Chapter

Iron Oxide Nanoparticles: A Mighty Pioneering Diagnostic Tool But Is It Really Safe for Carcinoma and Neurodegenerative Diseases?

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Abstract

Iron oxide nanoparticles have been used in medicine for around 90 years, and this time has demonstrated their versatility, therapeutic efficacy, and safety. The primary constituents of iron oxide nanoparticles (IONs) are either magnetite (FeO Fe2O3) or maghemite (-Fe2O3). The most major clinical application of IONs is based on MRI. To detect cancers and age-related diseases, IONs are being used in medical diagnostic imaging. The two IONs with the best clinical repute are Resovist and Feridex IV. In addition to being used to detect cancers, IONs are also adapted as gastrointestinal negative contrast agents and as slow-release iron supplements to treat iron deficiency anemia. With IONs exposed to alternating magnetic fields, targeted imaging and thermal energy production are both feasible. Radiation therapy, immunotherapy, or chemotherapy be facilitated by the effects of heat. A growing number of IONs are being studied in therapeutic settings as nanotechnology develops swiftly. How IONs are used in biomedicine is determined by their interaction with the human immune system.

Keywords: iron oxide, nanoparticles, MRI, diagnostic tool, role in cancer, neurodegenerative safety

1. Introduction

Due to their capacity to give anatomical (mainly dimensions) and functional characteristics of solid tumors and their environs, imaging biomarkers are becoming more crucial in cancer research. The characteristics of metabolism, tissue water diffusion, perfusion, chemical composition, and hypoxia are among those that PET, CT, and MRI may measure. Anatomical and functional information (physiological and pathophysiological) are only available with MRI, making it special. Noninvasive imaging probes like nanoparticles (NPs) have a lot of potential in this

field of study because they can be made to carry and release anticancer medications into the target tissue while also functioning as diagnostic tools by utilizing the physical and chemical properties of their constituents (or moieties) [1–4]. While further acting as tools for diagnosis. Clinical trial imaging biomarker-based response criteria ought to aid in directing early choices and reducing the likelihood that patients would get needless treatment. Size-based response assessment is typically ineffective in detecting responses in patients who are experiencing either cytostasis or pseudoprogression because it is frequently insensitive to early biological alterations. These situations are typically seen with innovative target therapy, where the cancer response is more variable than with cytotoxic drugs. Biological changes such apoptosis, necrosis, cystic degeneration, intralesional hemorrhage, edoema, and immune cell infiltration happen quickly after the start of treatment (up to 12 weeks later). It is possible that anatomical imaging would not be able to identify them, which could affect clinical outcomes. Judgment. Many of these modifications can be seen on MRI and may serve as preliminary therapeutic response indications. As a result, there is an urgent demand for particular MRI biomarkers for cutting-edge treatments.

This study will concentrate on one of the most fascinating uses of NPs in cancer imaging, specifically their role in the early evaluation of immunotherapy efficacy and their capacity to change macrophage polarization.

A cutting-edge therapeutic strategy called immunotherapy works by inducing an immunological response in cancer cells. The recruitment of immune cells to the tumor site, which may be accompanied by a decline in tumor growth, is a sign of an early response to immunotherapy. NPs' propensity to be internalized by inflammatory cells in vivo is correlated with their ability to act as diagnostic agents [5]. Their capacity to be internalized by various cells, both in vitro and in vivo, has been utilized for a variety of purposes throughout the previous 20 years.

As will be briefly stated in the first half of this study, the ability of iron oxide NPs to penetrate cells, including stem cells, can enable MRI detection of inflammatory cell recruitment and provide information on the fate of the cells when transplanted into living beings. Applications in cancer immunotherapies will be highlighted in the sections that follow. The final section of the study will focus on magnetic particle imaging (MPI), a cutting-edge tomographic imaging technique that uses iron oxide nanoparticles (NPs) as tracers and describes how iron oxide NPs can be directed toward lesions. MPI is anticipated to have a significant diagnostic role in cancer immunotherapy due to its high sensitivity.

2. Contrast-enhancing iron oxide nanoparticles for cellular imaging

Several iron-based MR contrast agents were created for MRI in the middle of the 1990s. They were referred to as ferrites, magnetites, ferumoxides, or superparamagnetic iron oxides (SPIOs) because they were often made up of tiny (30–200 nm) clusters of iron-containing crystals that formed single magnetic domains. Iron-based MR contrast agents are referred to as T2-relaxing contrast agents because they have higher transverse relaxivity and r2/r1 ratios than Gd chelates. They can also have a considerable effect on the T2 relaxation time since they considerably increase the inhomogeneity of the static magnetic field outside of their immediate neighborhood. On T2 weighted pictures taken close to the iron, iron oxide NPs therefore cause a signal attenuation (commonly referred to as the "blooming effect") [6].

Iron oxide nanoparticles (NPs) have been suggested as liver-specific contrast agents due to their size and affinity for collection by the reticuloendothelial system of the liver following intravenous injection [7]. Due to the variety of cells' ease of internalization, iron oxide nanoparticles (NPs) have been employed extensively during the past 20 years to identify and track cells administered as therapy for various disorders. A detailed summary of the experiment's approach, states that NPs are given to the medium for cell growth, maybe coupled with transfection agents. In terms of cellular iron content and cell survival, the ideal experimental parameters, such as incubation period, iron oxide NP concentration, and transfection agent addition, are identified.

Using MRI, the cells are tracked in vivo after being injected into the recipient's body [8]. The fate of many cell types, including stem cells [9–11], pancreatic islets [12, 13], dendritic cells [14], and even exosomes generated from stem cells [15, 16], has been investigated using this approach in a number of preclinical studies. Benefits and limitations of the approach have been demonstrated in preclinical research. The benefits of MRI include its high sensitivity, which can even detect single cells [17, 18], as well as its outstanding anatomical detail, which clarifies cell homing and allows transferability to the clinical setting [19].

The main drawbacks include the inability to differentiate between live and dead cells, the fact that MRI's signal void does not quantitatively report on the number of cells, label dilution due to in vivo cell replication, and the removal of iron oxide NPs that were previously approved for use as MRI contrast agents in clinical settings. [20] provides information on the most recent list of iron oxide (IO)-based contrast agents that have undergone clinical studies or received approval for use as MRI contrast agents as well as specifics on their intended purpose and current market position.

Another possibility is that SPIOs are absorbed by cells in vivo, where circulating monocytes that can enter tumors and transform into macrophages phagocytose iron oxide NPs that have been injected into the circulation. Consequently, immune cell recruitment in malignancies as well as in other organs and tissues can be detected using MRI. In a recent study, Kirschbaum et al. [21] have used high-field MRI to map inflammatory infiltrates in an experimental multiple sclerosis model using iron oxide NPs for cell tracking. They discovered an association between NP absorption and the innate immune cells-only disease's clinical severity. Their research opens the door for more accurate clinical and diagnostic treatment of a range of inflammatory diseases. in addition to therapeutic oversight [22]. Similar techniques have been applied in organ transplant experimental models, where the recruitment of macrophages is one indicator of transplant rejection. Additionally, studies have been done in clinical settings. In a recent clinical investigation, myocardial edoema and macrophage inflammation have been successfully visualized in patients who suffered myocardial infarction, utilizing T2 mapping and Ultrasmall SPIO-enhanced T2 MRI. The study concludes by showing that the technology can offer a noninvasive way to detect and track tissue inflammatory macrophage activity in the heart [23]. It is common practice to use iron oxide NPs to detect macrophages in solid tumors. This is because iron oxide NPs are not antibody-conjugated and can be administered directly into the vein and detected using a conventional 1 H radiofrequency coil and a T2 weighted sequence since they are primarily taken up by phagocytic cells like macrophages and Kupffer cells. To detect the spatial distribution of tumor-associated macrophages (TAMs) and quantify the amount of iron deposition, it is possible to collect a T2 map using a multi-gradient echo sequence. As an alternative, quantitative susceptibility mapping can be used to gauge the change in susceptibility brought about by the treatment by the contrast substance. Both of these methods have a linear correlation with the concentration of iron oxide NPs.

3. NPs' function in oncolytic virotherapy

Oncolytic virotherapy infects tumors with viruses, which kills cancer cells. Only attacking cancer cells is a capability of many distinct virus types. Along with this underlying effect, there is also significant inflammation in the cancer microenvironment. The tumor primarily targets the virus with the recruitment of inflammatory cells. The production of cancer-associated antigens as a result of virus-mediated cell lysis, however, may trigger an immune response that targets the tumor, such as by activating macrophages and T cells. The latter produce cytokines that actively stimulate the production of new immune cells as well as cancer cells. Both innate and adaptive immune responses produce an immunological memory that works in conjunction with the oncolytic action of the viruses to prevent cancer from coming back. Oncolytic virotherapy's effectiveness has been evaluated in a large number of preclinical and clinical investigations, mostly in patients with melanoma and brain tumors. Oncolytic virotherapy-induced intratumoral inflammation can be found using MRI. The effectiveness of oncolytic virotherapy may be monitored, virus sites can be indirectly identified and quantified, and new therapeutic virus strains can be improved utilizing 19F MRI [24] and iron oxide NPs [25].

Perfluorocarbon nanoemulsions (PFC) and 19F MRI were used by Weibel and colleagues [26] to establish a longitudinal, noninvasive monitoring of intratumoral inflammation during oncolytic virotherapy. By comparing in vivo and ex vivo 19F/1H MRI with histology, the authors demonstrated the potential of this imaging modality for the localization of the host immune response and for sentinel lymph node detection. Tumor viral colonization significantly altered the 19F signal distribution and intensity in solid tumors as well as in the nearby lymph nodes. Compared to virally infected tumors, which only displayed 19F-positive hot patches along the tumor margin, the mock-infected tumors had a uniform distribution of both the 19F signal and CD68 + -macrophages. The population of CD68+ macrophages displayed a similar pattern of distribution. According to our research, PFC NPs are more likely than intratumoral TAMs to detect circulating immune cells that enter the tumor after viral infection.

4. Magnetic particle imaging is a recent development in imaging technology

A new imaging method called magnetic particle imaging (MPI) has just been developed to find iron oxide nanoparticles (NPs). Some MRI flaws, such as poor specificity (caused by other low signal regions in MRI, such as hemorrhagic regions or those containing air) and challenging quantification, can be resolved with MPI. High tracer specificity is made feasible by leveraging MPI's direct detection of iron oxide NPs, which offer positive contrast without any underlying background signal from biological tissues. Iron (Fe) concentrations of 550 pg./L in vitro and 7.8 ng Fe in vivo, as well as detection limits as low as 1.1 ng Fe, have all been demonstrated. A static gradient field with a single, field-free parameter identifies signals in MPI. (FFR), which could be a line or a point. Then, using the particles already present in the FFR, a signal is produced by an oscillating magnetic field. Raster scanning the FFR throughout the entire field of vision produces images. Outside of the FFR, superparamagnetic particles are still fully magnetized and do not increase the signal [29].

Because MPI directly detects SPIO magnetization, the signal is very dependent on the SPIO tracer's physical characteristics. For NPs to be suitable for MPI, they must possess the following three characteristics: superparamagneticity, susceptibility to magnetic saturation, and a nonlinear magnetic curve.

Since many SPION agents for MRI have the aforementioned characteristics, their prospective application in MPI has been looked at. Resovist®, a previously developed MRI contrast agent for the liver, was used to produce the most efficient MPI [20]. Magnetic Insight, Inc. has unveiled VivoTrax®, a carboxydextran-coated iron oxide NP formulation, with the same reference standard. It is intriguing to note that MPI can locate the clinically approved ferumoxytol rapidly [30]. Other research teams are working to develop new MPI tracers as it was established that neither Resovist® nor VivoTrax® was the optimal MPI solution.

There are numerous MPI biological applications that are now being studied. Early cancers can be identified using MPI by utilizing the tumor's enhanced permeability and retention (EPR) impact [27, 28]. Due to the leaky capillaries with big holes that result in the EPR phenomena, tumor tissue is an excellent target for therapy with nanomedicines and nanosized contrast agents. As a result, MPI plays a crucial clinical role in the early detection of cancer.

Cell tracking is one of MPI's oldest and most promising applications due to its superior tissue penetration, absence of background noise, and high degree of sensitivity, which enables it to identify as little as 200 tagged cells. Recently, mesenchymal stem cells (MSCs) tagged with clinically relevant feromuxytol NPs have been found by Nejadnik et al. [31] using MPI. A noteworthy achievement for the therapeutic application of MPI technology was the precise in vivo identification and quantification of ferumoxytol-labeled stem cells.

5. Alzheimer's disease (AD)

The Alzheimer Association attributes 60–80% of dementia cases to Alzheimer's disease (AD), a degenerative brain illness. Depending on the stage of the illness, apathy, depression, decreased communication, disorientation, poor judgment, difficulties swallowing and walking, and behavioral changes are some of the characteristics that evolve to make doing daily tasks difficult [32, 33]. Age, genetics, and sex are some of the factors that influence how long it takes for a continuum of these symptoms to emerge, according to current estimates, and the COVID-19 pandemic has seen a 16% increase in the number of deaths (Alzheimer's Association, 2021). Amyloid-beta (Aβ) and tau protein buildup is linked to the progression of cognitive deterioration in AD. Beta-secretase and gamma-secretase sequentially cleave the amyloid precursor protein (APP), resulting in the formation of Aβ. Thus, the aggregation of Aβ produces hazardous oligomers for the neurons. Tau, on the other hand, is produced by alternative splicing from the soluble protein isoforms of the microtubule-associated protein tau (MAPT) gene. The damage to brain circuits and cognitive impairment in AD has been linked to a number of functional interactions between Aβ and tau. In the neuropathology of Alzheimer's disease, there is a loss of neurons and atrophy in the temporofrontal cortex, which results in inflammation and the deposition of amyloid plaques, an abnormal cluster of protein fragments, and tangled bundles of fibers. As a result, there is an increase in the presence of monocytes and macrophages in the cerebral cortex, and it also activates the microglial cells in the parenchyma [34–36].

6. Pathophysiology

The primary neuropathologic symptoms of AD include extracellular amyloid plaques, intracellular NFTs, synaptic deterioration, and neuronal death. Without detecting granulovacuolar degeneration in the hippocampus or amyloid buildup in blood vessels (congophilicangiopathy), the diagnosis can be made. According to the "amyloid cascade" idea, amyloid plaques interfere with synaptic transmission and trigger a series of following processes that eventually cause cell death.

7. Amyloid plaques

Even though amyloid plaques can be categorized into different groups depending on their structure, all types of -amyloid protein (A) are present in them. When APP is degraded proteolytically by - and -secretase, an amino acid peptide known as A is produced. The primary results of this cleavage are A1–40 and A1–42. The development of amyloid oligomers and fibrils, which come together to form amyloid plaques, is predisposed by a relative excess of A1–42. Since the generation, processing, and/or trafficking of amyloid is connected to the proteins encoded by APP, PS1, PS2, SorL1, and ApoE, this suggests that amyloid plays a significant role in the etiology of AD [39].

8. Neurofibrillary tangles (NFT)

Tau, a protein associated with microtubules, is required for normal neuronal development and axonal expansion. However, frontal association cortices, the lateral parietotemporal area, and the mesial temporal lobe (especially the hippocampus) neurons are where hyperphosphorylated tau protein aggregates are most frequently found as helical filamentous NFT. The relationship between the density and distribution of tau NFT and the symptoms and severity of AD dementia emphasizes the critical role of NFT in AD pathology.

9. Loss of neurons and synapses

Synapse loss and neuronal cell death have a similar distribution to NFT. Due to the death of neurons in the nucleus basalis of Meynert, acetylcholine (Ach), a neurotransmitter linked to memory, is decreased in typical AD. Most current therapies seek to remedy this cholinergic deficit. Serotonin and norepinephrine deficits result from the loss of neurons in the brainstem's locus ceruleus and median raphe. Dysfunctional serotonergic and adrenergic activity in the brain is probably the root cause of dysphoria and insomnia in AD [37, 38].

10. The metal ion theory

Metal dyshomeostasis has a role in the development and pathophysiology of illnesses, including as cancer and neurodegenerative disorders. A number of these compounds are employed in clinical studies. Ionosphere and metal chelators are

well-known modulators of transition metal homeostasis. Other medications besides the metal-binding ones can also target the homeostasis of transition metals. The balance of redox transition metals, primarily copper (Cu), iron (Fe), and other trace metals, is changing, according to current findings. In AD, their brain levels are observed to be elevated. Other neurological diseases also involve copper, manganese, aluminum, and zinc. The cholinergic theory Acetyl-cholinesterase inhibitors (AChEIs) and the impact of apo-lipo-protein E (APOE) genotype in Alzheimer's disease patients. The AchEI drugs are the cornerstone of AD treatment, and the most significant risk factor for AD is the APOE genotype [36].

11. Role of iron in AD

Iron is the most abundant transition element on Earth and one of the most important minerals in the body. It plays an indispensable role in many physiological and pathological processes of the body. Iron homeostasis is even more crucial in the brain to maintain its normal function. Iron dyshomeostasis within the brain can cause oxidative stress and inflammatory responses, leading to cell damage and finally neurological diseases. Ferroptosis, a programmed cell death process associated with iron dysregulation, has been supposed to be linked to neurological diseases, especially neurodegenerative diseases. Till date, it is impossible to explain AD with a single pathological path. Currently, metal dyshomeostasis in AD has been extensively studied. Studies have found intracellular iron deposition even before the formation of senileplaques and neurofibrillary tangles (NFT), and ferroptosis is proposed to be one of key causes of neuronal loss in AD patients [37].

12. Iron metabolism in healthy and Alzheimer's disease brain

About 48% of the iron in the body is bound to hemoglobin and is involved in oxygen transport in the body. About 17% of the iron is found as the cofactor in proteins to carry out functions in several crucial biological processes such as the tricarboxylic acid cycle, oxidative phosphorylation, DNA synthesis and repair, and iron homeostasis. In the brain, iron is involved in myelination, neurotransmitter synthesis, and antioxidant enzyme function, and its entry and exit are tightly regulated by a variety of molecules. Aging, inflammation, and oxidative stress, which disturb the functions of molecules involved in iron metabolism, present as the main contributors to iron dyshomeostasis. Iron transport across blood-brain barrier in the brain, transferrin receptor 1 (TfR1), responsible for the strict control of the level of iron transported into the brain, is expressed on the luminal side of the brain microvascular endothelial cells (BMECs) and the blood-cerebrospinal fluid barrier. After circulation, a complex was formed (holo-Tf) by iron with transferrin (Tf), it binds to TfR1 on the surface of the BMECs, followed by entry into the BMECs via clathrin-mediated endocytosis. Fe3+ detaches from Tf in the acidic environment of the endosome and is reduced to Fe2+ by six-transmembrane epithelial antigen of prostrate 3(STEAP3) or duodenal cytochrome b (DCYTB), both of which are metalloreductases. It then enters the cytoplasm via divalent metal transporter 1 (DMT1). Fe2+ in BMECs can then enter the brain by the secretion of ferroportin 1 (FPN1), followed by the oxidation by extracellular ceruloplasmin (Cp) or hephaestin. Non-transferrin-bound iron (NTBI) can cross the blood-brain barrier (BBB) via

receptor-mediated transcytosis after binding to heavy-chain ferritin (H-ferritin;Lf). It was also reported that Lf increased in the brains of aged individuals and those with AD, allowing large amounts of non-Tf-bound iron to enter the brain. Iron transport and storage within the brain neuronal iron metabolism TfR1 is highly expressed on the surface of neurons, and similar to BMECs, iron enters neurons via clathrin-mediated endocytosis of holo-Tf/TfR1 and exits the endosomes in the form of reduced Fe2+ via DMT1. NTBI can also enter neurons in a DMT1-dependent manner independent of Tf. Cellular prion protein (PrPC) is abundantly expressed on the surface of neuronal membranes. It functions as a ferrireductase partner for DMT1, mediating Fe2+ uptake in the plasma membrane in the form of complex PrPc/DMT1. PrPC knockout in mice can lead to iron deficiency in brain and uptake increase of holo-Tf. By comparing the brain tissues of juvenile, adult, and aged rats that had the pathological features of AD, it was found that DMT1 abnormally increased with age. They supposed that DMT1 may be one of the main reasons why the iron concentration in the brain gradually increases with age. Some Fe2+ undergo normal metabolism in the cytoplasm of neurons, while some are stored in ferritin in the form of nontoxic Fe3+; when neurons are low in iron, ferritin can be degraded by lysosomes to release the stored iron to meet the physiological needs of the neurons. Ferritin is positively correlated with iron overload and is found deposited in senile plaques in the AD brain. It had been shown that there was an age-dependent increase in ferritin in the brain, probably a contributor to the iron overload in aged and AD brains. Autopsy studies of AD patients have revealed that mitochondrial ferritin is upregulated. Ferritin in the cerebrospinal fluid (CSF) of AD patients has been shown significantly increased, which is negatively correlated with cognitive decline and hippocampal atrophy in AD. Additionally, iron can enter mitochondria to form iron ferroptosis and Alzheimer's disease sulfur cluster and participate in the process of aerobic respiration. Regarding the transport of excess iron out of neurons, FPN1 is the only known iron exporter to date. Both Cp and hephaestin (Heph) can oxidize Fe2+ and facilitate FPN1to export iron, so the FPN1/Cp and FPN1/Heph are the main iron efflux pathways. Decrease of any of these three export proteins can induce iron retention and consequently the memory impairment. It was reported that FPN1 was downregulated in the brains of AD patients and triple-transgenic AD mouse models; thus, excessive iron could not be excreted normally, initiating intracellular iron deposition. Since Cp is a crucial partner of FPN1 to oxidize Fe2+ before it is excreted by FPN1, the dysfunction of Cp serves as an upstream event of iron retention, which has been found in AD. Noteworthily, both of amyloid precursor protein (APP) and tau, which are the substrates of the AD hallmarks in pathological condition, are crucial for neuronal iron efflux. APP is defined as a metalloprotein involved in iron homeostasis. With the assistance of soluble tau protein, APP is transported to the cell membrane where it stabilizes FPN1 and facilitates the efflux of iron. APP or tau knockdown can lead to abnormal FPN1 function and the inability of neuronal iron to flow out normally, resulting in neuronal iron overload. APP with the pathogenic Italian mutation A673V is more prone to be cleaved by β-secretase to produce Aβ1–42, impeding its support of FPN1 and thus increasing iron retention. Because of the continuous cleavage of APP and hyperphosphorylation of tau in AD brain, the iron efflux was hindered in neurons. Glial support for neuronal iron metabolism glial cells help to maintain the iron availability at a safe level in neurons. Astrocytes and microglia respond during iron overload or deficiency in order to maintain neuronal iron homeostasis. As a buffer pool, astrocytes express abundant TfR1 and DMT1, which facilitates taking up of both holo-Tf and NTBI from the abluminal side

of BMECs and the brain interstitium, precisely regulating the iron concentration in neurons. Microglia also express TfR1 and reduce iron toxicity by promoting the influx of excess iron (for storage in ferritin) via the TfR1/DMT1 pathway. Microglia and astrocytes are capable of releasing ferritin carrying Fe3+ to supplement the iron deficiency or to support oligodendrocytes for myelination or remyelination. Iron is essential for myelination in oligodendrocytes, which are the most iron-rich cell type in the brain. TfR1 is absent in oligodendrocytes, while H-ferritin is the main source of iron for oligodendrocyte by interaction with T-cell immunoglobulin mucin domain 2 (TIM2). Noteworthily, when iron is overloaded, oligodendrocytes provide an antioxidant defense for neurons by secreting H-ferritin, scavenging extracellular extra iron [40–46].

13. Impact of iron overload on Alzheimer's disease pathology

Currently, the involvement of iron in the early pathology of AD has been well accepted since the discovery of the link between dysregulation of brain iron homeostasis and AD pathogenesis in 1953. In the preclinical stage of AD, there is significant abnormal iron elevation in cortical, hippocampal, and cerebellar neurons while much severe in the cortex and hippocampus, the main brain areas affected by AD [47]. The iron overload in the brain is corresponding to the severity of AD lesions and the rate of cognitive decline. It is also proposed that hippocampal iron deposition could be the predictor of the rate of cognitive decline caused by Aβ. Iron overload drives a series of events, including glial activation, formation of Aβ plaque and tau tangles, and even neuronal loss, pushing the progress of the disease and accelerating cognitive decline. Iron interaction with Aβ plaques and neurofibrillary tangles iron accumulation was demonstrated to accelerate senile plaque deposition and the production of neurofibrillary tangles [48, 49]. Autopsy evidence and magnetic resonance imaging analysis provide evidence that there are a large amount of iron deposition not only in and around senile plaques but also in the sites of cortical tau accumulation, indicating the potential cross talk of iron with both of senile plaques and neurofibrillary tangles. Perturbations in iron homeostasis is one of key players in Aβ deposition. High intracellular iron concentration enhances the interaction of IRP/IRE, inducing APP upregulation. Furthermore, the enzymes that cleave APP named α- and β-secretase are tightly balanced and modulated by furin. More β-secretase is activated when α-secretase is suppressed by furin impairment in the condition of excessive iron. Upregulated APP is cleaved by more β-secretase to Aβ40/42, accelerating the Aβ deposition [50, 51]. Meanwhile, APP can no longer assist FPN1, resulting in impaired iron efflux and aggravated iron deposition. Some researchers have even proposed that Aβ is nontoxic in the absence of redox metals and that aggregation of Aβ requires the involvement of metals. Soluble Aβ binds to Fe3+ when extracellular iron increases so as to remove excess iron, but it is difficult to dissociate them after they interact; Aβ can promote the reduction of Fe3+ to Fe2+, and the reactive oxygen species (ROS) released during this process allow Aβ to be deposited more easily and rapidly, forming more senile plaques. The interactions of iron with APP and Aβ greatly increase the formation rate and degree of senile plaques. Therefore, some researchers believe that iron deposition should be included in the "Aβ cascade hypothesis" of AD. Iron can also interact with tau. Reduced soluble tau in the brain of AD patients increased brain iron deposition by suppressing FPN1 activity. On the contrary, a diet high in iron can lead to cognitive decline in mice, increased abnormal tau phosphorylation in neurons, and

abnormal expression of insulin pathway-related proteins. Insulin supplementation can reduce iron-induced phosphorylation of tau, indicating that iron deposition may lead to tau hyperphosphorylation by interfering insulin signaling. In vivo research has found that iron can be involved in tau hyperphosphorylation by activating the cyclin-dependent kinase 5 (CDK5)/P25 complex and glycogen synthase kinase3β (GSK-3β). Excessive intracellular Fe2 + —induced production of oxygen free radicals can also promote tau hyperphosphorylation by activating the extracellular. Ferroptosis and Alzheimer's disease signal-regulated kinase 1/2 (Erk1/2) or mitogen-activated protein kinase (MAPK) signaling pathways. Glial activation and neuroinflammation has been demonstrated to be a prominent characteristic of AD pathology. Microglial are highly reactive cells responding to increased iron levels in the brain. When iron level increases in brain, microglia become activated, with soma volume increased and process length decreased. Iron may activate microglia through proinflammatory cytokines mediated by the nuclear factor-κB (NF-κB). After activated, they express more ferritin to scavenge the extracellular iron, resulting in intracellular iron retention, increased TNFα expression, and finally infiltrated with Aβ-plaques. Activated microglia also secret Lf, which can interact with APP, promoting the Aβ formation. Conversely, formation of Aβ induces more IL-1β expression in microglia in the environment of elevated iron, exacerbating the proinflammatory effects. Astrocytes are highly resistant to metal-induced toxicity within the brain as the critical cell type in maintaining a balanced extracellular environment and supporting the normal functioning of neurons. In the environment of high iron, astrocytes respond with a significant increase in glutathione, catalase, and manganese superoxide dismutase levels to resist the oxidative stress. They show less impairment by iron than neurons and oligodendrocytes. But later, the astrocytes were found activated with increased glial fibrillary acidic protein (GFAP). Activated astrocytes release inflammatory mediators and induce oxidative stress, which facilitate the formation of Aβ and tau tangles and hinder Aβ clearance. Iron overload induces oxidative stress and neuronal loss; iron toxicity is largely based on Fenton chemistry [52–54].

14. Conclusion

Along with the increasing importance of novel cancer immunotherapies in the fight against cancer and their translation from preclinical research to clinical practice, there is an increase in the demand for noninvasive imaging techniques that can measure macrophage responses. Although there are other imaging methods available, including PET, Gd-enhanced MRI, and 19F MRI, using MRI with superparamagnetic iron oxide contrast agents is probably the most promising. Theranostic properties, magnetic gradient actuation forces for transport to the target, and multimodal imaging capacity (MRI-MPI) are a few of the main advantages of these NPs. Additionally, despite the fact that clinical development of SPIOs has been stopped, a number of contrast agents, such as Resovist® and Feromuxytol, are still available.

As a redox-active transition metal, iron is a key player during the process of oxidative stress. Elevated iron promotes the production of ROS, which further depletes the cellular antioxidant GSH and promotes lipid peroxidation, finally triggering ferroptosis and neuronal loss.

As previously mentioned, oxidative stress, protein aggregation, and iron buildup all have a positive feedback loop where one factor encourages the other. By inducing iron buildup, oxidative stress, or protein aggregation, iron oxide nanoparticles

(IONPs) can turn on this loop. Additionally, IONPs could cause the neurons to undergo apoptotic cellular death. IONPs may cause neurodegeneration given the roles that iron buildup, oxidative stress, protein aggregation, and apoptosis play in neurodegenerative disorders. However, IONPs' properties, such as size, shape, concentration, surface charge, type of coating, and functional groups, have an impact on how toxic they are. Therefore, taking into account the properties of IONPs is crucial when applying them to the CNS.

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