ from previously released milk pools. Zn2+ levels in breast milk may thus be impacted by changes in ZIP3 expression or activity [166]. Later in the embryonic development, ZIP3 was expressed in the inner cell mass of the heblastocystallo.
ZIP3 was shown to be elevated in the embryonic brain and in several other tissues. When a zinc-deficient diet was administered to ZIP3 mutant mice during pregnancy or at weaning, a slight increase in susceptibility to aberrant embryonic morphogenesis and to thymic pre-T cell depletion was also seen [160]. In neural organs, such as the brain and the retina, ZIP3 is widely expressed. It formed a ternary postsynaptic complex with PKC-zeta and the GABA(C) receptor rho 3 subunit [167]. Zinc absorption into CA1 pyramidal cells has been shown to be slowed by ablation of ZIP1 and ZIP3 transporters [168]. A further investigation showed that ZIP1 and ZIP3 were widely distributed on somas and the majority of neuronal processes in neurons, with ZIP3 being mostly localized to the stratum lucidum and ZIP1 being primarily expressed in the CA3 stratum pyramidale. Zinc absorption in cultured mouse hippocampal neurons was 50% reduced when ZIP1 or ZIP3 was silenced [169]. These findings suggested that both ZIP1 and ZIP3 are important in zinc homeostasis in neurons.

ZIP code
The ZIP4 protein is mostly found on the plasma membrane and endosomal membranes [152], and it has a function in controlling the entrance of extracellular zinc 2+ into cells [171]. It is abundantly expressed in the kidney, small intestine, stomach, colon, jejunum, and duodenum [170].
Research on the control of ZIP4protein expression and activity is still scarce. According to a prior research, there is a negative correlation between intracellular Zn2+ concentration and ZIP4 protein expression level, implying that greater intracellular Zn2+ concentrations
tions are linked to reduced ZIP4 expression levels [172].
Additionally, by affecting the amount of Zn2+ in the intestinal tract, the gut microbiota may indirectly control the production of ZIP4 protein. Co-administration of flow-dose AZO drugs with probiotics
enhances intestinal ZIP4 expression, decreases fecal zinc excretion, increases zinc bioavailability, and guards against oxidative damage from high-dose ZnO and zinc coverload in the heliver [173].
Numerous types of tumors are initiated and progressed by ZIP4. Recent studies have shown that ZIP4 is a novel biomarker for cancer stem cells in epithelial ovarian cancer. It selectively increases the expression of histone deacetylase IIa (HDAC IIa), which makes HGSOC cells more sensitive to HDAC inhibitors [174]. Additionally, increased ZIP4 levels in pancreatic cancer trigger IL-6 transcription via the CREB pathway, which in turn activates STAT3 and causes increased cyclin D1 expression, ultimately promoting cell proliferation [175]. ZIP4 is a new prognosticator and therapeutic target linked to poor outcomes in individuals with hepatocellular carcinoma because it promotes cell migration and invasion while blocking apoptosis [176]. Additionally, ZIP4 has been shown to induce epithelial-mesenchymal transition and promote tumor migration and invasion via the PI3K/Akt signaling pathway in nasopharyngeal carcinoma [177]. There is a significant correlation between tumor size and ZIP4 expression in oral squamous cell carcinoma. In malignancies, ZIP4 knockdown decreases zinc absorption and inhibits cell division [178]. By raising cytoplasmic zinc levels, ZIP4 also regulates insulin secretion and glucose homeostasis, which in turn stimulates insulin release via a non-mitochondrial mechanism [179]. Furthermore, a study demonstrating that heterozygous knockout of ZIP4 in mice results in a hypersensitive response to zinc deficiency, resulting in a tenfold higher likelihood of abnormal development compared to wild-type control mice under conditions of zinc deficiency [180] further supports the notion that ZIP4 plays a crucial role in early development.

ZIP code 5
ZIP5 is mostly found on the cell membrane of basolateral epithelial cells and is expressed in the liver, kidney, pancreas, small intestine, colon, and spleen [181]. It plays a role in the transport of Zn2+ into
the cells [182], and controls TGF-β and bone morphogenetic protein
The regulation of ZIP5 translation is mediated by conserved elements in the 3'-untranslated region (3'-UTR), where ZIP5 translation is inhibited during zinc deficiency and rapidly translated upon zinc replenishment. The 3'-UTR of ZIP5mRNA is highly conserved and forms a stable stem-loop structure, with recognition sites

for miR-328 and miR-193a on both sides of the stem-loop. (BMP/TGF-β) signaling pathway, modulating the extracellular matrix proteins in the sclera and playing a crucial role in eye development [183]. The miRNA recognition sites and the stem-loop work cooperatively to improve the translation of ZIP5 mRNA when zinc levels are adequate [184].
Upon zinc supplementation, ZIP5 is increased in the duodenal tissue of mice, facilitating the absorption of intracellular Zn2+ [185]. In a mouse model of alcoholic liver illness, alcohol-induced down-
One of the causes of ethanol-induced hepatic zinc shortage may be the control of ZIP5 expression [186]. Additionally, zinc defi- ciency leads to the methylation-mediated silencing of miR-193b in esophagealcancercells,resultinginupregulatedZIP5expression,which
increasesintracellularZn2+levelstomaintainzincbalance[187].The
ZIP5 expression may potentially be influenced by Fe2+ consumption. According to a research, ZIP5mRNA levels were 3–8 times greater in the helix of rats with
ZIP5 is closely linked to the occurrence and development of tumors and inflammation. It is overexpressed in esophageal cancer, and its downregulation inhibits the proliferation and migration of esophageal cancer cells [189]. iron overload, suggesting a possible role for ZIP5 in hepatic iron/metal homeostasis during Fe2+ overload [188]. Zinc deficiency in liver cancer and the expression pattern of ZIP5 have been shown to be significantly correlated by bioinformatics studies, indicating that ZIP5 may play a key role in the formation of hepatic malignancies [26].

ZIP code 6
The breast, prostate, placenta, kidney, pituitary, and corpus callosum all have high levels of ZIP6 expression, but the heart and in-testinal tissues exhibit lower levels. It facilitates the entrance of Zn2+ into cells and is mostly found in the cell membrane [190,191]. The Fe2+ level may influence ZIP6.
expression, as iron supplementation in rat liver problems leads to
reduced expression of ZIP6 [188]. The activity of ZIP6 is impacted by phosphorylation. Tyrosine protein kinase ZAP70 is used by the T cell receptor to control ZIP6 phosphorylation during T cell activation, which influences
encing Zn2+uptake [192]. STAT3 can also activate ZIP6.
expression, which causes Zn2+ to enter and affects the epithelial-mesenchymal transition in breast cancer cells [193].
ZIP6 expression is elevated throughout the process of cadmium-induced brain developmental harm, which might be a mechanism for cadmium-induced brain developmental problems [194]. Estrogen also plays a role in breast cancer metastasis and regulates ZIP6 expression [195].
Compared to healthy controls, children with stunted growth have significantly lower ZIP6 expression levels, which may be related to lower levels of growth hormones [149]. Additionally, loss of ZIP6 in zebrafish resulted in a significant decrease in T lymphocytes and
increased caspase-related intracellular Zn2+ levels and Zip6 deficiency
cell death in human T cells and zebrafish cells [196]. Interestingly, ZIP6 has become one of the most prevalent Zn2+transport proteins in T cells. It reacts to activation of T-cell receptors via trans-
The immunological synapse is the location. T-cell responses may be inhibited by suppressing ZIP6 because it can reduce extracellular Zn2+ influx [192]. New research also shows that ZIP6 has a role in the formation and spread of tumors. When intracellular Zn2+ influx is mediated by ZIP6, glycogen synthasekinase 3β is inactivated.
(GSK3β), which eventually results in cell rounding and separation, highlighting ZIP6's critical function in tumor metastasis [193]. Furthermore, overexpression of ZIP6 in tumor cells has been linked to
had higher Zn2+ concentrations than typical breast cells. ZIP6 knockdown dramatically lowers the cellular Zn2+ content and causes mitosis.
chondrial membrane potential enhancement and suppresses cell death, indicating that ZIP6 could function as a suppressor rather than a fundamental process that initiates the development of breast cancer [197]. Furthermore, ZIP6 plays a vital role in the survival of breast cancer cells in a high-glucose environment, since high glucose levels trigger upregulation of ZIP6 expression to increase tumor migration[198]. In MIN6βcells, knocking down ZIP6 but not ZIP7 reduced the protective effects of GLP-1 against fatty acid-induced cell death, perhaps because of less activation of the p-ERK pathway. ZIP6 may also play a role in

the development of metabolic diseases [199]. Furthermore, ZIP6 expression is adversely connected with the inflammatory factor TNF-α, favorably linked with body fat percentage, and considerably reduced in female patients who are obese [200].

ZIP7
ZIP7iswidelyexpressedinvarioustissuesandprimarilylocalizedto
theERandGolgiapparatusmembranes,mediatingthetransportofZn2+from the ER/Golgi apparatus to the cytoplasm, therefore controlling the quantity and distribution of intracellular Zn2+[201,202]. MiR-139-5p directly regulates ZIP7, and miR-139-5p mimics and inhibits ZIP7.
expression to influence the migration, apoptosis, and proliferation of gastric cancer cells via the Akt/mTOR signaling pathway [203]. ZIP7 activity is controlled by phosphorylation, where the protein kinase CK2 phosphorylates ZIP7, resulting in the activation of MPK, PI3K, and
Cell development is regulated by mTOR signaling pathways [204,205]. Overexpression of ZIP7 in skeletal muscle cells controls insulin signaling pathways and glucose metabolism. ZIP7 is downregulated in insulin-resistant skeletal muscle and increased in normal skeletal muscle cells in response to glucose onset. Additionally, ZIP7 expression in mouse skeletal muscle may be downregulated by a high-fat diet, indicating that ZIP7 plays a crucial role in insulin signaling transduction in skeletal muscle [206].
ZIP7 is crucial for cellular Zn2+ metabolism.
In a study of tissue samples from colorectal cancer, ZIP7 demonstrated strong positivity in 55% (44 cases) of the samples. Additional research showed that ZIP7 is an independent prognostic factor for patients with colorectal cancer, and that its expression is significantly correlated with lymph node metastasis depth, tumor infiltration, and mortality rate [207]. Upregulation of ZIP7 in tamoxifen-resistant breast cancer cells led to the activation of
growth factor receptors, increasing the growth and invasion of cancer cells, whereas ZIP7 inhibition lowers intracellular Zn2+ levels.
reduced tumor cell resistance by inhibiting the activation of epithelial growth factor receptor signaling [208]. ZIP7 plays an important role in the development and homeostasis of zebrafish. During the early embryonic development of zebrafish, ZIP7 is necessary for the formation of eyes, brain, and skeleton. In Hela cells, inhibition of ZIP7 significantly upregulated the expression of Bax and E-cadherin and downregulated the expression of Bcl-2 and MMP2, demonstrating the positive role of ZIP7 in cervical cancer progression and its potential as a therapeutic target for cervical cancer treatment [209]. Zebrafish with ZIP7 loss exhibit morphological abnormalities, and zinc supplementation may partly correct the developmental abnormalities brought on by ZIP7 gene knockdown [210]. Additionally, ZIP7 is essential for the development of the skin. In mesenchymal stem cells, ZIP7 knockdown suppresses cell proliferation, limiting the normal development of the
dermis [211]. Asakey protein controlling Zn2+ metabolism, possibly ZIP7
linked to the development and course of immune-related disorders. It has been discovered that ZIP7 is significantly upregulated in the mitochondria of heart failure patients, which leads to the inhibition of mitochondrial autophagy and promotes myocardial perfusion injury [213]. A previous study also reported the regulatory role of ZIP7 in regulating glucose uptake in skeletal muscle, where inhibiting ZIP7 expression downregulates the expression of genes related to glucose metabolism [214]. ZIP7 mutations can cause an autosomal recessive inherited immunodeficiency disorder characterized by B-cell deficiency, agammaglobulinemia, and early-onset infections, indicating the essential role of ZIP7 in B-cell development and necessary for proper B-cell receptor signaling [212].
ZIP Code 8
It is mainly found in the cell membrane and lysosomal membrane [215], where it mediates the cellular uptake of Zn2+ and Mn2+ and transports Zn2+ from lysosomes to the cytoplasm [217]. Additionally, ZIP8 is involved in the uptake of cadmium, Fe2+, cobalt, and selenium [216,218,219]. The ZIP8 protein is widely expressed in a variety of tissues, with the highest expression level found in the pancreas [215,216].
increases the expression of ZIP8 and has a significant role in T cells.
vation [220]. During cadmium- and lead-induced endothelialcell toxicity, cadmium and lead promote ZIP8 expression by activating the NF-kB pathway and JNK pathway [221,222]. Additionally, in rat hepatoma cells, iron overload also raises ZIP8 expression and cell surface localization [223]. On the other hand, high

manganese consumption leads to
decreasedZIP8levelsintheliver,whichinturnreducesthereabsorption of Mn2+in bile to avoid manganese overload in the liver [224]. ZIP8's regulation mechanism is still mostly unknown.
By attaching to their putative binding sites in the ZIP8 promoter, the transcription factors MTF-1, Sp1, and CREB1 may control ZIP8 expression.
[162,225]. Through upregulating ZIP8, the HIF-2 signaling pathway may activate the Zn2+/ZIP8/MTF-1 axis in chondrocytes, increasing Zn2+ influx and activating downstream transcription factors.

MTF-1 [226]. Additionally, after bacterial infection and TNF-α exposure, ZIP8 expressions were elevated [227,228]. The complex chemical processes behind this behavior are yet unknown, however.
Through controlling cellular uptake of Zn2+, ZIP8 indirectly regulates innate
ZIP8 expression levels in peripheral blood monocytes are markedly reduced in patients with chronic hepatitis B and chronic hepatitis C, indicating its role in the initial control of infection[231]. ZIP8 modulates the expression of specific genes to protect cells from damage and death during inflammation by influencing immune function and inflammatory responses [229,230]. Additionally, ZIP8 plays a role in preserving healthy liver function; a decline in ZIP8 activity results in liver damage. Mice lacking ZIP8 demonstrate signs of inflammation, fibrosis, and hepatic damage as they form spontaneous liver tumor nodules [232]. Mice lacking ZIP8 show clear extracellular matrix buildup and reduced metalloproteinase in their hearts.
levels, which causes the left ventricular myocardium to not fully densify. This is most likely brought on by decreased transcriptional activity of MTF-1 and decreased cellular absorption of Zn2+ [233]. In addition, a
A research using genome-wide association analysis discovered a link between single nucleotide polymorphisms in ZIP8 and inter-individual variations in blood pressure. These polymorphisms result in ZIP8 mutations, which decrease cell viability, promote ERK2 and NF-κB activation, induce cellular cadmium buildup, and
result in decreased blood levels of Mn2+ and Zn2+ and increased urine levels.
This can encourage the development of cerebellar atrophy syndrome, a kind of autosomal-recessive intellectual impairment [234]. Furthermore, ZIP8 mutations decrease Mn2+-dependent enzyme performance, especially
The biosynthesis of β-1,4-galactosyltransferase is essential.
carbohydrates found in glycoproteins. Severe problems include limb shortening, severe epileptic seizures, hearing loss, and craniofacial abnormalities are caused by impaired galactosylation [235]. Similarly, ZIP8 mutations lower the amounts and ac-
activity of the mitochondrial Mn2+-dependent SOD enzyme,
Consequently, oxidative stress is increased and mitochondrial dysfunction is induced [236].

ZIP Code 9
While its expression is relatively low in ovarian and colonic tissues, ZIP9 is abundantly expressed in pancreatic, testicular, pituitary, renal, hepatic, uterine, cardiac, prostatic, and brain tissues [237].
mostly found in the nucleus, mitochondria, Golgi apparatus, and cell membrane [237], facilitating the absorption of Zn2+ by the cell and transporting it from the mitochondria or Golgi apparatus to the cytoplasm [238]. ZIP9 is involved in the regulation of B cell receptor signaling.
pathway by increasing Akt and Erk phosphorylation and controlling intracellular Zn2+ levels [239]. Transcription factors like Sp1 may
bind to the ZIP9 promoter directly in order to increase ZIP9 expression [240]. Additionally, ZIP9 expression may be increased by STAT3 activation, increasing Zn2+ homeostasis and reducing myocardial
injury caused by ischemia-reperfusion in mice [241]. The Notch signaling pathway
is also important in controlling ZIP9 expression, as shown by the fact that blocking the Notch signaling pathway causes mice's serotonin cells to express ZIP9 more [242].
concentration of Zn2+. Excessive Zn2+ supplementation decreases ZIP9 expression in fish liver tissues while increasing it in intestinal tissues [243]. Additionally, the depletion of Zn2+ in
ZIP9 expression is upregulated by mouse cardiomyocytes [241]. It is interesting to note that ZIP9 has characteristics of the androgen receptor (AR). Testosterone therapy increases the expression of ZIP9 in MDA-MB-468 and PC-3 cells, which activates G-protein and second messenger pathways and increases

intracellular free
concentration of Zn2+, which finally causes cell death [237]. Nevertheless,
Insecticides like imidacloprid and spirotetramat, along with flavonoids such as epicatechin and catechin, could compete with testosterone for binding to ZIP9, thereby inhibiting testosterone-induced downstream functionsofZIP9[244,245].EpigeneticmodificationsalsoaffectZIP9

expression.RadiationinducesthedemethylationofCpGdinucleotidesin the ZIP9 exon, which enhances ZIP9 expression and inducesradiation-induced skin fibrosis via the TGF-βsignaling pathway [240]. In fish ovaries, hypoxia also causes an increase of ZIP9 expression, which may facilitate ovarian follicular cell death [246]. A possible therapeutic target for breast and prostate cancer is ZIP9, which is increased in malignant breast and prostate tissues [237]. In glioma cells, ZIP9 can control cell migration by phosphorylating p53 and dephosphorylating GSK3β [248]. In contrast, ZIP9 expression levels are significantly lower in human liver cancer tissues, which polarizes M2 macrophages by promoting STAT6 phosphorylation and inhibits the polarization of M1 macrophages by inhibiting IκB phosphorylation [249]. ZIP9 expression levels are elevated in melanoma, and testosterone can promote melanoma proliferation by activating ZIP9 [247]. High expression of ZIP9 was also shown in zebrafish ovaries in a prior study. Female fish with ZIP9 knockout exhibit aberrant cortical vesicle development in fish eggs, which results in a marked reduction in fertilization rate, embryo viability, and offspring growth. These results imply that appropriate zinc regulation by ZIP9 is essential for reproduction [250].

ZIP Code 10
ZIP10 is extensively expressed in numerous tissues and showshigh expressioninthethyroid.Itisprimarilylocalizedtothecellmembrane
andmediatestheentryofZn2+intothecell[251].Thetranscription
Factor MTF-1 contributes to the downregulation of ZIP10 and displays
unique regulatory pathways in contrast to other zinc transport proteins [252]. The JAK/STAT signaling pathway controls the expression of ZIP10 in early B cell development, which affects the Zn2+
B cell homeostasis [253]. Thyroid hormones also play a role in the
control of ZIP10 expression. In-testinal and renal cells derived from hyperthyroid rats exhibit increased ZIP10 expression, while hypothyroid rats exhibit downregulated ZIP10 expression [254]. Zinc deficiency also stimulates the elevation of ZIP10 expression in red blood cells, and erythropoietin may cause a sharp rise in ZIP10 expression in these cells [255]. In a similar vein, exposure to cadmium also markedly increases ZIP10 expression, which contributes to oxidative damage and redox imbalance in the brain [256].
Patients with osteosarcoma undergoing chemotherapy have shown increased expression of ZIP10 in tumor tissue. By increasing Zn2+ uptake, this overexpression of ZIP10 may cause CREB phosphorylation, which would then activate PI3K/AKT.
signaling pathway that promotes cell division and resistance to disease
[257]. Additionally, ZIP10 expression levels are elevated in breast cancer and renal cell carcinoma, and they have a strong correlation with cell invasion [258,259]. Additionally, there is a negative correlation between ZIP10 expression and thyroid cancer sensitivity to mannose. In mannose-insensitive cells, ZIP10 knockdown dramatically reduces tumor development.
by decreasing Zn2+ levels and enzyme activity [260]. ZIP10 is
abundantly expressed in the outer root sheath of hair follicles, where it facilitates Zn2+ absorption and plays a critical role in triggering the p63 signaling pathway. Here, ZIP10 deletion leads in reduced
early B cell development, the loss of epidermal development [261].
By activating caspase family proteins, ZIP10 triggers apoptosis, indicating its significance in immune system maintenance [253]. Through the p53 signaling pathway, ZIP10 also enhances the survival of macrophages in response to inflammatory stimuli [134]. According to the aforementioned studies, ZIP10 has a significant functional role in the development of the epidermis, immunological response, and cancer progression.

ZIP Code 11

ZIP11 expression is mostly found in the cell membrane, golgi apparatus, and nucleus and lacks tissue specificity, facilitating the transport of Zn2+ into the cell [262]. At the moment, there is little

studies on ZIP11. The transcription factor MTF-1 directly binds to the MRE region in the ZIP11 promoter to control ZIP11 expression [263]. ZIP11 decreases when Zn2+ supplementation is restricted.
expressing a restricted problem, whereas ZIP11 expression is elevated in
ZIP11 expression may also be downregulated by the Zn2+chelator N,N,N',N'-tetrakis (2-pyridylmethyl) ethylenediamine (TPEN), potentially by interfering with the cellular Zn2+ concentration [265]. Additionally, Zn2+ supplementation dramatically raises Zn2+ levels and ZIP11 expression in the heliver, according to a prior research.
and pancreas, improving immunological response and antioxidant capability [266].
In glioblastoma, ZIP11 is downregulated and significantly correlated with lower-grade (grade I and grade II) glioblastoma progression. In glioblastoma samples with isocitrated ehydrogenase1 (IDH1) mutations, ZIP11 expression is significantly higher than in samples without IDH1 mutations [267]. High expression of ZIP11 is also linked to a poor prognosis in patients with colorectal cancer. Knock-down of ZIP11 inhibits the proliferation, migration, and invasion of Hela cells and causes mitochondrial damage [262]. In individuals with pancreatic cancer, ZIP11 expression is also elevated and substantially associated with a worse prognosis. The ERK1/2 pathway and Capan-1 cell growth are inhibited by ZIP11 deletion [86]. Additionally, patients with gastritis were found to have three distinct single nucleotide polymorphisms in the ZIP11 intron sequence, which are linked to chronic gastritis brought on by a spicy diet [268].

ZIP Code 12
TheZIP12proteinisexpressedinthebrainandeyes,predominantly
localizedtothecellmembrane,whereitfacilitatesthetransportofZn2+intocells[269,270].Supplementationofzinc inzinc-deficientTcells
may increase ZIP12 expression, which in turn affects T cell activation [271], indicating that Zn2+ concentration regulates ZIP12 expression. It is hypothesized that HIF-1α induces ZIP12 expression and subsequent
subsequently control the ERK signaling pathway to promote the phenotypic change of pulmonary artery smooth muscle cells in response to hypoxia [272]. On the other hand, oxidative stress has been shown to increase cellular apoptosis by downregulating ZIP12 expression [273]. However, the exact molecular process is yet unknown.
Neurite outgrowth in neuroblastoma cells is inhibited when ZIP12 is lost due to mitochondrial malfunction [274]. ZIP12 expression is elevated in the smooth muscle cells of the pulmonary arteries of rats with pulmonary arterial hypertension brought on by colchicine. By promoting the migration and proliferation of these smooth muscle cells via the AKT/ERK signaling pathway, ZIP12 contributes significantly to the pulmonary vascular remodeling brought on by colchicine [275]. It was shown that hypoxia increases ZIP12 expression in pulmonary arteries and pulmonary artery smooth muscle cells after three weeks of exposing rats to a hypoxic environment and cultivating primary rat pulmonary artery smooth muscle cells under hypoxic circumstances. The phenotypic flip of hypoxia-induced pulmonary artery smooth muscle cells may be inhibited by ZIP12 knockout [272]. Additionally, it was discovered that the polymorphism of ZIP12 is linked to alterations in susceptibility-weighted magnetic resonance imaging in the brain by secondary study of adult brain magnetic resonance imaging, genome-wide association studies, and exome sequencing data. In neurons, loss of ZIP12 may result in elevated superoxide and protein carbonylation, as well as compromised mitochondrial activity [276]. Furthermore, it has been shown that mouse testicular tissue has greater levels of ZIP12 expression than other ZIP family members. Additionally, the expression of ZIP12 in obese testes
mice is considerably reduced, which is linked to a decrease in Zn2+
male infertility, low sperm quality, and high ROS levels in sperm [273].

ZIP13
Numerous tissues and cell types exhibit widespread expression of ZIP13, mainly

located in the ER and Golgi apparatus, mediating the movement of Zn2+ from the ER to the cytoplasm [277,278]. In Drosophila,
Iron homeostasis is another function of ZIP13 [279]. Research on the control of ZIP13 expression levels and activities is still scarce. Vitamin D3 may also enhance ZIP13 expression in human peripheral blood mononuclear cells [279]. Zinc shortage can cause upregulation of ZIP13 expression [280]. Additionally, the expression of ZIP13 is elevated following treatment with TGF-β and is essential for collagen formation during dermal development [278].
Mice experiencing cardiac ischemia-reperfusion have downregulated ZIP13 in their heart tissues, which results in calcium-calmodulin-dependent protein kinase phosphorylation. Additional research has shown that a specific loss of ZIP13 in the heart results in an increase in mitochondrial
ROS, mitochondrial volume, and Ca2+ exacerbate myocardial
infarction in mice after ischemia-reperfusion. On the other hand, ZIP13 overexpression decreases the size of the infarction [281]. ZIP13 also plays a role in controlling cardiovascular homeostasis. Neonatal cardiomyocytes from ZIP13 mutant mice show aberrant irregular rhythmic contractions, and treatment with the cardiotoxic medication doxorubicin resulted in reduced expression of ZIP13 in primary neonatal cardiomyocytes and mouse heart tissues [282]. High ZIP13 expression is an independent predictor of poor survival in patients with ovarian cancer. The tyrosine kinase Src/FAK signaling pathway is activated by ZIP13, which encourages the activation of genes linked to migration in tumor cells. On the other hand, the malignant features of ovarian cancer are suppressed when ZIP13 is knocked out, suggesting that it may be a therapeutic target [283]. Mutations in ZIP13 may result in compromised zinc homeostasis in the ER, which can cause the hereditary congenital tissue condition Ehlers-Danlos syndrome [280]. Furthermore, ZIP13-deficient animals show aberrant collagen fibers, circular collagen molecules, and noticeable incremental lines in the dentin matrix of mandibular molars, as well as impaired immunological responsiveness to type I collagen [284].

ZIP Code 14
Numerous tissues express ZIP14, with the liver and pancreas expressing the most of it [285]. The cell membrane, endosomal membrane, and lysosomal membrane are its primary locations [191,286]. It also facilitates the transfer of Zn2+, Fe2+, and Mn2+ into cells [287].
The ZIP14 protein's expression is controlled by several factors, including
transcriptional factors and p53. The transcription factors ATF4 and ATF6α may increase the expression of ZIP14 under ER stress [288].
conditions of cellular Fe2+depletion, proteasomes break down ZIP14, and Fe2+ replenishment prevents ZIP14 from internalizing and degrading
ZIP14 protein levels are thus regulated by dation from the cell membrane [289]. According to a prior research, p53 interacts with ZIP14 and facilitates its ubiquitination and degradation. While p53 overexpression resulted in decreased ZIP14 expression, p53 knockdown causes upregulation of ZIP14 expression [290]. Lipopolysaccharide has the ability to increase ZIP14 expression in macrophages, which contributes to the upregulation of inflammatory cytokines [291]. On the other hand, the inflammatory
ZIP14 expression can also be increased by the cytokine IL-1β to aid the Fe2+
absorption by astrocytes [292].
Increased cellular absorption of Zn2+ during glucose uptake is caused by overexpression of ZIP14. Mice with ZIP14 deletion have zinc deficiency, which impairs the functions of insulin-degrading enzymes.
cathepsin D and enzyme (IDE) while boosting insulin receptor activity. Additionally, ZIP14-mediated insulin receptor activity and glucose homeostasis in liver cells are regulated by ZIP14, as evidenced by the increased hepatic glycogen synthesis, impaired glucose metabolism, and impaired glycolysis in ZIP14 knockout mice [293]. Notably, ZIP14 knockout mice also showed hyperinsulinemia and impaired insulin secretion under high glucose conditions, suggesting that ZIP14 may be a potential target for treating beta cell dysfunction [294].
Zn2+ influx may have a direct impact on peroxisome activity.
PPARγ, a proliferator-activated receptor, which controls the

growth and function of adiposetissue. A prior research found that ZIP14 is downregulated in obese people but increased following weight reduction. ZIP14 also has a negative correlation with insulin resistance, triglycerides, and body mass index [295]. These investigations demonstrate the important function of ZIP14 in controlling the metabolism of glucose. Additionally, carcinogenesis and the advancement of cancer are influenced by ZIP14. The malignant development of metastatic colon cancer, lung cancer, and breast cancer models is significantly influenced by ZIP14 upregulation. Increased ZIP14 levels are associated with worsening illness in individuals with pancreatic ductal adenocarcinoma [296]. Furthermore, ZIP14 influences bone mass since ZIP14 knockout mice show significant decreases in cortical and trabecular bone mass [297].

Then, non-classical zinc carriers

In addition to ZnTs and ZIPs, a number of proteins, including ferroportin (FPN), transient receptor potential (TRP) channels, transmembrane protein 163 (TMEM163), and metallothioneins (MTs), have the capacity to transport Zn2+ (Table 3). As a result, we have spoken about the
the section that follows.

MTs
Because of their extremely conserved structure and function, MTs are mammalian proteins that control intracellular metalion metabolism. They include numerous cysteine residues that may bind to metal ions, allowing them to participate in processes including metal ion transport, storage, and detoxification within cells [298,299]. While MT3 is mostly expressed in brain astrocytes, MT1 and MT2 are significantly expressed in the liver and kidneys [300]. MT1 primarily localizes to the cell nucleus and cytoplasm [301,302], and it plays a role in a variety of
Zn2+ is one of the metalion transport processes [303]. By binding to metal
ions, MTs have a role in controlling cellular functions as development, aging, apoptosis, and antioxidants [304–306]. There are many variables that control the protein production and function of MTs. MTs protein expression may be induced by exposure to metal ions (such as zinc, calcium, copper, silver, cadmium, and mercury) and other substances [307,308]. Oxidative stress can also drive MTs expression by activating the Nrf2 [309,310]. Furthermore, by attaching to MTs promoter regions, transcription factors MTF-1 and p53 increase the production of MTs [311,312]. Furthermore, MTs expression may also be induced by specific inflammatory agents such as TNFα and IL-6 [313,314].
MTs protein expression is linked to the development and spread of a number of malignancies, such as gastric cancer [318], breast cancer [317], lung cancer [316], and liver cancer [315]. Additionally, the expression levels of MTs protein have been thoroughly investigated in metabolic illnesses such as obesity [320], diabetes [321], and hypertension [322]. It is also thought that MTs protein plays a role in controlling tumor drug resistance [319]. By modulating intracellular oxidative stress, glucose metabolism, and lipid metabolism, among other routes, MTs protein may have a role in controlling metabolism [321,323].

TRP channels
With 28 members separated into 6 subfamilies, TRPchannels are essential for controlling Ca2+ influx and depolarizing membrane action potentials [324]. The traditional transientreceptor
Zn2+transport involves potential canonical (TRPC), transient receptor potentialcular melastatin (TRPM), transient receptor potential vanilloid (TRPV), and transient receptor potential ankyrin (TRPA) channels [325].
TRPM2 is widely expressed in many different tissues and exhibits high
expression in peripheral blood cells and the brain [326]. It plays a role in the transport of Ca2+ into cells and is mostly found in the cell membrane and lysosomes [327,328]. TRPM7 is also extensively expressed.
in many tissues, with the parathyroid gland expressing it at a high level.
mostly found in the cell membrane and has a role in transport

**Table3**
Locationsandfunctionsofthenonclassicalzinctransporters.

| Subty | Tissues | Celltypesin brain | Localizatio | Functions | Modulatingfactors | Referenc |
|---|---|---|---|---|---|---|

| pe | | | ns | | | es |
|---|---|---|---|---|---|---|
| TRPM 2 | brain, peripheral bloodcells | excitatoryneurons,inhibitoryneurons, microglia | cellmembrane, lysosome | transports$Ca^{2+}$,$Zn^{2+}$intocell | extracellularpH,cytoplasmicATP, arachidonicacid,diphenylboronic acid-2-aminoethylester | [326–328, 330–333] |
| TRPM 7 | parathyroid gland | excitatoryneurons,inhibitoryneurons, astrocytes,oligodendrocyteprecursor cells,oligodendrocytes,microglia | cellmembrane | transport$Ca^{2+}$, $Zn^{2+}$ intocell | hypoxia,cerebralischemia, prostaglandins,inflammatory factors | [329, 334–337] |
| TRPA1 | intestine, stomach, | lowexpressionlevel | cellmembrane | transportmetal ions, painperception, | cytokines,TRPVchannelinhibitors, scorpiontoxins,TRPVchannel | [340,341] [341–346] |
| TRPV6 | bladderstomach,intestine | lowexpressionlevel | cellmembranecellmembrane | sound perceptiontransport$Ca^{2+}$,$Zn^{2+}$,$Mn^{2+}$,$Cd^{2+}$intocell | agonists,hyperoxia estrogen;inflammatoryfactors;vitamin D; ruthenium redTRPC5 inhibitors | [347–354] |
| TRPC5 | brain | excitatoryneurons,inhibitoryneurons, oligodendrocytes | | transport$Ca^{2+}$, $Zn^{2+}$ intocell | | [355–357] |
| MTs | liver,kidney,brain | astrocytes | nucleus,cytoplasm | transportmetalions ($Ca^{2+}$,$Zn^{2+}$,$Cu^{2+}$,$Cd^{2+}$) | metalions,toxicexposure, oxidative stress, MTF-1, p53, IL-6,TNFα | [298–312] |
| TMEM163 | | brain,pancreas | oligodendrocyteprecursorcells endosome,vesicles | | cellmembrane, | |

transports$Zn^{2+}$outofcell $Zn^{2+}$ [358–361]

FPN carries Fe2+Co2+ across the cell membrane of neurons, astrocytes, and microglia with minimal tissue specificity. Zn2+ and Mn2+ out of cells, Fe2+, hepcidin [365–367,369], and Ca2+ and Mn2+ within cells [329]. Extracellular pH, cytoplasmic ATP depletion, arachidonicacid, and 2-aminoethyldiphenylborinate [330–333] all affect the expression and activity of TRPM2. Prostaglandins, inflammatory agents, and cerebral ischemia all have a role in controlling TRPM7 expression and activity [334–337].

Zn2+transport is also regulated by TRPM2 and TRPM7. Excess Zn2+ stimulates the generation of ROS, which causes brain damage. High H2O2 and Zn2+ concentrations cause cell death in microglial cells, which is reduced by TRPM2 channel inhibitors and TRPM2 knockout [338]. Subsequent research showed that Zn2+ causes the production of ROS and the activation of poly-(ADP-ribose)polymerase-1 (PARP1), which is Zn2+-driven TRPM2 activation mechanism. Additionally, elevated calcium influx mediated by TRPM2 activates the proline-rich tyrosine kinase 2 (Pyk2)/MEK/ERK signaling pathway, which uses a positive feedback loop to increase TRPM2 activation [338]. H2O2 causes neuronal death in rat hippocampus neurons, and both TRPM2 deletion and TRPM2 inhibitors dramatically reduce H2O2-induced neuronal death. This protective effect is most noticeable when in conjunction with the Zn2+chelator TPEN. These results show showed changes in intracellular Zn2+ levels and TRPM2 activation promote oxidative stress-induced hippocampus neuronal death [339].

The tissues of the colon, stomach, and bladder have significant levels of TRPA1 expression, while fibroblasts exhibit low levels of this protein [340]. Primarily found on the cell membrane [341], TRPA1 controls a number of metal ion transports and contributes to the sense of pain and sound [342]. Cytokines, coronatoxins, TRPV channel activators (such as benzyl isothiocyanate, iodoacetamide, thiol-reactive agents, N-methylmaleimide, N-ethylmaleimide, and 2-aminophenylboronic acid esters), and TRPV channel blockers (such as ruthenium red, A-967079, AP-18, HC-030031, and arylsulfonamide derivatives) all affect its activity [341–345].

Additionally, TRPA1 regulates the transport of Zn2+. Zinc poisoning causes pain and stimulation after being carried into cells by TRPA1 and activated by cysteine and histidine residues [346].

TRPV6 is mostly found in the cell membrane and is abundantly expressed in the gastrointestinal tract [347]. It mediates the transfer of Ca2+ into the cells [348]. A number of stimuli, including estrogen, inflammatory It is well known that cytokines, vitamin D, and ruthenium red regulate the TRPV6 activity and expression level [349–352]. Zn2+ transport is similarly regulated by TRPV6. Overexpression of TRPV6

increases permeability to Ca2+, Mn2+, Zn2+, and Cd2+ [353]. Additionally, overexpression of TRPV6 enhances the toxicity of zinc and cadmium [354].
The embryonic brain has significant levels of TRPC5 expression [355]. It is mostly found in the cell membrane and is essential for allowing Ca2+ to enter cells [356].
Calmodulin-dependent myosin light-chain kinase that is activated by calcium
TRPC5 aids in the regulation of Zn2+ transport and promotes its localization to the cell membrane [356]. In particular, TRPC5 increases cellular oxidative damage in brain cortical neurons and resulting cell death brought on by exposure to Zn2+. However, Zn2+-induced cytotoxicity is avoided by inhibiting TRPC5 with certain blockers [357].

TMEM163
The transmembrane protein TMEM163 is abundantly expressed in the pancreas and brain [358]. It is involved in intracellular Zn2+ transport to the extracellular area and is mostly found in the cell membrane, endosomes, and intracellular vesicles [359,360]. At the moment, there is
There is still little research on TMEM163 and how it relates to diseases.
early on in the process of discovery. There is still much to learn about TMEM163's regulatory network. According to research, TMEM163 may combine with ZnT1, ZnT2, ZnT3, and ZnT4 proteins to create homodimers or heterodimers without changing the location of these proteins in the plasma membrane. Zinc homeostasis in certain tissues or cell types may be aided by the interaction between TMEM163 and various ZnTs [360]. Furthermore, via its N-terminus, TMEM163 interacts with transient receptor potential channel 1 (TRPML1) to control cellular zinc homeostasis. The plasma membrane localization of TMEM163 is drastically decreased in HEK-293 cells when TRPML1 is overexpressed. Nevertheless, overexpression of TMEM163 had no effect on TRPML1 channel activity. This implies that cellular zinc balance is influenced by the interaction between the proteins TRPML1 and TMEM163 [361].
The expression level of TMEM163 in fibroblasts from patients with Niemann-Pick disease type C is decreased, which is linked to exposure to elevated Zn2+ levels, suggesting that Zn2+ concentration may also control TMEM163 expression [361].
The TMEM163 protein is involved in a number of diseases.
Using genome-wide association analysis, TMEM163 is a significant gene linked to type II diabetes. Increased intracellular zinc, total insulin content, and cellular glucose absorption were observed in mouse insulinoma cells (MIN6) that were TMEM163 knocked out. Additionally, one-third of individuals with type II diabetes had new missense mutations.

in the TMEM163 gene, and those who had these mutations had higher glycemic indices [358]. Patients with Hermansky-Pudlaksyndrome have much lower levels of TMEM163 expression, which is directly related to the production of platelet-dense granules. Two novel heterozygous variations of TMEM163 were discovered using whole-exome sequencing in a study of individuals with hypomyelination leukodystrophy. TMEM163 knockout disturbs cellular zinc homeostasis, perhaps playing a critical role in initiating Hermansky-Pudlaksyndrome [362]. Myelin sheath deficits, motor impairments, and developmental abnormalities were reported in zebrafish with TMEM163 deletion [363]. It is still unclear whether these effects are directly linked to TMEM163-mediated zinc homeostasis. The exact function of TMEM163 in these effects requires further investigation.

FPN
A transmembrane protein called FPN is widely expressed in multiple sclerosis.
mostly found in the cell membrane and sues. It is in charge of intracellular Fe2+ outflow [364] and may also carry Co2+, Mn2+, and Zn2+ [365–367]. Remarkably, treatment with hepcidin (the FPN degradation inducer) produced noticeable hypoferremia in only four hours, yet
had no effect on serum zinc levels in mice [368], indicating that FPN is an iron-preferring cellular metal-efflux transporter with a narrow sub-stratum profile that includes zinc and cobalt. In addition, zinc can transport zinc and shield zinc-sensitive cells from high zinc toxicity [369], suggesting that FPN is a possible therapeutic target for zinc toxicity.

## 3. Zinc's physiological roles

### Signaling with zinc

The signaling of extracellular zinc

Although zinc plays a key in preserving enzyme activity and protein structure, its function in cellular signaling is less well understood. At the axon terminal, Zn2+ accumulates in synaptic vesicles and neurons, acting as Zinc may operate as a first messenger in this process by interacting with postsynaptic membrane receptors to trigger intracellular responses, thereby commencing intercellular communication. Neuromodulators are released from presynaptic vesicles and taken up by postsynaptic membranes [370]. Zinc released into the synapse can interact with neurons' N-methyl-D-aspartate receptors (NMDAR) [371], γ-aminobutyric acid receptors (GABA) [372], glycine receptors (GlyRs) [373], L-type and N-type voltage-gated calcium channels (VGCCs) [374], P2X purinergic receptors, and TRPA1 channels [375] to mediate excitatory or inhibitory neural signaling. Additionally, extracellular zinc may activate growth factor receptors such insulin-like growth factor receptor (IGFR) and EGFR, which controls growth, survival, and cell proliferation [376]. Extracellular zinc specifically targets zinc-sensing G protein-coupled receptor 39 (ZnR/GPR39), which produces a to activate downstream signaling pathways, complex with Zn2+.
Cells include neurons, colonic cells, keratinocytes, pancreatic cells, prostate cells, and salivary gland cells all have high levels of ZnR/GPR39 expression.
and thyroid cells [377], and following activation [378], its primary role is to activate intracellular Ca2+ signaling pathways. Furthermore, ZnR/GPR39 may control other ion transporters including Na+, K+, and Cl-, which are crucial for preserving the functionality of neurons and epithelial cells [377,379].

The intracellular signaling of zinc

Extracellular zinc affects the start of intracellular signaling pathways by reducing the bioavailability of different ligands and their affinity with matching receptors. Intracellular zinc plays a critical role in cell signaling transduction by regulating intracellular signaling by promoting protein phosphorylation and inhibiting phosphatase activity [380]. Intracellular zinc primarily interferes with the activity of proteins like MAPK, calcium/calmodulin-dependent protein kinase 2 (CaMK-2), protein kinase C (PKC), and P70S6kinase (P70S6K).
protein tyrosine phosphatases (PTPs) and phosphodiesterases (PDEs). The main source of intracellular zinc signaling is thought to be cellular absorption of extracellular Zn2+, which neurons and presynaptic cells may absorb.
To control phosphorylation signals, zinc is released into the synapses [381]. On the other hand, FcεRI activation causes rapid zinc release from the ER (known as zinc waves) in mast cells (MCs), which encourages the production of inflammatory factors. This supports the idea that zinc inside cells may self-regulate in response to outside stimuli [382]. The existence of zinc transporters in cell organelles such the ER, golgi apparatus, and mitochondria, which contribute to the control of zinc flux in intracellular signaling, was further validated by subsequent studies on different cell types [379]. Although many studies have shown that ZIP and ZnT are the main regulators of zinc flux, under extracellular stimulation, zinc released by MTs is primarily responsible for the increase of cytoplasmic zinc [376]. Although the majority of intracellular zinc is directly bound to zinc-binding proteins such as MTs and glutathione (GSH), a small fraction of free zinc still plays a crucial role in intracellular signaling as a second messenger [383]. Intracellular zinc functions as a signal transducer, collecting signals from cell surface receptors triggered by growth factors, hormones, and cytokines, much like other second messengers. It subsequently sends these outside stimuli to the nucleus or cytoplasm, which results in downstream consequences. As a result, changes in Cellular activity can be significantly impacted by Zn2+ [384]. Based on
Three primary categories of intracellular zinc signals have been distinguished based on their characteristics and endurance. Zinc flux and zinc waves are transcription-independent zinc signaling events that primarily generate downstream effects by rapidly changing cytoplasmic zinc levels [376]. The third type of zinc signal depends on the transcriptional regulation of zinc transporters and can last for a day or longer. The primary distinction between zinc flux and zinc waves is their duration; the former is short-lived, while the latter can persist for at least an hour after induction.

Proliferation and Zinc

Both mitotic and anti-proliferative signals, which are restricted by cyclin-dependent kinases (CDKs), cyclins, and CDK inhibitors, tightly control cell proliferation [385]. A structural and catalytic component of DNA synthesis, transcription, and ribosomal function, zinc also seems to play a role in cell proliferation and serves as a signaling messenger during mitosis [386]. By controlling growth factors [387] and their receptors, as well as the structure and function of enzymes and phosphorylation processes [388], zinc may either directly or indirectly improve the mitotic signaling pathway. Zinc stimulates the mitotic signal through at least three mechanisms: (1) modulating cell proliferation hormones, (2) activating protein phosphorylation, and (3) inhibiting phosphatase

activity. Zinc has strong regulatory effects on the activities of kinases and phosphatases involved in cell division and proliferation. The main inducers of cell proliferation are growth factors, cytokines, and hormones [386]. These molecules facilitate cell growth and proliferation by activating the MAPK, PI3K/AKT, and PKC signaling pathways [389,390]. Growth factors like IGF-1 and IGF-2 activate the MAPK cascade through phosphorylation reactions, which ultimately result in the activation of ERK and transcription factors that regulate important cell cycle events. Notably, both zinc deficiency and supplementation affect mitotic signaling. Fetal growth retardation results from reduced levels of IGF-1 in zinc-deficient fetal plasma [387]. In contrast, zinc supplementation increases IGF-1 and IGF-2's affinity for the IGF receptor, which in turn promotes protein tyrosine phosphorylation and MAPK signal transduction, ultimately promoting cell proliferation [391]. Zinc signaling also regulates the PI3K/AKT, PKC, and MAPK signaling pathways, similar to MAPK. Zinc and insulin

promote AKT phosphorylation in a synergistic manner, which facilitates cell proliferation [389]. Zinc may also activate PKC, which in turn promotes the proliferation of pulmonary arterial smooth muscle cells by overactivating the metal responsive transcription factor 1 (MTF-1)/placental growth factor (PlGF) signaling pathway [392]. Thymidine kinase (TK), another kinase implicated in the advancement of the cell cycle, is highly activated throughout the G1 and S phases [393]. DNA synthesis and cell division depend on TK's ability to catalyze the phosphorylation of thymidine into thymidine monophosphate [394]. Although TK is not a zinc metalloenzyme, zinc is necessary for its transcriptional regulation because zinc-dependent proteins bind to the promoter region of TK1 to stimulate RNA synthesis. Low zinc levels and inhibited DNA synthesis are closely linked to low zinc conditions, but zinc supplementation effectively reverses these effects [394]. Therefore, a decrease in zinc content may inhibit cell proliferation by reducing TK synthesis.
NF-κB is essential for immune responses and inflammation.
control and has a major role in cell differentiation and proliferation [395]. Recent studies have shed light on the structural features of NF-κB, revealing the absence of a zinc-binding domain in its architecture. NF-κB undergoes translocation to the cell nucleus in response to cytokine and growth factor stimulation, which modulates the transcription of genes involved in critical cellular processes, such as cell growth, proliferation, differentiation, apoptosis, inflammation, and immune functions [396]. Interestingly, however, zinc seems to affect NF-κB's capacity to bind to DNA targets. The relationship between zinc shortage and NF-κB-dependent gene expression is unclear, as indicated by inconsistent results from many studies [380,396,397]. Scholars suggest that the effect of zinc on the NF-κB signaling pathway may be very cell-specific and context-dependent because of the striking heterogeneity in its influence on NF-κB-mediated downstream events across various cellular contexts and animal models [396].

Zinc and Cell Death

A balance between cell division and death is essential to preserving an organism's regular physiological processes. Zinc is thought to be an anti-apoptotic factor [390], and it has a coordinated function in these two important processes [398]. Zinc deficiency, for example, affects mitochondrial dynamics and function, causing higher ROS levels and greater acetylation of the antioxidant enzyme SOD2, which in turn causes oxidative stress and early cell death [399]. Additionally, zinc may reduce neuroinflammation and mitochondrial ROS production, enhance sirtuin 3-mediated autophagy, regulate cytokine release linked with the NLR family pyrin domain containing 3 (NLRP3) inflammasome, and eventually prevent cell death [400]. However, zinc may also have pro-apoptotic effects if the intracellular concentration of zinc above the range of homeostatic regulation [401]. Because high zinc levels enhance mitochondrial membrane permeability, which results in the release of cytochrome c and inhibits mitochondrial respiratory chain processes, the intracellular zinc pool is intimately related to the control of cell death [397]. Cell death results from this imbalance brought on by dox homeostasis disturbance and detrimental interactions with biomolecules [401], indicating that cellular buffering capacity seems to be a key determinant of cell destiny. Setting thresholds for anti-apoptotic and pro-apoptotic effects may depend critically on the expression or activity state of molecules that maintain zinc homeostasis, such as ZIPs, ZnTs, and MTs [401]. Zinc's anti-apoptotic properties also rely on the type of cell and surroundings. Zinc typically has anti-apoptotic qualities under normal circumstances, but it may cause apoptosis in some cells [402]. Zinc injected into the synaptic cleft, for example, enters post-synaptic channels quickly in neurons, causing the production of extremely neurotoxic ROS and inducing cell death [376].

The environment also affects zinc's effects because many reports show that, in contrast to its anti-apoptotic effects in normal cells, zinc promotes apoptosis in malignant cells like ovarian, pancreatic, and prostate cancer cells [376]. Cell apoptosis is determined by a number of cellular events, including cell cycle arrest, decreased expression of anti-apoptotic proteins, and increased expression of

pro-apoptotic proteins. In neurons, low zinc conditions are closely linked to decreased phosphorylation of ERK and AKT, downregulation of NF-kB-dependent pro-survival genes, and activation of caspase-3 [390]. Zinc can also activate proliferative and pro-survival molecules like ERK, AKT, and NF-kB, as well as regulate apoptosis-regulating factors like p53, caspases, and the BCL-2 family of anti-apoptotic and pro-apoptotic proteins [403].
Although the precise process causing apoptosis is unknown, two well-known starting causes include DNA damage and p53 activation [404]. Zinci is involved in stabilizing and activating p53, and insufficient or excessive zinc levels can lead to p53's misfolding, ultimately resulting in its loss of function [405]. Therefore, although p53 is upregulated under zinc deficiency, it is often accompanied by protein activity dysregulation [398]. P53 accumulates in the cell nucleus in response to stress signals like DNA damage, binds to specific DNA regions, and regulates the expression of effector genes associated with anti-proliferation, DNA repair, apoptosis, and senescence [405]. Zinc tightly regulates the structure and activity of p53, and only when zinc is at an appropriate level can p53 function normally. A previous study demonstrated that low intracellular zinc levels increase DNA damage and p53 expression while impairing p53's ability to bind to target cells [406]. Therefore, elevated p53 levels may be a stress response to increased DNA damage under conditions of zinc deficiency.

Zinc and DNA Damage

As an auxiliary factor or substrate for enzymes involved in DNA repair, methylation, and synthesis, zinc plays a critical role in preventing DNA damage caused by endogenous and exogenous factors [407]. The presence of zinc as a component of several DNA-interacting enzymes suggests that zinc may be involved in the regulation of DNA damage and repair processes [408]. One of the main types of DNA injury is DNA oxidative damage. As a component of SOD1 and SOD3, zinc catalyzes the conversion of superoxide anions to hydrogen peroxide, limiting the production of harmful free radicals and their derivatives (such as hydroxyl or peroxynitrite radicals). Zinc has considerable antioxidant action. Potentially positive effects on zinc-dependent antioxidant enzymes, including plasma SOD (pSOD) and erythrocytic SOD (eSOD), were found in a research examining the effect of zinc supplementation on antioxidant enzyme activity in healthy elderly people [409]. Additionally, transition metal-catalyzed redox reactions are inhibited by zinc, which competes with oxidative-active transitionmetalslikeFe2+andCu+forbindingsitesonmembranes,
Zinc also works as a physiological inducer of MTs, which maintains zinc homeostasis and lowers oxidative stress [410]. This limits their capacity to transfer electrons to H2O2 in the Fenton reaction, hence lowering ·OH production [396]. The Keap1-Nrf2 signaling pathway is another way that zinc has antioxidant effects. Nrf2 is a crucial transcription factor that protects cells by controlling the expression of genes that code for antioxidant proteins and enzymes, including GSH and SOD [383]. Usually, Nrf2 is suppressed by attaching to the zinc-binding protein Keap1. In circumstances of oxidative stress, the
The Nrf2-Keap1 combination is disrupted when several cysteine residues in Keap1 oxidize, causing structural alterations that liberate Zn2+ and cause Nrf2 to separate from the complex [397].
increases the production of antioxidant proteins and, eventually, protects cells from ROS damage by activating Nrf2 and its subsequent nuclear translocation, which causes Nrf2 to connect with antioxidant response elements (ARE) in the promoter regions of target genes.

[397].
It is notable that zinc's significance in maintaining genomic integrity and function extends beyond antioxidant damage prevention. Zinc is a structural element and necessary cofactor for several DNA-binding proteins as well as DNA damage response (DDR)/repair proteins. Zinc is also essential for the proper functioning of DDR proteins like PARP1,8-oxoguanineDNAglycosylase (OGG1), apurinic/apyrimidinic endonuclease (APE), xeroderma pigmentosum complementation group A (XPA), replication protein A (RPA), p53, and DNA ligase III. It is also a structural component and cofactor in enzymes involved in base excision repair (BER), nucleotide excision repair (NER), single-strandbreak (SSB), and double-strandbreak (DSB) repair [411]. Two unique zinc fingers on PARP1, the main sensor for SSBs, are able to identify and attach to damaged DNA [412]. The dual-function DNA glycosylase OGG1, a zinc finger protein, is mainly engaged in the BER pathway by identifying and eliminating 8-oxo-7,8-dihydroxydro-2'-deoxyguanosine (8-OHdG) from DNA double strands [413]. Within the BER pathway, APE2, which has a zinc finger domain, takes involved in the repair of DNA damage caused by H2O2 [406]. A key protein in the NER pathway, XPA also has zinc finger motifs that are essential for identifying and binding to DNA single-strand regions from helix destabilization damage and for attracting other proteins, such as RPA [414]. In addition, under irreparable damage conditions, p53 either triggers cell apoptosis or senescence

[415] or induces the expression of repair genes. Genomic stability is impacted by zinc deficiency because p53 failure prevents DNA damage from being effectively eliminated [406]. The interaction between zinc and other ions

Iron and zinc

Iron and zinc are vital trace metals that the human body needs for a variety of physiological and biochemical processes. It is important to note that certain zinc transporters may also be implicated in iron homeostasis. ZnTs and ZIPs are the primary mediators of the transfer of zinc-containing organisms [416]. According to earlier research, ZIP14[417] and ZIP8[216] may have iron-transporting properties. The primary basolateral efflux protein for iron is FPN, and studies show that zinc therapy increases the expression of the divalent metal transporter (DMT1) and stimulates iron export via FPN, hence promoting iron absorption [418]. For the control of iron homeostasis, iron regulatory proteins (IRP) are essential. Zinc may disrupt IRP1's iron-responsive element (IRE)-binding activity [419], which would increase FPN expression by preventing IRP1 from binding to the IRE in the FPN. Ferroptosis is a novel mode of death that differs from necrosis, pyroptosis, and apoptosis. Iron overload may cause ferroptosis by generating reactive oxygen species (ROS) through the Fenton reaction and lipid peroxidation of polyunsaturated fatty acids (PUFA) on the cell membrane. Additionally, ferroptosis suppressor protein 1 (FSP1), glutathione peroxidase 4 (GPX4), acyl-CoA synthetase long-chain family member 4 (ACSL4), and glutamate antiportersolute carrier family 7member 11 (xCT) also prevent ferroptosis by stopping the production of ROS [8420,421]. In a genome-wide RNAi screen of ferroptosis, zinc-related genes were examined, and ZIP7 was shown to be a new genetic determinant of ferroptosis. By encouraging ER stress-mediated overexpression of homocysteine-responsive ER-resident ubiquitin-like domain member 1 protein (HERPUD1), ZIP7-protected cells may be genetically and chemically inhibited against ferroptosis. Zinc can also eliminate the ferroptosis protection following ZIP7 knockdown.

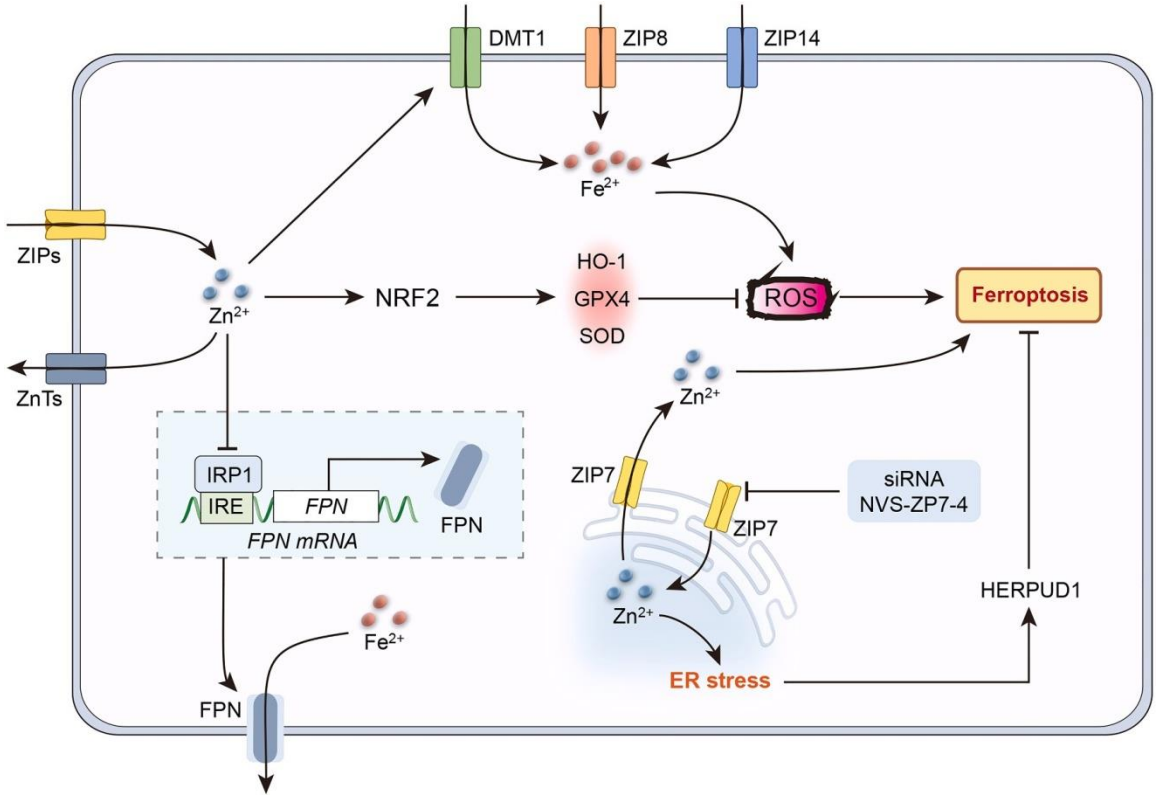


**Fig. 1.Zinc involves in iron metabolism and ferroptosis.**

By preventing IRP1 from binding to the IRE in FPN mRNA, zinc supplementation increases the production of DMT1 and FPN, which in turn controls cellular iron metabolism. Iron may be transported into cells via the zinc transporters ZIP8 and ZIP14, which might lead to ferroptosis. By activating NRF2, zinc may increase the expression of HO-1, GPX4, and SOD, which would habituate ROS production and consequent ferroptosis. Ferroptosis is sensitized by ZIP7-mediated ER z-flux, while inhibition of ZIP7 by

siRNA or NVS-ZP7–4 decreases ER z-flux and hence suppresses ferroptosis by enhancing ER stress-mediated HERPUD1 expression.

supplementation[422], indicating a role for the zinc redistribution mediated by ZIP7 in ferroptosis. Notably, a recent research discovered that zinc activates the Nrf2/GPX4 defense system, which attenuates ferroptosis and increases functional recovery in cases of continuous spinal cord damage. This suggests that zinc is a possible regulator of ferroptosis [423] (Fig.1). Dietary iron insufficiency has been associated to lower zinc levels and higher mRNA levels of ZIP14 in the heliver. On the other hand, excessive dietary iron consumption was linked to higher zinc concentration and up-regulation of ZIP5 expression, as well as down-regulation of ZIP6, ZIP7, and ZIP10 expressions in the heliver [188]. This suggests that iron may play a role in the control of zinc homeostasis via influencing ZIP expression. As they vie for absorption and distribution, zinc and iron do, in fact, exhibit antagonistic effects in many plants because of their molecular similarities. Iron and zinc interactions impact homeostasis and mineral absorption, which in turn impacts soybean plant development. Additionally, raising iron supply levels may reduce toxicity, and the elevation of ferric reductase oxidase 2 (FRO2) and Fe-shortage-induced transcription factor 1 (FIT1) expression may be crucial in reducing zinc-induced iron deficiency symptoms.
surplus of soybean plants [424].

Calcium and zinc

As previously indicated, extracellular zinc may attach to the cell membrane's GPR39 receptor to activate intracellular Ca2+ signaling [377]. Once attached, extracellular zinc stimulates inositol 1,4,5-triphosphate (IP3), which causes intracellular Ca2+ release and results in
controlling intracellular phosphorylation pathways, including PI3K/AKT and MAPK pathways, which are crucial for cell survival and proliferation [377]. The signaling cascades in neurons that arise from ZnR/GPR39 activation are also essential for synaptic transmission.

ticity, memory, and learning [379]. However, intracellular zinc pools can affect Ca2+mobilization in addition to the extracellular zinc that controls Ca2+signaling [425]. Micromolar doses of Zn2+ may prevent caffeine-induced intracellular Ca2+release in the smooth muscle of the guinea pigileum, indicating that the mechanisms controlling Ca2+

In cardiac myocytes, an increase in cytosolic Zn2+ released from the ER also controls the release of Ca2+ from calcium pools [425]. release may be downstream targets of Zn2+ [426]. Furthermore, Zn2+ may activate PKCin in a Ca2+-dependent way during cell proliferation, which suggests that Zn2+ might control cell mitosis via Ca2+signaling [394]. Ca2+ signaling may be positioned ahead of Zn2+ signaling, even though zinc signaling often plays a role in controlling downstream Ca2+ signaling. For example, when Ca2+/calmodulin promotes nitric oxide

Protein-bound zinc is released by nitric oxide (NO) synthase (NOS), which in turn triggers the release of intracellular "zinc waves" to control phosphorylation signaling [381]. Zinc may activate antioxidant and repair processes in the heart, since an increase in intracellular free Ca2+ causes Zn2+ release and ROS formation [427].
Cellular Redox Balance Response Store [381].

Copper and Zinc

Cu2+-containing enzymes are essential for many physiological activities. The copper/zinc-binding SOD is an unusual enzyme that converts superoxide anion radicals into hydrogen peroxide by catalyzing their dismutation [428]. Superoxide anion radical conversion is crucial in living cells because, despite the low activity of these radicals, their derivatives, like hydroxyl radicals (·OH) (through the Fenton reaction), can harm essential biomolecules like DNA, lipids, and proteins. In a study on age-related muscle mass and strength, mice deficient in SOD showed age-related muscle mass and functional loss [429]. Additionally, research on the Copper-zinc interaction indicates that the Cu2+/Zn2+ ratio is
a predictor of death and disability in the elderly [430]. Furthermore, a high zinc intake may change the body's copper balance in different organs [431], and zinc application can reduce copper toxicity by controlling copper absorption, antioxidant enzyme activity, and enhancing summer squash physiological traits [432]. It is uncertain, therefore, whether zinc may control copper toxicity in mammalian cells.

Manganese and zinc

As previously established, the zinc transporters ZIP14 and ZIP8 contribute in manganese transport in addition to iron transport [433]. The zinc transporter ZNT10 also plays a role in the intracellular Mn2+ efflux [434,435]. Human mutations
It has been discovered that the ZIP8, ZIP14, and ZNT10 genes cause hereditary anomalies in manganese metabolism. Pathological investigations including ZNT10, ZIP8, and ZIP14 have shown mutations in the ZNT10 gene in Parkinson's syndrome patients, who have an excessive build-up of manganese in their liver and brain [121]. Patients with progressive childhood-onset parkinsonism-dystonia and manganese over-accumulation have also been discovered to have ZIP14 mutations [287]. In addition to controlling zinc homeostasis, these genetic disease results indicate that ZIP8, ZIP14, and ZNT10 are essential for preserving the body's regular manganese metabolism. Considering the expressions of ZIP8, a prior research found that zinc protects HepG2 cells against manganese-induced cytotoxicity, presumably as a result of manganese's lower bioavailability [436].

The Zn2+ content controls ZIP14 and ZNT10; zinc may prevent manganese-induced cytotoxicity by upregulating the ex-

ZIP8, ZIP14, and ZNT10 compressions. Since Mn2+transport involves the zinc transporters ZIP8, ZIP14, and ZNT10, manganese may also control zinc cytotoxicity by targeting ZIP8. Understanding the molecular mechanism of illnesses may be aided by studying the crosstalk between zinc and manganese, which is ZIP14 and ZNT10.

Otherions and Zinc

Through ZnR/GPR39, extracellular Zn2+ largely controls the intracellular transports of Na+, K+, and Cl-. When the cytoplasm is acidified, the expression of the Na+/H+exchanger (NHE) is increased to raise the pH within cells [437]. ZnR/GPR39 activation brought on by zinc may increase NHE activity in neurons and colonic cells [438,439].

so offering a Zn2+-dependent method of preserving intracellular pH stability. Moreover, the synaptic release of Zn2+ activates ZnR/GPR39 and increases NHEactivity, improving neural recuperation from acidity inside cells [438]. The K+/Cl-cotransporters (KCC) family is in charge of generating Cl-extrusion, therefore

preserving neuronal excitability, ion transport, and cell volume [440]. A crucial role for KCC2 in neurons is to mediate Cl-extrusion [441]. Zn2+ increases KCC2 expression by activating ZnR/GPR39, which in turn triggers a change in the hippocampal GABA(A) reversal potential that is hyperpolarizing [442]. Additionally, the basolateral side expresses KCC1, which facilitates the colon's absorption of Cl-. By increasing KCC1 activity, ZnR/GPR39 activation in colonic epithelial cells or tissues improves Cl-transport and lowers fluid loss during diarrhea [443].

3. Zinc dysmetabolism's effects on neurodegenerative diseases

ZincandAD

The most prevalent neurodegenerative disease, AD, is characterized by the formation of neurofibrillary tangles (NFTs) by hyperphosphorylated tau protein and the deposition of Aβ asenile plaques in the extracellular space [444]. Aβ is made up of 39–43 amino acid residues and is produced by amyloid precursor protein (APP) through the sequential proteolysis of β-secretase and γ-secretase. The two most prevalent types seen in senile plaques are Aβ40 and Aβ42; however, Aβ42 is more cytotoxic and more prone to form oligomers than Aβ40 in vivo [445]. Ectopic Aβ

buildup in the brain causes neuroinflammation, synaptic dysfunctions, oxidative stress, and neuronal death, all of which are factors in the development and course of AD [8], [446]. In addition to Aβ, hyperphosphorylation of tau is another risk factor for AD. Tau is a microtubule-associated protein that is widely expressed in the central nervous system and regulates microtubule homeostasis and axonal transport [447,448]. Hyperphosphorylation of tau is more conducive to aggregate in the neurons to form NFTs that cannot be broken down by proteases, which causes disruptions in axonal transport, microtubule synthesis, and synaptic plasticity, ultimately leading to neurotoxicity and neurodegeneration [8449]. Interestingly, Aβ could effectively accelerate tau hyperphosphorylation and spread [450], and tau could mediate the cytotoxicity of Aβ[451], indicating that Aβ-tau interactions promote the development and progression of AD.

80% to 90% of Zn2+ in the brain is tightly bound to proteins to enhance enzymatic activity or provide structural stability, while the remaining 10% to 20% of Zn2+ is mostly deposited in glutamatergic nerve terminal synaptic vesicles, where it is released during neural activity to control several biological processes and synaptic transmission [452]. Zinc has both neuroprotective and neurotoxic effects, and changes in the amount of zinc in the cytosol are linked to the progression of AD [453]. Zinc homeostasis disruption inside cells may significantly impair cognitive function and lead to neurodegenerative diseases. disorders [46,454]. It has been discovered that the main role of Zn2+ released at synapses can inhibit glutamate signaling, and the reversal of this inhibition can cause glutamate-mediated excitotoxicity, ultimately leading to toneuronal death [455]. Research has shown that dietary Zn2+ supplementation can lower the levels of tau phosphorylation and Aβ in the hippocampal regions and markedly improve memory function that is reliant on the hippocampus in transgenic mice with AD [456]. On the other hand, elevated Zn2+ concentrations may greatly increase Aβ's neurotoxicity [457].

Iron, copper, and zinc concentrations in Aβplaques in the hippocampal region of APP/PS1transgenic mice were found to be significantly higher in the plaques than in the surrounding neutrophils. Only the zinc level remained elevated in the plaques after adjusting for tissue density [458].

Zn2+ binding to Aβ decreases its solubility, aggravating neuronal damage by increased Aβ aggregation [459]. Aβ also causes mitochondrial and lysosomal dysfunction and a rise in intracellular concentrations of Zn2+ and Ca2+. Nevertheless, these Aβ-induced events are efficiently inhibited by the Zn2+-specific chelator TPEN [460], indicating that zinc may indirectly control Aβ cytotoxicity.

In addition to modulating Zn2+-dependent Aβaggregation, intelligent resveratrol-loaded supramolecularvesicles (RES-

loadedvesicles) with a Zn2+chelation function also reprogramme macroglia from a proinflammatory M1 phenotype to an anti-inflammatory M2 phenotype,thereby reducing cognitive impairment in AD mice models [461]. Additionally, Zn2+ plays a role in APP processing, aszinc promotes APP-C99 dimerization via blocking the formation of Aβ by directly binding to the histidine residues His-6, His-13, and His-14 of APP-C99. Zinc, however, significantly increases the production of aggregation-prone Aβ43, which is present in the senile plaques of AD brains, at a concentration of 15μM. Zinc also raises the Aβ43:Aβ40 ratio by binding to Lys-28 of APP-C99[462]. ADAM10 mediatesthenon-amyloidogenic pathway of APP, and mutation of the zinc-binding site in ADAM10 significantly reduces its activity [463], indicating that zinc levels may also regulate Aβ production by modulating ADAM10 activity. Zinc can also activate matrix metalloproteinases (MMPs) to promote the maturation of brain-derived neurotrophic factor (BDNF) via a pathway that affects BDNF signaling, which raises BDNF levels in AD mouse brains and ultimately delays hippocampal-dependent memory deficits [456]. Together, these results imply that although zinc may prevent Aβ generation at a specific dose, excessive zinc exposure may increase Aβ43 production and Aβ aggregation in neurons.
Additionally, too much zinc can cause aggregation and the development of

NFTs. According to earlier research, Zn2+ forms short filaments and oligomers by exhibiting a moderate binding to the third repeat unit of tau's microtubule-binding domain (R3) [464].
Compared to Zn2+ or R3 alone, Zn2+-bound R3 dramatically increases endogenous Aβ and taupathology and results in neuronal damage [465].
Additionally, via activating GSK3β, ERK1/2, and JNK, zinc may enhance the phosphorylation of tau protein [466,467]. Additionally, zinc promotes hyperphosphorylation of tau protein by inducing the inactivation of proteinphosphatase 2A (PP2A) via a Src-dependent mechanism (Fig. 2). Zinc chelators decrease tau phosphorylation and aggregation and block Src activation in transgenic mice with elevated production of mutant human tau protein [468,469]. Significantly, zinc supplementation was linked to lower risk and slower cognitive decline in individuals with AD and mild cognitive impairment [470]. The male APP/PS1 mice fed a zinc-deficient diet (3 mg/kg zinc) showed worsened memory deficits without altering the brain's Aβ burden. The mechanistic study showed that zinc deficiency in microglia increased the response of NLRP3 to inflammatory stimuli like Aβ oligomers, whereas zinc supplementation prevented this situation. Zinc-loaded nanoparticles also suppressed the production of IL-6 and IL-18 in APP23 transgenic mice, which is consistent with our findings [471]. According to our early study, zinc transporters and the development of Aβ plaques in AD are correlated. Zinc transporters (ZnT1,3,4,5,6,7) have been shown to be abundantly expressed in Aβplaques in the human AD brain and the APP/PS1 animal model [472,473]. Additionally, ZIP1 mRNA levels were significantly upregulated in the postmortem brain tissues of AD patients [474]. The outflow of zinc from presynaptic neurons and astrocytes may result from upregulation of ZnT1.
aggravating Aβdeposition. As Zn2+ availability declines in the neuronal cytoplasm, the induction of ZIP1 may be prompted to ingest Zn2+ from the external environment to preserve zinc homeostasis. Zinc may be released into the synaptic cleft when ZnT3 expression is upregulated, which may enhance Ca2+ influx into post-synaptic cells and eventually cause excitotoxicity in neurons [475].
Excessive zinc release from astrocytes and presynaptic neurons may trigger microglia and NOX and ROS generation in neurons, which can worsen neuronal death [140]. Zn2+ concentration in the extracellular space may rise as a result of the increase in ZnT6 levels.
and thus intensify Aβ deposition. However, elevated
ZnT6 expression may cause Zn2+ to enter the trans-Golginetwork (TGN), which might exacerbate Aβ aggregation [80]. Zinc has a function in
regulating glutamatergic neurotransmission and plasticity in glutamatergic neurons, where free zinc is loaded onto presynaptic vesicles by ZnT3. ZnT3knockout mice showed learning and memory deficits at 6 months of age, but not at 3 months, which were linked to significant decreases in key learning and memory-related proteins in the hippocampal region, suggesting that imbalanced synaptic zinc homeostasis mediated by ZnT3 may be one of the risk factors promoting AD pathology [52,476]. Studies have also reported a decrease in ZnT10 in the aging octopus brain, which may contribute to the formation of amyloid-like plaques, tau phosphorylation, and changes in glial homeostasis [477].
ZnT10 deletion inhibits Mn2+-induced neurotoxicity [479], and expression has been seen in the frontal cortex of APP/PS1transgenic mice [478], indicating that modifications in the expression of specific ZnT
Interestingly, MT3 expression levels in neurons are much lower in AD brain tissues [480], whereas the number of glial cells positive for MT1 and MT2 rises in the cortical areas of early-stage AD patients [481]. Family proteins may possibly contribute to AD pathophysiology via zinc-independent processes. The observed downregulation of MT3 in AD neurons may worsen AD pathophysiology via oxidative damage since MT3 controls zinc in a copper-related way, where zinc in MT3 may exchange with copper in Aβ-Cu complexes and decrease oxidative damage produced by Aβ-Cu complexes [482].

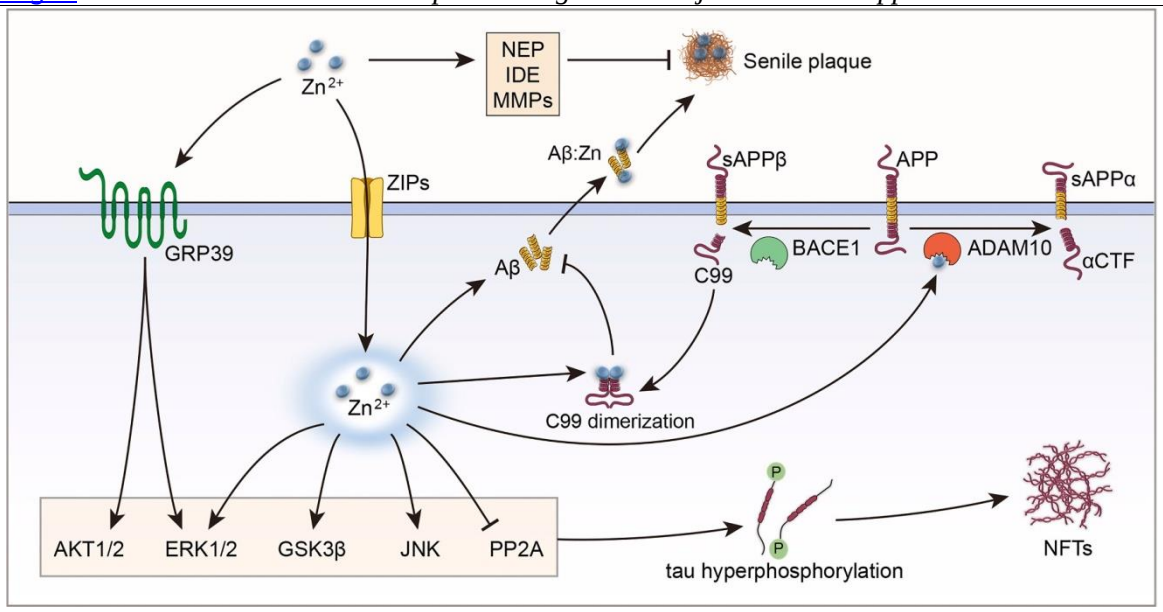


**Fig.2.ZincdysmetabolismpromotesADprogression.**

By activating GRP39, zinc enhances the activation of AKT1/2 and ERK1/2. Zinc also inhibits PP2A activity, which promotes tau hyperphosphorylation and the development of NFTs, and zinc coverload also stimulates the activation of ERK1/2, GSK3β, and JNK. Zinc may inhibit the synthesis of Aβ by encouraging the dimerization of C99 and support the non-amyloidogenic pathway by activating ADAM10. Additionally, to prevent Aβ deposition, the zinc-binding proteins MMPs, IDE, and neprilysin (NEP) might directly destroy Aβ. On the other hand, zinc excess could encourage the development of senile plaque by directly binding to Aβ. ZincandPD

After AD, PD is the second most common neurodegenerative disease. It is a progressive neurodegenerative illness. Bradykinesia, stiffness, and tremors are common motor symptoms of Parkinson's disease (PD), and its pathological hallmarks include the formation of Lewybodies (LB), the deposition of α-synuclein, and the death of dopaminergic neurons in the substantia pars compacta [483–485]. Aggregation and misfolding of α-synuclein are strongly linked to the pathophysiology of Parkinson's disease. α-synuclein is a 140 amino acid protein with three distinct regions: a highly acidic C-terminal domain, a central hydrophobic region, and a positively charged N-terminal region. It is primarily found in the presynaptic terminals of neurons and is essential for vesicular packaging and trafficking as well as synaptic plasticity [486]. It is believed that α-synuclein oligomers are the toxic species that can cause neurodegeneration by inducing microglial activation, oxidative stress, mitochondrial dysfunction, synaptic deficits, and dopaminergic neuron loss [488]. Post-translational modifications of α-synuclein, such as phosphorylation and nitration, favor its oligomerization and aggregation [487]. Furthermore, these oligomers may cause α-synuclein disease in linked areas across the brain [489,490]. Targeting α-synuclein aggregation has therefore been identified as a promising therapy approach for Parkinson's disease. Numerous studies have examined the role of trace in recent years. iron, zinc, and copper metals in Parkinson's disease etiology. These trace metals have been shown to encourage the production of free radicals, which causes oxidative stress and aids in the development of Parkinson's disease [491]. Excessive Zn2+ levels have been linked to dopami- Decreased dopamine levels and neurodegeneration in relation to Parkinson's disease [492,493]. PD patients had lower zinc levels in their blood, plasma, and cerebrospinal fluid (CSF) than healthy controls, according to meta-analysis studies [494,495]. Reduced levels of zinc in serum and plasma are associated with a greater chance of developing Parkinson's disease (PD). Older people who don't get enough zinc are more likely to develop PD. Moreover, conversion to dementia in PD patients is linked to decreased blood zinc levels [496]. Although excessive zinc consumption might have harmful consequences, the toxicity brought on by high zinc concentrations can be prevented by antioxidant therapy, zinc chelators, and overexpression of ATP13A2 [497]. One area of intense inquiry is the connection between zinc consumption and Parkinson's disease risk. Zinc consumption has been linked to a decreased risk of Parkinson's disease (PD) in a number of studies [498], although other research have indicated that high zinc concentrations do not diminish the incidence of PD [499,500]. According to earlier research, persons with idiopathic Parkinson's disease had an overabundance of zinc deposited in their striatum and substantia nigra [6501].

By controlling the transient A-type potassium (KA) channels, zinc exposure may alter the intrinsic excitability of dopaminergic neurons in the striatum and sub-stantia nigra [502]. Zinc exposure in male Wistar rats caused significant zinc accumulation in the substantia, which led to dopaminergic neuron depletion, decreased striatal dopamine levels, and increased α-synuclein expression and aggregation [493]. Zinc overload also increased TNF-α, IL-1β, and IL-6 expressions by activating the NF-κB signaling pathway, which resulted in behavioral abnormalities and decreased dopamine and its metabolites [503,504]. Additionally, the mechanism of dopaminergic degeneration caused by Zn2+
It is important to note that zinc, an essential component of SOD, catalyzes the conversion of superoxide anions into hydrogen peroxide and oxygen. Eration in the substantia nigra and striatum may also be related to the inhibition of neuronal NOS activity, and the use of NO donors can reverse dopamine depletion, tyrosine hydroxylase expression, and consequent behavioral changes [505]. Additionally, zinc can upregulate heme oxygenase-1 (HO-1) through the Nrf2 and BTB and CNChomology1(Bach-1) signaling pathways to inhibit dopamine-induced neurotoxicity [145]. Zinc supplementation can also reduce dopamine neurotoxicity by increasing the expression of MTs, which prevents the generation of ROS [507,508] and inhibit oxidative stress caused by 6-hydroxydopamine (6-OHDA) [506]. Furthermore, in cell cultures, zinc therapy may reduce the production of α-synuclein, the primary cause of methamphetamine-induced LB [509]. Since elevated zinc levels have been linked to exacerbated PD symptoms, the positive effects of zinc supplementation in PD may be explained by the restoration of zinc homeostasis within neurons. Zinc is released by the synaptic-specific zinc transporter ZnT3.

Co-released with neurotransmitters, synaptic vesicles function as modulators of neuronal transmission [510]. striatal neurons' synaptic Zn2+ release may be a factor in the behavioral, motor, and and memory abnormalities in mice, but ZnT3 knockout animals may mitigate the recall and motor impairments brought on by 6-OHDA [511]. Additionally, the influx may be triggered by activating alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionicacid (AMPA) receptors.
of Zn2+ into striatal dopaminergic neurons and substantia, so taking role in the processes underlying PD-like disorders brought on by 6-OHDA [512]. In mice injected with PD patient-derived LB-extracts carrying toxic α-synuclein aggregates, the consumption of a diet enriched with clioquinol, a zinc ionophore that facilitates the redistribution of zinc within cells, demonstrated a significant protective effect against dopaminergic neurodegeneration and alleviated α-synuclein-related pathology [3]. These findings suggest that disturbances in zinc metabolism in substantia nigra and striatal dopaminergic neurons may be potential risk factors for the pathogenesis and progression of PD, and that PD pathology may be effectively alleviated by modulating intracellular zinc redistribution.
The upregulation of MT1 and MT2 expression in astrocytes in PD patients and PD animal models may result in the release of MTs from astrocytes to dopaminergic neurons, preventing intracellular oxidative stress [323,513,514]. MTs may bind to copper in addition to zinc. Copper-induced α-synuclein aggrega-tion may be inhibited by MTs' competitive binding to copper, according to studies [515,516]. These results imply that by inhibiting α-synuclein aggregation and oxidative damage, MTs may ameliorate PD pathogenesis. Additionally, early signs of Parkinson's disease and dystonia have been linked to mutations in the zinc transporter ZIP14 [517]. Mice with intestinal-specific ZIP14 deletion, systemic and Mn2+ buildup has been seen in the brain. Defects in intestine ZIP14 expression may contribute to PD pathogenesis by boosting brain Mn2+ accumulation rather than Zn2+ buildup, as shown by the motor impairment and brain Mn2+ accumulation seen in ZIP14 knockout mice when supplemented with Mn2+ [518].

ZincandHD

The increase of CAG repeat sequences in exon 1 of the huntingtin (HTT) gene results in a mutation in the huntingtin protein (mHTT), which causes HD, a hereditary autosomal dominant neurodegenerative disease [519]. HD is characterized pathologically by significant atrophy of the caudate nucleus and putamen, glial proliferation, and neuronal loss in thestriatum, especially in medium spiny neurons (MSNs), as well as neuronal loss in late-stage cortical layers III, IV, and VI [520]. The longer the CAG repeat length, the earlier the onset and the faster the clinical progression of HD. A growing body of research has shown that mHTT causes HD through a variety of pathological mechanisms, such as altered axonal trafficking, early transcriptional dysregulation, synaptic dysfunction, oxidative stress, mitochondrial dysfunction, extra-synaptic excitotoxicity, and impairments of the proteostasis network and nuclear pore complex function [522,523]. However, clinical studies showed no discernible advantages from targeting these downstream pathways [524], indicating the need for the development of alternative treatment approaches for HD.
In the R6/1 model of HD, zinc deficiency exacerbates the disease progression by impairing hippocampal long-term potentiation

(LTP) and lowering the levels of AMPA receptors [527]. Vesicular zinc deficiency has been shown to induce neuronal apoptosis and impair memory in HD patients. Observations in HD patients indicate that zinc is involved in the progression of HD, as evidenced by reduced levels of zinc in the CSF and elevated levels of zinc in the blood [525,526]. ZnT3 expression in motor neurons is downregulated as a consequence of the mHTT blocking the transcription factor Sp1's binding to the ZnT3 promoter. As a result, synaptic vesicular zinc is depleted, which causes a decrease in neuronal dendritic spines, anomalies in postsynaptic density 95 protein (PSD95) and presynaptic synaptosome-associated protein 25 (SNAP25), early synaptic dysfunction, neurodegeneration, and cognitive decline [528]. Nonetheless, recent studies have shown that long-term zinc treatment successfully alters body parameters, improves locomotion, and reduces developmental delay in an HD model utilizing C. elegans [529]. According to these results, systemic zinc supplementation could not be a promising treatment approach for HD. Rather, a clinical study employing the zinc ionophore PBT2, which facilitates the intracellular redistribution of metals, supports the idea that cellular zinc redistribution might be a therapy option for HD [530].

Zincandals

ALS is a neurodegenerative illness that affects motor neurons in the brain, brainstem, and spinal cord. It is age-dependent. The most common genetic cause of familial ALS is a mutation in the SOD1 gene [531]. Although the precise etiology of this disease is unknown, a number of mechanisms have been proposed, including neuroinflammation, glutamate excitotoxicity, oxidative stress damage, mitochondrial dysfunction, protein misfolding and aggregation, and defects in neurotrophic factors [532]. About 5–10% of cases are familial, while 90% are sporadic.
Prior research has shown that people with ALS had significantly higher amounts of inzinc in their CSF [533,534]. Furthermore, it was shown that the spinal cords of individuals with sporadic ALS had lower expressions of the zinc transporters ZnT3 and ZnT6 [535]. Additionally, MTs levels were elevated in SOD1 mutant mice, whereas MTs knockdown showed lower survival periods and quicker disease development [536,537]. These results imply that zinc dysmetabolism plays a role in the development of ALS. SOD1 is a homodimeric metal enzyme, and each subunit has an active site that binds a structural zinc ion and a catalytic copper ion. SOD1 acquires enzymatic activity by dimerizing and binding to zinc and copper ions. Reduced affinity of the SOD1 protein for zinc is caused by mutations in the SOD1 gene. Motor neuron toxicity results from SOD1 being enzymatically inactive due to zinc loss from its active site [538]. When a supersaturated solution of components spontaneously splits into two phases—a dense phase and a dilute phase—that thereafter coexist steadily, the physical process known as protein phase separation takes place [539]. It has been shown that SOD1 builds up in stress granules (SGs) created by liquid-liquid phase separation (LLPS). Although zinc supplementation efficiently reverses these effects in both metal-free SOD1 and the ALS I113T mutation, zinc deficiency causes structural instability within two loop areas of SOD1, resulting in SOD1LLPS and aggregation [540]. Additionally, SOD1's membrane attachment via the two loop areas is greatly impacted by the lack of zinc, but not copper, which promotes aggregation caused by lipid-induced conformational changes [541]. Furthermore, mutations in the zinc-binding loop of SOD1 raise the risk of amyloid aggregation considerably and may also cause fibrillar aggregation and misfolding, two clinical features of familial types of ALS [542].
An essential part of the ER-associated degradation is Derlin-1.
machinery, interacts with SOD1's Derlin-1binding region (DBR). In a previous work, it was shown that pathogenic mutations in SOD1 associated to ALS cause persistent ER stress by means of particular interactions with Derlin-1. Interestingly, even the wild-type SOD1 has a comparable impact when zinc shortage is present, which may help to explain why zinc deficiency exacerbates ALS symptoms [543]. Additionally,
The coordination of zinc directly controls the folding process of the ALS-associated SOD1. First, Zn2+ catalyzes the folding activity by momentarily attaching itself to the copper ligands of SOD1, which are situated within the nucleus that folds. As the global folding transition occurs later in the folding process, the Zn2+ moves to the higher affinity zincsite, which develops considerably later. As a result, when a mutation occurs cursin the zinc-binding site of SOD1 or in conditions where zinc is deficient,

Zinc coverload in motor neurons is also reported, and it may directly bind to immature SOD1, encouraging its aggregation and consequent neurotoxicity [545]. SOD1 prefers to clump [544]. Zinc-modulated ALS development includes other signaling pathways in addition to SOD1. TAR DNA-binding protein 43 (TDP-43), a diverse, highly conserved
ALS patients' motor neurons often include aggregates of nuclearribonucleoprotein (hnRNP). Zn2+ may bind to the RRM domain

of TDP-43, facilitating solid-like phases separation (SLPS) of TDP-43C-ter-ALS is characterized by an imbalance in the nucleocytoplasmic distribution of splicing factor pro-line and glutamine-rich (SFPQ), and zinc may promote the cytoplasmic aggregation of SFPQ [548]. Minal fragments, therefore, contribute to neurodegeneration [546,547]. Notably, two SFPQ variants linked to familial ALS have been found, N533H and L534I, which cause amino acid changes close to the SFPQ zinc-coordinating core. These studies indicate that zinc dysmetabolism may also contribute to the progression of ALS by modulating SFPQ aggregation. Both variants exhibit increased zinc-binding affinities, and overexpression of these mutants significantly increases the formation of cytoplasmic SFPQ aggregates in primary neurons, resulting in dysregulation of AMPA receptor subunit composition [549] (Fig. 3).

A promising approach to treating ALS is to regulate copper and zinc metabolism in motor neurons. A previous study showed that SOD1G37R mice had copper deficiency in SOD1, and that treatment with diacetyl-bis(4-methylthiosemicarbazonato)copper(II)[Cu(II)(atsm)] greatly enhanced locomotor function and survival of the ALS mice by raising copper content in SOD1[550]. Crucially, zinc supplementation also reduced SOD1G37Rmice's ALS pathogenesis by promoting binding of copper to SOD1 [551]. These data provide a theoretical foundation for more research into the possible therapeutic benefits of Zn2+ supplementation in ALS.

Zinc and prion disease

Prion diseases are deadly neurological conditions that include kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinkers syndrome (GSS), chronic wasting disease (CWD) in deer, scrapie in sheep, and bovine spongiform encephalopathy (BSE) in cattle. Similar characteristics are shared by several prion illnesses, including a very lengthy incubation period, a delayed onset of symptoms, the development of amyloid-like plaques, and late-stage brain alterations that resemble sponges [552]. The buildup of aberrant scrapie-like prion protein (PrPSc) in the brain, synaptic degeneration, and spongiform degeneration of neurons and glial cells are the pathological hallmarks of prion illnesses [553]. A glycosylphosphatidylinositol (GPI) domain binds the 30–35 kDaglycoprotein that makes up the normal cellular version of prion protein (PrPC) to the cell membrane. The liver, heart, and brain are among the many parts of the body where PrPC is extensively dispersed. Mice deficient in PrPC have a range of neurological deficits, including memory loss, synaptic malfunction, and cerebellar Purkinje cell death.

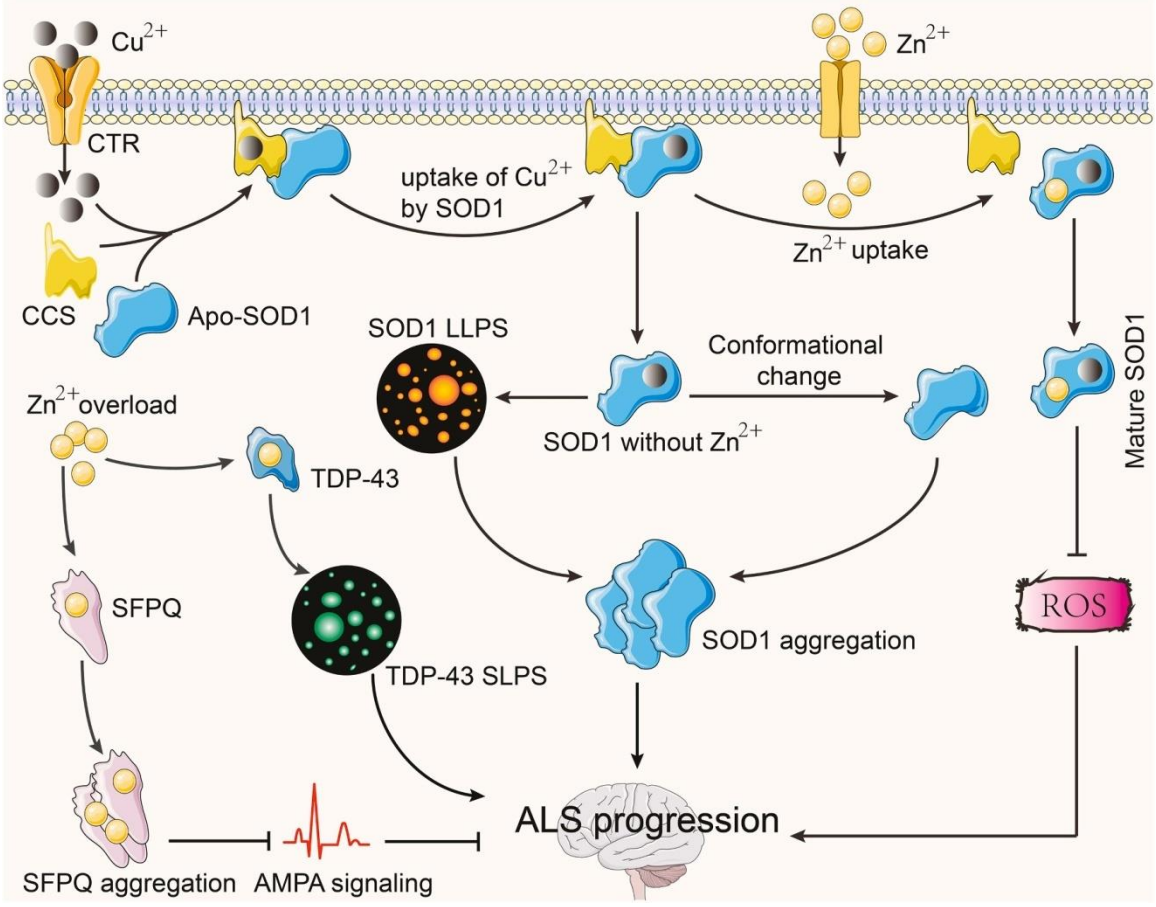


**Fig. 3.Zinc dysmetabolism promotes ALS progression.**

The copper inflow is mediated by the copper transporter (CTR). Through a copper delivery chaperone (CCS), the plasma membrane serves as an ascaffold during the copper transfer process to apo-SOD1 (metal-free non-functional SDO1). When there is enough zinc, SOD1 attaches itself to the zinc to acquire the catalytic capacity, which successfully prevents the production of ROS. When zinc levels are low, SOD1 is unable to bind to zinc, which causes SOD1 LLPS and conformational changes, which ultimately cause SOD1 to aggregate and hasten the course of ALS. Furthermore, by directly binding to TDP-43, zinc excess causes TDP-43SLPS to worsen ALS pathogenesis. Zinc overload also causes SFPQ to aggregate in the cytoplasm, which inhibits AMPA signaling and ultimately speeds up the development of ALS.
deficiencies [554,555]. The transformation of the normal cellular prion protein PrPC into the disease-associated isoform PrPSc is thought to be the pathophysiology of prion disorders. PrPC and PrPSc differ in their enriched β-sheet secondary structure, a tendency to form irreversible amyloid fibrils, and resistance to proteolytic degradation, even though they have the same chemical characteristics and primary amino acid sequences. Misfolded PrPSc evades proteolytic clearance and enters the central nervous system, where it assembles into aggregates and amyloid fibrils after entering the body by contaminated food or iatrogenic methods. The misfolding and aggregation of nearby PrPC molecules are further catalyzed by these abnormal conformers.
According to earlier research, PrPC is a metal-binding protein that is essential for preserving cellular metal homeostasis [556]. PrPC has been shown to improve neuronal cells' absorption of zinc [557]. At synapses, PrPC functions as a Zn2+sensor and co-immunoprecipitates with the GluA1 and GluA2AMPA receptors. so encouraging zinc inflow. Nevertheless, the capacity of PrPC to promote zinc uptake is reduced in cells that express mutant variants of the protein linked to familial prion illnesses and in cells infected with prion, indicating that PrPSc-mediated zinc signaling may be implicated in neurodegeneration [558,559]. Three main mechanisms allow PrPC to maintain neuronal zinc homeostasis: (1) zinc that undergoes simple diffusion during synaptic transmission attaches

to PrPC and is inertly sequestered before being transferred to high-affinity membrane transporters that help return the metal ions to intracellular stores;
(2) PrPC directly participates in zinc uptake through endocytosis, where a decrease in endosomalpH promotes the release of zinc from PrPC proteins into the cytoplasm. Apo-PrPC then recycles to the cell surface to obtain more zinc.
(3) PrPC also serves as a zinc sensor, tracking the levels of metal ions in the extracellular matrix. If the concentration of zinc surpasses a threshold, it sets off signaling pathways that increase the expression of metal transporter genes [560]. PrPC can cause MTs to be expressed, indicating that the conversion of
Zinc homeostasis regulated by MTs is disrupted in prion illnesses by PrPC to PrPSc. Research has shown that the presence of Zn2+ or Cu2+ during aging inhibits β-sheet formation by the PrP(106–126)peptide and lowers its neurotoxicity to rat hippocampus neurons in primary culture. Additionally, Zn2+ or Cu2+ reduces the production of amyloid-like fibrils by the PrP (106–126)peptide [552]. Additional research has shown that the binding of a single Zn2+ to the N-terminal domain of PrPC via four channels
In the C-terminal α-helices 2 and 3, tidine residues from the octarepeat region cause a structural change. N-terminal-C-terminal tertiary contacts in PrPC are driven by this transition, which may subsequently obstruct misfolding and the production of PrPSc [561,562]. Crucially, PrPC aggregation may be inhibited by substoichiometric zinc concentrations, but an excess of zinc can speed up the synthesis of cytotoxic fibrils. The formation of amyloid-like fibrillar structures by the PrP(58–93)peptide, which is derived from the unstructured N-terminal domain of human PrPC, is promoted by high concentrations of zinc [563]. Furthermore, the interaction between Zn2+ and PrPC has been demonstrated to generate large quantities of PrPC with low solubility, potentially changing the aggregate
PrPC aggregation structure and tion route [564,565]. Consequently, preserving cellular zinc levels within a typical physiological range may aid in the prevention of prion disorders.

Zincandepilepsy

Sudden abnormal neuronal discharges in the brain cause temporary deficits in brain function in epilepsy, a common chronic neurological condition [566]. Epilepsy is a chronic brain disorder that predisposes people to spontaneous, unprovoked seizures, which is different from a seizure, which is a brief episode of abnormal, excessive, or synchronized neuronal activity in the brain accompanied by signs and/or symptoms and can be triggered by a variety of factors like brain trauma, injuries, drugs, temperature, or hypoxia [567]. The main underlying cause of epileptic seizures

includes an imbalance between glutamate, an excitatory neurotransmitter, and GABA, an inhibitory neurotransmitter. Excessive neuronal firing and the start of epileptic seizures result from this imbalance, which interferes with neurons' normal ability to operate [568].
Zinc is closely linked to neuronal excitability and inhibition [571]. M-type potassium channels, also known as Kv7 or KCNQ channels, are protein molecules that regulate neuronal excitability. Intracellular zinc has been found to activate KCNQ channels. Patients with epilepsy have shown a significantly lower concentration of zinc. via lessening their need on 4,5-bisphosphate phosphatidylinositol [572]. Additionally, Zn2+ has been shown to alter the excitability of the hippocampus network and block synaptic GABAA receptors. Additionally, synaptically produced Zn2+ works as a neurotransmitter.
mitter signal by activating mZnR/GPR39, which raises Cl-transport and improves postsynaptic cell inhibitory tone [573]. In particular, Zn2+ has been shown to generate a concentration-dependent, noncompetitive, and reversible blockade of the
Dentate gyrus granule cells have a tonic current that is responsive to allopregnanolone. When Zn2+ is infused into the hippocampus, it may quickly cause epileptiform activity and drastically alter the antiseizure effects of medication. nanolone in the epileptic kindling model [574]. Similarly, zinc preferentially blocks extrasynaptic δGABA-A receptors in the hippocampus, reducing the antiseizure effects of ganaxolone [575]. These results suggest that zinc modulates neuronal excitability in a variety of ways, which may have consequences for our knowledge of and approach to treating epilepsy.
Seizures that often start in the hippocampus and cause neuronal death there are some of the symptoms of temporal lobe epilepsy [576]. An increase in extracellular glutamate concentration in the hippocampus causes individuals to have spontaneous seizures.

[577], and glutamate is promoted by synaptic release of Zn2+ release, which makes seizure activity easier [573,578]. Inhibiting ZIP3 expression lowers the absorption of Zn2+ by dentate granule cells from synapses, which benefits mature neurons. Following kainic, removing CA3 neurons from the neurodegenerative effects convulsions brought on by acid [579]. Additionally, another research showed that ZIP3 deletion decreased Zn2+uptake by hippocampus CA1 neurons and relieved CA1 cell damage brought on by kainic acid [168]. Moreover, TC-G1008 has been shown to worsen pentylenetetrazol (PTZ)-induced epileptogenesis by specifically targeting GPR39, as documented in a prior work [580]. Additionally, the deletion of ZIP1 also mitigates seizure-induced neurodegeneration in hippocampus tissue [168]. Further studies showed that whereas chronic treatment of TC-G 1008 raised the maximum seizure severity and the proportion of totally kindled animals on a zinc-adequate diet, acute administration of the drug lowered the seizure threshold in mice on a zinc-deficient diet [581]. These results suggest that the TRPM7-mediated zinc translocation has a role in neuronal death during seizures, and that disruptions in systemic zinc levels contribute to epilepsy. By preventing zinc buildup in neurons, TRPM7 inhibitors have been shown to decrease seizure-induced cell death [582]. Furthermore, in male Wistar rats, large dosages of PTZ-induced convulsions for three weeks cause inflammation, apoptosis, and neuronal loss in the hippocampus. Supplementing with zinc worsened these effects and further decreased SOD activity [583]. On the other hand, the latency to forelimb clonus was enhanced and the severity of pilocarpine-induced limbic seizures was reduced by modest dosages of zinc and valproic acid, either alone or in combination [584]. The loss of neural zinc signaling may accelerate the course of epilepsy, as shown by the notable enhanced vulnerability of adult mice missing the zinc receptor mZnR/GPR39 to seizures induced by a single intraperitoneal injection of kainic acid [585]. In fact, compared to wild-type mice, ZnT3-null mice are more prone to seizures brought on by kainic acid [586]. Hypozincemia may also cause seizures by preventing the formation of the

inhibitory neurotransmitter GABA, SOD, and glutathione peroxidase (GSH-Px)[587], and oral zinc supplementation has been demonstrated to shorten seizure duration and increase the latency of PTZ-induced seizures [588]. Additionally, a kindling model of epilepsy has shown that hippocampus zinc infusion delays the development of after discharges and seizures [576], and a similar antiseizure effect has been observed with intraperitoneal zinc administration in a PTZ-induced rat model [589]. Taken together, these research findings highlight the critical regulatory role of zinc in epilepsy. Zn2+ levels, it is feasible to affect the incidence and development of seizures, providing new approaches and methods for treating epilepsy.

Zincandstroke

There are two primary forms of stroke: ischemic stroke and hemorrhagic stroke. Stroke is an acute cerebrovascular illness that is defined by an abrupt rupture of cerebral blood vessels or a blockage of blood flow to the brain, resulting in damage to brain tissue. About 80% of strokes are ischemic strokes, which may be brought on by a number of conditions, including atherosclerosis, cardioembolism, and blockage of tiny cerebral arteries [524,590]. Platelets and immune cells build up at the site of vascular damage in ischemic stroke, impairing the blood-brain barrier and causing neuroinflammation, microglial activation, and excitotoxicity, which eventually leads to neuronal death [591,592]. According to a research, ischemic stroke patients' blood zinc concentrations were considerably lower than those of age- and gender-matched healthy controls [593]. Low zinc levels may be a risk factor for ischemic stroke, as shown by subsequent studies that found an inverse relationship between blood zinc levels and the occurrence of the disease, especially in women [594]. Zinc is necessary for preserving endothelial integrity, and its deficiency can impair endothelial barrier function [597]. Zinc's antioxidant and membrane-stabilizing qualities help prevent metabolic and physiological imbalances in endothelial cells and combat atherosclerosis [595,596]. Prior research showed that zinc buildup in microvessels triggered the super-matrixmetalloproteinase-9/oxide pathway, which results in the loss of In rats with cerebral ischemia, endothelial cell death and tight junction proteins (occludin and claudin-5) are found in the cerebral microvessels [598]. Zinc is also produced from glutamatergic neuron synaptic vesicles during ischemic stroke, and its aberrant buildup triggers microglial activation [599]. Additionally, zinc aggregation in neuronal mitochondria causes mitochondrial malfunction, which in turn causes neuronal death [600,601]. Zinc release may

either directly encourage ROS development or activate NOX to increase ROS production under pathological circumstances of ischemic stroke, which can lead to brain injury [602]. Furthermore, it was shown that zinc colocalizes with ROS and interacts with them in a synergistic manner to increase ischemic brain damage in rats [603]. Additionally, zinc promoted angiogenesis during the healing stage of cerebral ischemia by dramatically raising the protein levels of HIF-1α, VEGF-A, and VEGF-R2 inastrocytes. This reduced brain atrophy and enhanced the recovery of neurological function [604]. Zinc buildup in the synaptic cleft of neurons in rats with middle cerebral artery occlusion (MCAO) sped up the development of brain infarction, but blocking excessive zinc release stopped brain damage after ischemic stroke [605]. Zinc may also worsen neuronal death in ischemic stroke and activate CDK5 by causing CDK5 phosphorylation in the hippocampus [606]. The release of inflammatory cytokines like TNF-α and IL-6 may be inhibited by zinc chelators through the activation of the PI3K/Akt/NF-κB signaling pathway in MCAOrats [607,608]. A prior study found that normobaric hyperoxia therapy reduces zinc accumulation in the penumbratissue, which in turn reduces ischemic injury in experimental models of ischemic stroke [609]. Zinc may promote neuro-inflammation to aggregate the progression of stroke. Furthermore, giving MCAO animals the zinc chelator ZnEDTA dramatically lowers infarct size, neuronal damage, and improves neurological function [610]. It has also been reported that Cerium (Ce)-doped Linde Type A (LTA) zeolite-based nanomaterials (Ce/Zeo-NMs) may reduce cerebral ischemia-reperfusion (I/R) damage by altering the oxidative and zinc microclimate [611]. As zinc homeostasis regulators, MTs can balance the body's free and bound Zn2+ following transitory cerebral ischemia. following an ischemic stroke, the levels of MT1 and MT2 increased by astrocytes and macrophages, shielding the organism from oxidative stress [612,613]. Additionally, exogenous MTs have been shown to be effective in preventing ischemic brain damage in a mouse model of stroke [614]. According to these findings, MTs may influence the nervous system's health in the event of a stroke by controlling oxidative stress reactions.

## 3. Zincchelators' roles in neurodegenerative diseases

The first metal ligand investigated for treatment of AD was clioquinol (CQ, Fig. 4A), a derivative of 8-hydroxyquinoline. CQ can cross the blood-brain barrier and has the capacity to bind Cu2+ and Zn2+. solubilize Aβplaques; additionally, CQ could lower Aβ production by APP, beta-site APP cleaving enzyme 1 (BACE1), and presenilin-1 (PS1) expression inhibition, which led to enhanced cognitive function in AD patients and animal models [615,616]. However, in a small randomized double-blind research, the CQ did not have any favorable clinical benefits on AD patients, and long-term CQ therapy resulted in sub-acute myelooptic neuropathy [617]. Notably, via activating the AKT/mTOR pathway, CQ was also shown to significantly ameliorate the motor and non-motor impairments in the MPTP-induced monkey model of Parkinson's disease [618]. Furthermore, CQ suppressed α-synuclein aggregation in animal models of Parkinson's disease and decreased dopaminergic neuron loss via lysosome and zinc redistributions in neurons [3619], indicating that CQ may possibly be a viable medication for the treatment of PD. [(dimethylamino)methyl]—8-hydroxyquinoline 5,7-dichloro-2-Cu2+ and Zn2+ are additionally chelated by the 8-hydroxyquinoline derivative (PBT2, Fig. 4B). PBT2 was used to slow the course of AD and HD. It quickly increased cognitive function with little negative effects. Mechanic investigations shown that PBT2 may lower Aβ levels by sequestering the Zn2+ that promotes the extracellular production of protease-resistant Aβ in AD patients in phase II double-blind trials [620]. [621] Zn aggregates, and lowers tau hyperphosphorylation by raising PP2A's phosphatase activity and protein level [622]. Additionally, phase II double-blind studies were used to examine the therapeutic benefits of PBT2 in HD. The results showed that PBT2 was safe and well tolerated, and that PBT2 at a dosage of 250 mg might enhance HD patients' cognitive function [530]. Regretfully, the PBT2 structure was changed upon large-scale production, much like the CQ, which may significantly limit the PBT2's potential uses [623].

Injection of Aβ1-42 into the lateral ventricle causes Zn2+ to enter dentate granule cells, which results in neurodegeneration in the hippocampal dentate granule cell layer, but co-treatment with either an internal zinc chelator (ZnAF-2DA, Fig. 4F) or an external zinc chelator (CaEDTA, Fig. 4C) successfully reversed the neurodegeneration in the dentate granule cell layer and enhanced the mice's cognitive function [624,625]. According to these research, ZnAF-2DA and CaEDTA may prevent Aβ-induced neurotoxicity by PD pathogenesis is promoted by extracellular zinc influx and sequestering zinc.

In nigrostriatal dopaminergic neurons, 6-hydroxydopamine-induced Zn2+influx and subsequent nigrostriatal dopaminergic neurodegeneration may be inhibited by CaEDTA and ZnAF-2DA [512]. The effects of therapeutic studies have assessed the effects of CaEDTA in patients with cystic fibrosis who have bloodstream infections and lung infections caused by pseudomonas aeruginosa [626,627]. As a result, ZnAF-2DA and CaEDTA may potentially be used in the therapeutic treatment of neurological illnesses. The cell-permeant zinc chelator TPEN (Fig. 4G) was demonstrated to

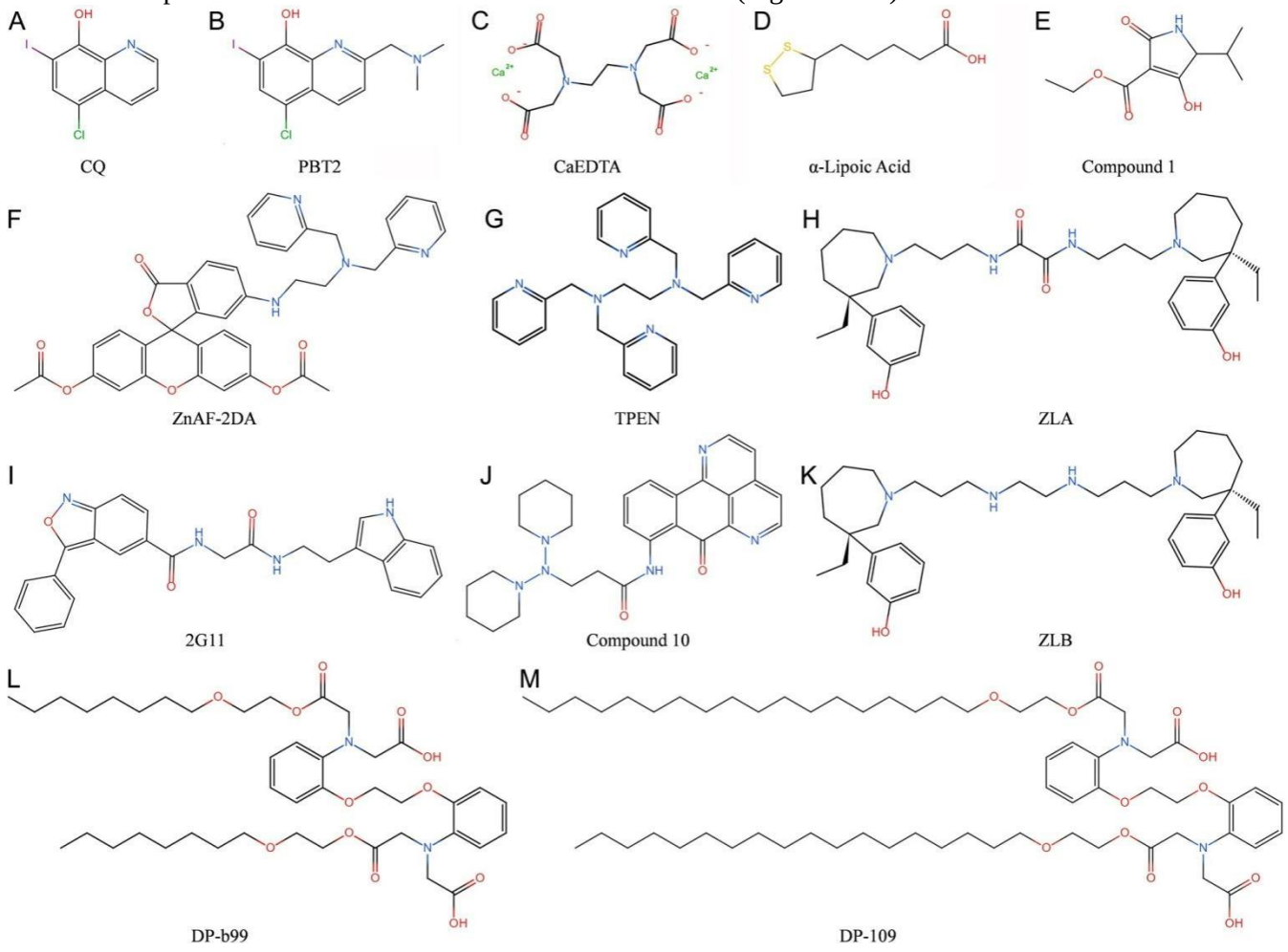


**Fig. 4.**Chemical structures of thezincchelators.

suppress the rises in intracellular Zn2+, Ca2+, and ROS levels brought on by Aβ25–35, hence preventing Aβ25–35-induced neuronal death [628]. However, zinc supplementation may fully reverse these effects. The high dose of TPEN (0.5–3 mM) caused neuronal death and glial cell death. These investigations also revealed that neuronal survival depends on zinc homeostasis.
2G11 is an isanovelzincchelator (Fig. 4I). In global cerebral ischemia (GCI) rats, 2G11 administration successfully inhibited the release of zinc from synaptic vesicles and AMPK phosphorylation, which in turn prevented hippocampal neuronal death [631]. It was also demonstrated to inhibit zinc-induced oxidative stress, excitotoxicity, and apoptosis in neurons [630]. Nevertheless, nothing is known about how 2G11 affects other neurodegenerative illnesses.
α-Lipoic Acid (Fig. 4D) is a Cu2+, Fe2+, and Zn2+ chelator. Our earlier research showed that α-lipoic acid enhanced the cognitive capacity of P301S tau transgenic mice by reducing oxidative stress, inflammation, and ferroptosis and boosting glucose availability [632,633]. Additionally, α-Lipoic Acid reduced Aβ-induced apoptosis and inflammatory stress in BV2 cells and increased the Aβ phagocytosis [634,635]. It is still unknown, nevertheless, whether α-lipoic acid might directly control the distribution of Zn2+ in the AD brain.
Potential pharmacological agents for neurodegenerative illnesses include lipophillic derivatives of the effective calcium chelator 1,2-bis(2-amino phenyloxyethane)-N,N,N′,N′-tetraaceticacid (BAPTA), DP-b99 (Fig. 4L) and DP-109 (Fig.

4M). Pre-application of DP-b99, a moderate chelator of Zn2+ and Ca2+, may significantly reduce the amount of Zn2+ in neurons and zinc-mediated neuronal death [636]. Additionally, by inhibiting MMP-9activity and modifying neural plasticity, DP-b99 postponed the onset and intensity of PTZ-induced seizures in mice [637]. According to a research based on a multicenter, double-blind, placebo-controlled, randomized trial, DP-b99 may help people recover from acute ischemic stroke without having serious side effects [638]. A disappointing outcome of a subsequent clinical study with more participants was that DP-b99 had no impact on the management of acute ischemic stroke [639]. In addition to Cu2+ and Ca2+, DP-109 can also chelate Zn2+. In Tg2576 transgenic mice, it was shown that DP-109 could lower the Aβ load and promote the conversion of Aβ from insoluble to soluble forms [640]. Additionally, by preventing neuroinflammation, oxidative damage, and neuronal death, DP-109 therapy enhanced motor function in an animal model of ALS [641]. 3-((S)—3-ethyl-3-(3-hydroxyphenyl)azepan-1-yl)propyl) N1,N2-bis(3-( N1,N2-bis(3-((S)—3-ethyl- 3-(3-hydroxyphenyl)azepan-1-yl)propyl)-ethane-1,2-diaminehydro-chloride (ZLA, Fig. 4H) and N1,N2-bis(3-((S)—3-(3-hydroxyphenyl)azepan-1-yl)propyl)-ethane-1,2-diaminehydro-chloride (ZLB, Fig. 4K) are the derivatives of apotent dualbinding site acetylcholinesterase (AChE) inhibitor bis-(—)-nor-meptazinol (bis-MEP), which can complex metal ions like Zn2+ and Cu2+. Zinc-induced Aβaggregation and AChE activity may be inhibited by ZLA and ZLB [642]. The twin roles of ZLA and ZLB provide significant promise for the management of neurodegenerative diseases. Unfortunately, there are presently no in vivo research on these compounds. A number of 8-aminoalkylamide ampangine derivatives were recently developed and synthesized; both compounds demonstrated strong chelating selectivity for Zn2+, high blood-brain barrier penetration capability, and strong acetylcholinesterase inhibitory action. Of them, compound 10 (Fig. 4J) has the best Zn2+ chelating activity and may significantly suppress Aβ-induced oxidative stress and inflammation as well as Zn2+-induced Aβ aggregation [643]. Tenuazonicacid (TA) is a naturally occurring substance with anti-oxidant and anti-amyloidogenic properties. The structure of TA served as the basis for the design and synthesis of compound 1 (Fig. 4E). Subsequent research showed that compound 1 is an excellent chelator of Cu2+, Fe2+, and Zn2+, and as such, has the capacity to prevent Aβ aggregation [644]. The zinc chelator's area of interest is tiny molecular peptides. The TEDELQDKIHP-Zn complex, a well-absorbed biological particle that facilitated the transepithelial transport of zinc, was formed when casein-derived peptides (TEDELQDKIHP) were shown to chelate zinc [645]. The illetbran protein hydrolysates also yielded anovelsmallpeptide (SDDVL), which demonstrated a better zinc transport capacity than ZnSO4 and zinc gluconate in Caco-2 cells and an outstanding zinc-chelating capacity (13.77 mg/g) [646]. The development of biopharmaceutical technology also led to the design and synthesis of several tiny peptides, including PLLK, PPMWPFV[647], DHTKE[648], and chicken skin collagen peptides (CCP)[649], each of which shown a potent zinc-chelating ability. Unfortunately, only a small number of them were studied for neurodegenerative disease treatment, which might be a goldmine of potential medications for future neurodegenerative disease treatment.

## 3. Findings and viewpoints

Since Zn2+ is the most prevalent metal ion in the brain and is implicated in Aβ dynamics, oxidative stress, cell death, excitotoxicity, and other processes, metal ion dysmetabolism is an undeniable risk factor for neurodegeneration. Zinc should thus get increased attention in the therapy or prevention of neurological disorders. A possible treatment approach for neurodegenerative illnesses may be to target ZIPs or ZnTs, given the imbalance of the zinc regulatory network. Notably, neural regeneration is a crucial healing technique for replacing the dead neurons, and neural loss is a notable characteristic of the majority of neurodegenerative illnesses. Since zinc controls cell division, altering the brain's zinc level may help neural stem cells proliferate and differentiate, slowing the onset of neurodegenerative illnesses by boosting their capacity for self-healing. Moreover, disruption of zinc homeostasis speeds up the advancement of neurodegenerative illnesses, potentially by lowering the capacity to repair DNA damage. Neuronal DNA damage was often seen over the course of these diseases. The metabolism of zinc may also accelerate the development of neurodegenerative illnesses by interfering with the ion currents of LTP neurons and interacting with other ions including Ca2+, Na+, K+, and Cl-. Furthermore, as a significant number of transcriptional factor and enzymatic activities depend on Zn2+ content, the functions of zinc demand further research. Molecular biology and integrated multi-omics technologies may be able to uncover additional physiological roles for Zn2+. For example, zinc-induced particular cell death may also occur in the cells due to the detection of cuproptosis and offerroptosis. All things considered, further research is required to fully understand the functional functions of zinc in neurodegenerative disorders.

By redistributing or lowering Zn2+ in the brain, zinc chelators are promising medications for the treatment of neurodegenerative illnesses. However, they lack the brain-targeting capacity and may have major adverse effects if used for an extended period of time. In order to combat neurodegenerative illnesses, zinc chelators may be better engineered utilizing nanotechnology or modified chemically. Few of the recently developed zinc chelators were used to assess the therapeutic effects on neurodegenerative diseases, which may be due to the researchers' limited scope of study. However, numerous groups have designed and synthesized numerous zinc chelators using click chemistry or molecular docking technologies. Therefore, research on zinc chelation-based treatments for neurodegenerative illnesses may be accelerated by the cooperation of scientists from diverse domains and the cross-integration of disciplines. Since there are several factors that contribute to the development and progression of neurodegenerative diseases, using a zinc chelator alone may not be enough, and using a zinc chelator in combination with other therapeutic medications, such as anti-oxidative or anti-inflammatory drugs, may have significant effects. Together, zinc chelators may play a key role in the progression of neurodegenerative diseases, and more research into the roles of Zn2+ and the targeting of zinc-induced events may help develop new approaches to treating these conditions.

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