**Nanomaterials were formed into various shapes, with functionalization aimed at various internalization processes. Their nanoscale size allows drugs to reach cells or extracellular environments**

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ABSTRACT

Iron issues have been linked to a rising variety of refractory diseases, raising doubts about whether iron is the primary connection in etiology and pathology. Nanomaterials were transformed into diverse forms with functionalization aiming at diverse internalization processes. Their nanoscale size permits medications to penetrate cells or the extracellular environment. The original iron enrichment could be employed to fight diseases, including cancer. The effects of IONPs and intracellular iron load on macrophages is also unknown, giving the possibility for future alteration of macrophage phenotypes based on diverse situations.

The data may be utilized to establish important patterns for disease risk prediction and prevention. Nano-sensing technology that reveals iron-regulating situations may deliver fresh insights into safety assessment of iron-based nanomaterials. Long-term stress caused by iron in cells and tissues does not create acute toxicity, but rather long-term damage. A better knowledge of iron homeostasis will result in further diagnostic and therapeutic applications employing nanotechnology.

1 INTRODUCTION

Iron has long been recognized as a significant trace element involved in a variety of critical processes. Organisms have evolved to utilise iron as charge carriers and biocatalysts by integrating it into proteins and prosthetic groups due to its abundance and amazing ability to interconvert redox states (Andrews, Robinson, & Rodriguez-Quinones, 2003). The critical functions of iron in erythropoiesis, energy metabolism, and DNA synthesis and repair highlight the need to keep iron levels in people at a healthy level (Muckenthaler, Rivella, Hentze, & Galy, 2017). However, if iron is not adequately regulated under aerobic circumstances, it can be hazardous because it forms reactive oxygen species (ROS) that are harmful to organic systems (Puntarulo, 2005). In healthy people, a delicate equilibrium is reached in which enough iron is delivered for necessary movement while surplus components are carefully handled by storage, recycling, and adaptive replenishment (Ganz, 2013). Furthermore, because of its extensive engagement in cellular functions, numerous variables interact with the iron level, and they are frequently correlated with one another. It's critical to identify indices that can accurately and fully represent iron status and management in organisms, giving valuable information for iron disease diagnosis, appropriate therapy, and treatment prognosis.

Serum ferritin and transferrin saturation are important indicators in iron status testing because they show the cellular iron reserve and released iron in plasma (Cook, Finch, & Smith, 1976). However, as situations have become more complicated (such as many comorbidities and disputed therapy in refractory illnesses), standard indexes have become insufficient (Hershko, 2018; Wish, 2006). As we learn more about how iron homeostasis and diseases work (Hentze, Muckenthaler, Galy, & Camaschella, 2010), certain novel biomarkers appear to have specific benefits in disclosing specific information about iron status and dynamic balance. Meanwhile, current research in the sector has turned nanotechnology into a strong tool in biological applications, including iron. Because biomolecular detection is one of their most researched domains, nanotechnology has been used to detect iron status (Mu et al., 2013). Furthermore, nanotechnology has been used in the therapy of various iron-related medical conditions (D. I. A. Pereira et al., 2014). Many diagnostic indicators and therapeutic targets have been established based on the nature of iron regulatory pathways, for not only monitoring iron status and associated disorders (Park et al., 2019; Theurl et al., 2009), but also for enabling therapeutic administration through iron metabolism (Crielaard, Lammers, & Rivella, 2017). Nanomaterials, particularly iron oxide nanoparticles (IONPs), are particularly easy to incorporate into iron metabolic pathways, and they may potentially have additional impacts on iron-related systemic activities.

Here, we briefly discuss systemic iron homeostasis and its general control in living cells, demonstrating the guiding importance of iron status, which has been demonstrated in several health studies (Ambroszkiewicz et al., 2017; Dewey & Oaks, 2017). More emphasis will be placed on how nanotechnology has been used in iron homeostasis, illustrating its involvement in the diagnosis and treatment of iron problems and illnesses involving iron.

2 HOMEOSTASIS OF IRON

The relevance of iron homeostasis has received great attention in many new areas, in addition to the well-established iron-related hematological diseases, as our awareness of the vast and critical roles that iron has been playing in physiological activities has deepened. Although comprehensive studies of iron homeostasis have been published from a variety of viewpoints (Ganz, 2013; Hentze et al., 2010; Muckenthaler et al., 2017), a brief overview of iron in life is given here to tie the subsequent applications together in a more methodical manner.

2.1 Iron homeostasis in the body

The typical human body includes 3–4 g iron, which is largely found in the form of porphyrin-complex (also known as heme) in erythrocyte hemoglobin (2–3 g) (Ganz & Nemeth, 2012). Iron is also dispersed in myoglobin, with a similar function but a much smaller amount. Only 2–4 mg of iron is linked to the iron transporter protein transferrin (Tf) in plasma, the majority of which is used for erythropoiesis in the bone marrow (Muckenthaler et al., 2017). The iron balance is mostly stored in hepatocytes and macrophages in the ferrous state of the iron storage protein ferritin, but it can also bind to a small amount of ferric ion simultaneously (Treffry & Harrison, 1979).The ferroportin-hepcidin axis is an important regulatory route for regulating iron homeostasis. In vertebrates, ferroportin (Fpn) is the sole known cellular iron exporter (Donovan et al., 2000, 2005). It can be inhibited by attaching to the hepcidin receptor, which causes internalization and destruction (Nemeth et al., 2004). An iron sensing system that comprises human hemochromatosis protein (HFE), Transferrin Receptor 2 (TfR2), and hemojuvelin (HJV) monitors systemic iron (T. Goswami & Andrews, 2006). Sensing factors will regulate the expression of hepcidin in response to iron status in order to maintain overall balance (Core, Canali, & Babitt, 2014). Every day, macrophages recycle around 0.8 percent of senescent erythrocytes by endocytosis. Their iron will be released from macrophages via Fpn and returned to the plasma iron pool, where it will be used to make new red blood cells. Minor iron losses owing to normal epithelial cell desquamation and excretion (Green et al., 1968) can be compensated for by adequate food absorption by duodenal enterocytes and subsequent introduction into the system via Fpn. Excess iron is kept mostly in hepatocytes and can be released as needed. Systemic iron level is dynamically constant during aging and recycling, storage and release, loss and absorption, and is largely dependent on the Fpn regulating function of hepcidin, whose gene production is feedback-regulated by iron status and repressed by erythropoiesis (Ganz, 2013). In systemic iron control, there is a significant amount of iron flow. The majority of iron in plasma is linked to transferrin (Tf) and circulates in the blood. The majority of iron in Tf is taken and consumed by bone marrow in order to make new erythrocytes, while the older ones are recycled by macrophages and returned to the pool. Hepatocytes may also store iron, which may then be released depending on the situation. The total systemic iron balance is maintained by duodenal iron adsorption from meals and medications, which compensates for iron loss. Ferroportin (Fpn), which is negatively regulated by hepcidin, a peptide released by hepatocytes 2.2, is responsible for iron export from cells to plasma. Iron homeostasis in cells

The coordination of iron absorption, export, storage, and use regulates cellular iron homeostasis. Transferrin (Tf), which securely binds two ferric iron (Tf-Fe2), is the principal iron source for cellular iron absorption. The Tf-Fe2/TfR1 complex will be absorbed by clathrin-mediated endocytosis after binding to the transferrin receptor (TfR1) on the cell membrane. In the acidic environment of the early endosome, Fe (III) is released from the complex. Members of the six-transmembrane epithelial antigen of prostate (STEAP) family proteins (primarily STEAP 3; Ohgami et al., 2005; Ohgami, Campagna, McDonald, & Fleming, 2006) convert free ferric iron to ferrous state and release it to the cytosol via divalent metal-ion transporter 1. (DMT1). Under physiological pH conditions, the empty-handed transferrin (apotransferrin) and TfR1 complex returns to the cell membrane and dissociates. After being converted to Fe (II) by STEAP, duodenal cytochrome b (Dcytb) (McKie et al., 2001), or in certain circumstances, prion protein, nontransferrin-bound iron (NTBI) can enter the cell (Tripathi et al., 2015). Fe (II) is subsequently delivered into the cell via DMT1 (Gunshin et al., 1997), Zrt-and Irt-like protein 14 (ZIP 14) (Liuzzi, Aydemir, Nam, Knutson, & Cousins, 2006), and perhaps ZIP 8 with the help of these ferrireductases (C. Y. Wang et al., 2012). Other forms of iron can be taken up by specific types of cells via phagocytosis and pinocytosis, including the porphyrin-ion complex in hemoglobin (by CD163) and heme (by CD91), extracellular ferritin (light chain by SCARA5; heavy chain by TFR1), and iron-laden siderophore (by lipocalin-2 and its receptor Lcn-2R) (Hentze et al., 2010). Iron homeostasis and cellular iron metabolic pathways. Iron is normally uptaken by the cell in free form, bound with transferrin (Tf), heme alone, or heme in hemoglobin, except from the cancer-specific mechanism through lipocalin 2 (Lcn-2). Iron is usually released into the LIB as a ferrous form for subsequent distribution, depending on its respective receptors and internalization process. The iron-sequestering protein ferritin stores some of the available iron for later use, while the remainder is transferred to mitochondria and used to make important components like heme and iron-sulfur clusters. The 1b isoform of FLVCR (feline leukemia virus subgroup C cellular receptor) allows iron-loaded heme to escape mitochondria and then be secreted from the cell via another isoform, FLVCR1a. Excess iron in LIB is excreted from the cell by ferroportin (Fpn)-mediated efflux, where it is quickly oxidized to ferric form and returned to the blood via transferrin binding.

Internalized iron enters the cytosol's labile iron pool (LIP), with the majority of it being allocated to either mitochondria for future use or the ferritin nanocage for storage. Mitoferrin transports iron from the LIP into mitochondria for the production of later-export heme and Fe-S clusters (Shaw et al., 2006). The amount of active iron in LIP is tightly regulated through storage and export, as too much would produce oxidative stress in the cell. Iron export is a key element of cellular iron trafficking, unlike the systemic iron metabolism system, which lacks an initial iron export mechanism. In LIP, free Fe (II) can escape the cell via Fpn channels in conjunction with ferroxidases that relate to ceruloplasmin (CP) in general, hephaestin (HEPH) for enterocytes (Fuqua et al., 2014), and zyklopen (HEPL1) for placental cells (Fuqua et al., 2014). (Chen et al., 2010). The exported iron binds to serum Tf after being oxidized from Fe (II) to Fe (III) on the cell's basolateral side. Furthermore, iron in heme and ferritin can both depart the cell through separate mechanisms (Krishnamurthy, Xie, & Schuetz, 2007; Truman-Rosentsvit et al., 2018).

The iron-responsive element/iron-regulatory protein (IRE/IRP) system is primarily responsible for regulating cellular iron metabolism, based on the above-mentioned iron trafficking channels and locations. IRP1 and IRP2, two orthologous RNA-binding proteins, can detect cellular iron levels based on Fe-S and LIP levels, respectively (Walden et al., 2006; Wilkinson & Pantopoulos, 2014). IRE is an RNA sequence found in the 5′ untranslated regions (UTR) of ferritin, Fpn (Drakesmith, Nemeth, & Ganz, 2015), and other mitochondrial and hypoxia-relevant mRNAs, as well as the 3′ UTR of TfR1 and DMT1 mRNAs (Muckenthaler et al., 2017). When cellular iron is depleted, IRP's RNA-binding capacity is preserved, but it is decreased in iron-replete cells. Binding of IRP to IRE at the 5′ UTR prevents mRNA transcriptional start, whereas binding at the 3′ UTR enhances stability by shielding mRNAs from ribonuclease destruction. As a result, the cellular iron deficiency is compensated by down-regulation of storage, export, and utilization, as well as increased expression of proteins involved in iron intake. The excess iron is dealt with in the other direction, i.e., to recover the iron expenditure while inhibiting intake.

2.3 Iron disorders: Symptoms, Causes, and Treatment

The presence of iron throughout the living system has made its role extremely complex, and each aspect of it might be expanded into a full-length review, thus it is mostly neglected here. Nonetheless, we felt it was important to include a few intriguing iron-participated biological systems since they have the potential to give compelling diagnostic and therapeutic implications for a variety of critical disorders.

Hematological diseases are frequently caused by general iron insufficiency and overload due to systemic iron's primary role in erythropoiesis. Exogenous iron problems are most commonly caused by imbalanced meals, blood loss, blood transfusion, and intravenous (i.v.) iron, and are less difficult to treat if not combined with excessive iron metabolism. Endogenic iron disorders, such as iron-refractory iron deficiency anemia (IRIDA) caused by hepcidin overexpression, hereditary hemochromatosis (HH) caused by gene mutations in iron sensing systems and resulting low hepcidin expression, and-thalassemia with ineffective erythropoiesis and persistent inhibition of hepcidin expression, are more problematic due to their close correlations with iron deficiency anemia. Additionally, cellular iron retention or even anemia is a typical result of inflammatory disorders, particularly in chronic disorders. High hepcidin levels act as a type of host defense by removing iron from the plasma, which is also required for infection (Weinberg, 2009).When chronic disease anemia (ACD) is combined with iron deficiency anemia (IDA), the erythropoiesis-induced down-regulation of hepcidin outweighs the inflammation-induced boosting impact (Theurl et al., 2009). Similarly, when pathogens infect the organism when it is iron-deficient, the production of hepcidin is persistently suppressed, weakening the anti-inflammatory regulation.

Under varied systemic iron status, hepcidin-mediated iron control acts as a host defense and interacts with macrophage and inflammatory effects. (a) Pathogens will induce inflammation and hepcidin expression to sequester iron from pathogens when systemic iron is balanced. When there is an excess of iron in the body, the impact is amplified, blunting the immune response to infections. (b) Hepcidin expression is suppressed when iron is low. Chronic inflammation is frequently accompanied by iron deficiency anemia because the necessity for erythropoiesis outweighs the host defensive mechanism.

The polarization of pro-inflammatory macrophage M1 has been found to be triggered by excessive iron accumulation in the cells (Sindrilaru et al., 2011). This implies that iron and inflammation are mediated by each other in separate ways. Hepcidin expression and cellular iron retention generated by inflammatory cytokines can both retain the iron supply from invading bacteria and control an excessive immune response by decreasing the generation of inflammatory cytokines (Pagani et al., 2011). However, if too much iron accumulates in macrophages, they might become polarized to the M1 phenotype and induce long-term inflammation. The machinery is also found in a variety of pathogen-free chronic inflammatory and autoimmune disorders (Recalcati, Locati, Gammella, Invernizzi, & Cairo, 2012). It has been suggested that iron shortage may contribute to the pro-inflammatory state because erythropoiesis suppression reduces hepcidin's anti-inflammatory impact (Ganz & Nemeth, 2012). Similarly, systemic iron excess promotes hepcidin expression, resulting in a reduced response to inflammatory simulation and polarizations of macrophage M2 that appear to be mediated by "macrophage iron excess" (Agoro, Taleb, Quesniaux, & Mura, 2018). In terms of real iron overload in macrophages, increased cellular iron content, which frequently occurs in vitro or as a result of the introduction of iron-based nanoparticles, is largely linked to inflammatory polarization.

Apart from the harmful oxidative stress generated directly by LIB, the newly discovered ferroptosis, a kind of nonapoptotic cell death, appears to be a possibly more dangerous aspect of the LIB-induced oxidative stress. Ferroptosis is a type of controlled cell death characterized by an iron-dependent buildup of toxic reactive oxygen species (ROS) from lipid peroxidation (Dixon et al., 2012). It's caused by a malfunction in the lipid antioxidant (glutathione) synthesis, and it's been linked to a variety of diseases linked to local iron overload, including neurodegenerative diseases (e.g., Alzheimer's, Huntington's, and Parkinson's diseases) and cancers (e.g., breast cancer and squamous carcinoma) (Stockwell et al., 2017). (Toyokuni, Ito, Yamashita, Okazaki, & Akatsuka, 2017). Surprisingly, increased iron levels contribute not only to tumor initiation through the production of free radicals, but also to tumor growth and subsequent spread as an essential nutrition (Torti & Torti, 2013). The accumulation of iron in the brain, which is relatively independent of systemic iron (Zecca, Youdim, Riederer, Connor, & Crichton, 2004), is one cause of neurodegenerative diseases, partly due to the presence of its additional blood–brain barrier (Zecca, Youdim, Riederer, Connor, & Crichton, 2004). (BBB).

New treatment techniques have been developed over the years to target these qualities, such as inducing ferroptosis in particular types of tumor cells as an anticancer treatment (Jiang et al., 2015) and iron chelation for slowing the course of neurodegenerative illnesses (Jiang et al., 2015). (Masaldan, Bush, Devos, Rolland, & Moreau, 2019).

3 IRON HOMEOSTASIS IN COORDINATION WITH NANOTECHNOLOGY

Various methodologies and platforms have arisen as popular answers to biological problems, owing to the immense interest and vast amount of research work that has been poured into the subject of nanotechnology. Iron appears to play a role in the development and development of numerous illnesses, according to growing data. Accurate iron status sensing and target delivery for therapeutic intervention are often required methods, which are some nanomaterials and nanodevices specializations. As a result, intricately tailored nanoparticles might be useful for detecting iron status both systemically and locally, as well as therapies that target iron-related pathways or activities.

3.1 Nano-sensing for determining iron levels

Systemic iron status has been clinically assessed for decades, and it has evolved into a rather efficient array with just a few commercially accessible indicators (Cook, Flowers, & Skikne, 2003; Hercberg et al., 1986). Following the discovery of certain new iron metabolic pathways and regulators, other indicators have emerged (Camaschella & Nai, 2016; Girelli, Nemeth, & Swinkels, 2016). People proposed various indices for diagnosis and condition follow-up based on pathology and statistics, such as hepcidin and soluble transferrin receptor (sTfR; Ambroszkiewicz et al., 2017), and predicting the response to erythropoiesis-simulating treatment of patients with dyserythropoiesis using flow cytometry R. (Park et al., 2019). Hematologic disorders can be diagnosed using hemoglobin (Hb), mean corpuscular volume (MCV), reticulocyte Hb content (CHr), percentage of hypochromic red cells (percent HYPO), transferrin saturation (TSAT), NTBI, ferritin, sTfR, and hepcidin, with ferritin and TSAT being the most common for determining iron status (Hershko, 2018; Wish, 2006). Other illnesses that are heavily reliant on iron metabolism have local iron abnormalities that aren't clearly linked to systemic iron status (K. S. Kim, Son, et al., 2012; Gregory & Hayflick, 2005). Local assessments of cellular and microenvironmental iron status should be more meaningful in such circumstances (Crielaard et al., 2017), despite the fact that such data is reportedly more difficult to gather. However, due to the intricacy and cross-functionality of these players, the true indicators of iron status and particular disorders will vary by pathology and can only be proven via clinical statistics.

The circulation system's soluble or serum transferrin receptor (sTfR) level is linked to the expression of transferrin receptor on the cell membrane (R'zik, Loo, & Beguin, 2001), indicating the cells' iron requirements (Sposi et al., 2000). It tends to be higher when there is an iron deficit or when erythroid activity is increased (Wish, 2006). Similarly, serum ferritin concentration is proportional to intracellular ferritin concentration, demonstrating how much iron is stored in the body. It's also a promising option for storing and disclosing parts of the iron metabolic pathways. With a few exceptions in the half-isolated central nervous system (CNS), where Tf acts as a marker for neurological iron abnormalities, Tf and its saturation level are primarily attributable to a systemic iron status (Hoshi et al., 2017). Hepcidin, on the other hand, is considered a complementary part for stating the iron metabolism pathways, the cause of some iron dysregulations, and a therapeutic hint for complicated medical situations due to its irreplaceable function of regulating iron efflux and refined position on the interface of systemic and microenvironmental conditions. Other measures have more indirect erythroid consequences than iron status indicators, hence they will not be discussed further.

3.1.1 Systemic iron assessment using general protein detection platforms

The essential premise of any biomolecule detection sensing technology is to recognize the target molecules specifically and convert the information into a readable signal. These markers are often detected in several generic protein detection technologies, according to reports. For example, immunochromatographic test strips were used to determine sTfR and ferritin simply by swapping binding antibodies, demonstrating tremendous potential in point-of-care testing (Srinivasan et al., 2018; Srinivasan, Finkelstein, O'Dell, Erickson, & Mehta, 2019). The enzyme-linked immunosorbent assay (ELISA) method for detecting ferritin and sTfR, which uses functionalized magnetic IONPs for target capture and separation with a photonic crystal (PC) as the primary transducer, has also been described with minor changes (Peterson, Chen, Cunningham, & Andrade, 2015; Peterson, Cunningham, & Andrade, 2014). Similarly, ferritin detection was discovered to be possible employing a dual-mode fluorometric/colorimetric sensing technology based on gold@carbon dot nanoconjugates (Priyadarshini, Rawat, Bohidar, & Rajamani, 2019). The antigen binding-induced colorimetric change and fluorescence quenching impact were then calibrated into a standard output. Furthermore, a recently published study developed a capillary microfluid channel-based localized surface plasmon resonance (LSPR) biosensing platform employing gold nanoparticles (AuNPs) (Y. Liu et al., 2019). Antitransferrin-modified AuNPs were coated on the inner side of the capillaries. The incident and transmitted light was steered by optic fibers, and the transmission and dispersed light was captured by complementary metal-oxide-semiconductor (CMOS) image sensors. As a result, the computed refractive index and sample concentration were associated. The gadget may be multiplexed and used as part of a detecting array to determine the iron status. Another example of a universal biosensing platform that works for the markers that we focus on is the fabrication of a horn-like polycrystalline-silicon nanowire field-effect transistor (FET) for ferritin detection (Yen, Pan, Lee, & Chao, 2016). The antigen–antibody reaction was still used for recognition, but the performance was increased because of the well-designed nanoarchitectures.

Detection of important participants in iron homeostasis using general nano-sensing platforms. Antigen–antibody interaction (a–e) and tailored MIP binding (f–h) are used to capture particular targets. Protein detections on (a) ELISA with AuNPs, (b) photonic crystals with IONPs, (c) dual-mode fluorometric/colorimetric sensing with AuNPs and carbon dots, (d) LSPR detection in a microfluid device with AuNPs, and (e) semiconductor sensing on a nanostructured FET device with a poly-Si nanowire were all modified with corresponding antibodies. In (f) SPR sensing, (g) fluorescence detection with magnetic NPs, and (h) electrochemical measurement, MIP protein recognition was used.

There are several ways that use the universal sensing concept, but focus more on specialized uses for the iron status indicators, in addition to the above-mentioned generic solutions. People were able to identify sTfR by segmenting the protein into multiple peptides using molecularly imprinted polymers (MIPs), allowing them to screen the best sTfR replacements and MIP synthesis templates (L. Liu, Zhong, Xu, & Chen, 2015). The target peptide would then be enhanced and measured using coupled liquid chromatography-tandem mass spectrometry (LC-MS/MS) after binding to MIPs. One advantage of MIP is that it may be used as a flexible binding site for selecting and recognizing the target molecule in numerous forms once the production mechanism is established. Intriguingly, the MIP has been used to detect a variety of other iron status markers, including hepcidin quantification using SPR and pseudo-ELISA methods (Cenci et al., 2015; Cenci, Piotto, Bettotti, & Maria Bossi, 2018), separation and detection of Tf using so-called magnetic fluorescence molecularly imprinted nanoparticles (MFMINPs) (Y. D. Zhang (Cai et al., 2010). A dual-functional microfluidic paper analytical device (PAD) for Fe3+ and ferritin measurement has been created to better display the iron status in point-of-care testing (Hu et al., 2017). Serum on the PAD will first diffuse to the nonfluorescence QDs (nF-QDs)/AuNPs area for colorimetric ELISA ferritin detection, then to the fluorescent QDs (F-QDs) area, where Fe3+ quantitatively quenches the fluorescent. This is especially interesting since it merged two easy detection methods and merged them into a new platform with the goal of improving the iron status profile by adding more important signals.

All of the detection methods presented here have the potential to be applied to various protein sensing settings, and the larger number of detection systems that have not been evaluated with iron-related markers may potentially present promising future development opportunities. Nonetheless, the practicality of obtaining more effective information on the condition of iron homeostasis should constantly be addressed.

3.1.2 Protein recognition based on trait for local assessment

Some iron status indicators have distinct features that can be used to describe indicators at the cellular level. The biological qualities can be used in bioimaging, while the physicochemical features may aid in the creation of novel signal transduction systems. Ferritin, being an iron-sequestering protein, has certain distinct iron-related characteristics. Through surface absorption, the iron stored in ferritin appears to influence the magnetic resonance property of nanodiamonds containing nitrogen-vacancy (NV) defect centers, which are quickly modified into ferritin sensors with a single protein detection sensitivity via NV's characteristic spin state-dependent fluorescence (Ermakova et al., 2013). A microfluidic system with an ensembled NV sensor, which provided spatial resolution at the sensing region (Ziem, Götz, Zappe, Steinert, & Wrachtrup, 2013), used a similar idea. The ability of (apo) ferritin to bind iron has been the subject of some research. A ferric ion and apoferritin detection system has been created based on the mechanism of Fe3+ quenching effect on synthetic fluorescent carbon dots (CDs) and the fluorescence restoration owing to competitive ion deprivation in the presence of apoferritin (Han et al., 2016). Fe (III) was effectively identified via its catalytic impact in addition to the fluorescence quenching effect (W. Zhang et al., 2019). In this scenario, BSA-stabilized AuNPs were associated with histamine and glutaraldehyde by self-assembled cross-linking polymerization, inhibiting BSA-AuNP fluorescence. Endocytosis allows the Au-nanocomposite to enter the cell, imitating the Tf function of transporting iron but via a different channel. The composite structure was disrupted by cellular Fe (III) catalytic hydrolysis with histamine, and AuNPs were liberated as a result of the amide bond breakage, followed by fluorescence recovery. As a result, the fluorescence distribution may be used to visualize the cellular iron level. Free iron can also be identified using a different method involving biological recognition. For ferrous detection, a ferrous iron-binding binding protein (FBP) from Haemophilus influenzae was produced and attached onto the inner surface of a nanopipette system (Bulbul et al., 2018). The presence and concentration of ferrous iron may be measured in real time using two Ag/AgCl electrodes within and outside the nanopipette, followed by current monitoring. Because of the nanoprobe's small size, it's conceivable to use the sensing platform in a cellular or extracellular milieu, which has sparked a lot of attention in recent years. Local iron problems were identified by visualizing their atypical iron metabolic pathways, which are frequently linked to significant illnesses. For this reason, many methods for detecting iron dysregulation in specific tissues or cells have been developed. Due to its significantly increased expression of TfR and iron intake, a transferrin functionalized gold nanoclusters/graphene oxide nanocomposite (Tf-AuNCs/GO) has been described for bioimaging of cancer cells (Y. Wang, Chen, & Yan, 2013). Through TfR binding, the GO quenching effect on NIR fluorescent Tf-AuNCs was abolished, and fluorescence was restored inside the cell via Tf-TfR-induced endocytosis. Recently, a research using superparamagnetic iron oxide nanoparticles (SPIONs) coupled with Tf to target the aberrant expression profile of TfR in brain cancer cells was published (Weerathunge et al., 2019). The colorimetric signal was achieved here by using enzyme-mimic catalytic SPIONs to catalyze a color reaction. Furthermore, similar routes appear to be particularly beneficial in drug delivery and target treatment, which will be described in the next sections.

3.2 Nanotherapy that takes use of iron-participating activities

3.2.1 Chelation and iron supplementation

SPION ferumoxytol (Feraheme) has been authorized by the Food and Drug Administration (FDA) for use in iron replacement treatment for chronic renal disease (Lu, Cohen, Rieves, & Pazdur, 2010). However, some people are concerned about the rapid i.v. dose and its possible link to anaphylaxis and hypersensitivity responses (C. Wang et al., 2015). Recently, a clinical trial on the efficacy and safety of a novel oral iron treatment using nano iron hydroxide adipate tartrate (IHAT) in treating iron deficiency and anemia in young children was proposed (D. I. Pereira et al., 2018), potentially expanding the toolbox for iron-deficiency anemia remedies. Iron shortage is most typically found at the systemic level, but iron excess can take many distinct forms, with variable distributions throughout the body, organs, and cells of various kinds and phenotypes. More disorders, such as osteoarthritis (Camacho et al., 2016), type 2 diabetes (Fernández-Real, McClain, & Manco, 2015), atherosclerosis (Kraml, 2017), and others, are now deemed significant (Dunaief et al., 2005; B. J. Kim, Ahn, et al., 2012). As a result, iron chelation therapy and iron limitation have been shown to be beneficial in the treatment of atherosclerosis (F. Vinchi et al., 2017, 2019). A protective zwitterionic polymer coating has been added to a design of iron chelation therapeutic nanoparticles to prevent early saturation before reaching the lesion location in the brain (N. Wang, Jin, et al., 2016). The technique reversed symptoms in Parkinsonian animals by loading non-Fe hemin (NHF) as an iron chelator inside zwitterionic polymer capsuled BSA-based nanoparticles modified with HIV-1 trans-activating transcriptor (TAT) on the surface to promote BBB permeability. A polymeric version of the nanoparticle delivery method with iron-chelating function has been developed for the same objective (You et al., 2018). The amphiphilic polymer monomethoxy-poly (ethylene glycol) (mPEG)-poly (lactic-co-glycolic acid) (PLGA) nanoparticles were produced, allowing iron chelation with the hydrophilic drug deferoxamine (DFO). BBB penetration was controlled by surface functionalization of the rabies virus glycoprotein (RVG), a brain-targeting peptide, perhaps by receptor-mediated endocytosis. DFO, for instance, is a traditional iron chelator; other options include deferiprone (DFP), deferasirox, and penicillamine, all of which are clinically accessible (Singh, Pandey, Vishwakarma, & Modi, 2019). Although iron overload appears to be a critical intermediary cause in the whole cascade of neurodegenerative diseases, target chelation of iron in neurons, as well as other aging-related diseases that are notably associated with iron accumulation, has not been thoroughly investigated as a therapeutic approach.

3.2.2 Cancer treatment with nano-iron

Cancer cells are recognized for their fast growth, but they also have a higher requirement for iron, which manifests itself in increased iron intake and storage, as well as less iron export (Dong et al., 2019). Overexpression of TFR1 on the membrane and the reductant STEAP increase iron absorption through the main route Tf-TFR. Other pathways, such as SCARA5/TFR1 for ferritin and lipocalin2 receptor (Lcn-2R) for lipocalin-2 (Lcn-2), which are frequently implicated in tumor invasion and metastasis, appear to receive comparable boosts, as seen by their enhanced levels of involved receptors (Chung et al., 2016; J. Yang et al., 2009). Meanwhile, increased ferritin expression and decreased Fpn expression via hepcidin promote iron retention in cancer cells and are negatively connected with prognostic outcomes (Lee, Song, & Eo, 2016; Pinnix et al., 2010). There are also some intriguing interactions between tumor cells and immune cells. Macrophages identify tumor cells as foreign pathogens early in carcinogenesis and polarize into the pro-inflammatory M1 phenotype (hepcidin high; Fpn low), which is followed by iron sequestration and ROS generation as host defensive actions (Nairz, Haschka, Demetz, & Weiss, 2014). However, cells that survive the circumstances eventually develop a certain tolerance and, in certain situations, compel the immune system to provide them with a tumor-friendly microenvironment (Schreiber, Old, & Smyth, 2011). Not only do the transformed M2 macrophages (ferritin low; Fpn high) interfere with immune cells, causing them to bypass the area (Mazzone, Menga, & Castegna, 2018), but they also feed iron to cancer cells in the form of iron-loaded ferritin (Alkhateeb, Han, & Connor, 2013), Lcn-2 (Mertens et al., 2018), and Tf. The development of cancer medicines has been pushed in numerous areas to target these iron-involved characteristics: target drug delivery through iron metabolism routes, immune response recovery, and activation of ferroptosis.

The universal route Tf-TfR-mediated endocytosis also contributes to increased iron absorption in cancer cells. TfR1 expression has been found to be much greater in many malignancies (Torti & Torti, 2013), making the route appealing for the development of novel target delivery methods. However, more thought should be put into the design of conjugated nanoparticles to account for the creation of protein corona in a complex biological environment, which might result in Tf's ability to target TfR being lost (Salvati et al., 2013). Rather than direct surface functionalization, which may readily form a protein-corona and be scavenged away from the target, a typical technique is to construct nanoclusters (NCs) that entangle the delivery molecules with Tf. The hydrophobic region of Tf was exposed to bind the NIR dye IR-780 iodide as a photosensitizer for photothermal and photodynamic treatment (PTT/PDT) by decreasing the disulfide links in the protein (K. Wang, Zhang, et al., 2016). The Tf-IR780 complex self-assembled into nanoparticles, keeping the capacity to attach to the target and allowing them to infiltrate tumor cells for further treatment. Tf was also discovered to be integrated with copper, allowing for the creation of Tf-templated luminous blue copper nanoclusters (Tf-Cu NCs) (U. Goswami et al., 2018).

The anticancer drug doxorubicin (Dox) was then electrostatically attached to Tf-Cu NCs and formed into Tf-Cu-Dox NPs, which emitted a brilliant red luminescence generated by Dox, whose energy came from the emitting light of Tf-Cu NCs, thanks to the fluorescence energy resonance transfer (FRET) effect. After internalization by TfR1-overexpressed cancer cells, the drug was progressively released into the acid cytoplasm environment. Tf-Cu NCs' blue luminescence was recovered together with Dox release, resulting in an effective tracking mechanism for drug delivery monitoring in vitro and in vivo. Ultrasmall copper sulfide (CS) nanoparticles were produced in the cavity of ferritin, functioning as a PTT agent that notably accumulated in tumors due to ferritin absorption, similar to the PTT/PDT example we reported before in partnership with Tf (Z. Wang, Huang, et al., 2016). Drug loading and surface bio-functionalization were used to create a more complex ferritin-based target delivery system (Fracasso et al., 2016). The ferritin was coated with a peptide shield that was rich in proline, serine, and alanine residues to increase circulation time and loading capacity (PAS). Matrix metalloproteinases (MMPs) are overexpressed in the tumor microenvironment, and the PAS peptide includes cleavage sites for them. Removing nanoferritin's PAS barrier would restore TfR1-mediated binding and internalization, guaranteeing that most drug release took place inside tumor cells.

Nanomaterials only make up a small part of current cancer immunotherapy efforts when compared to the massive research that has gone into the field. The discovery that uptake of NPs, particularly SPIONs, can transform the growth-promoting, iron-releasing M2 macrophage into a pro-inflammatory, iron-sequestering phenotype (Reichel, Tripathi, & Perez, 2019; Rojas et al., 2016) has made SPIONs particularly interesting for the development of immunotherapy targeting tumor-associated macrophages (TAMs). The intrinsic therapeutic activity of SPION Ferumoxytol (Feraheme) has been proven by tumor growth suppression and enhanced pro-inflammatory M1 macrophage presence (Zanganeh et al., 2016). SPIONs absorption produced iron overload in macrophages, which increased M1-like polarization and inhibited tumor development and metastasis. A study in nonsmall cell lung cancer patients revealed a local macrophage M1 polarization change in hemorrhagic regions, which are rich in iron-containing RBCs, corroborating the findings (Costa da Silva et al., 2017). The impact appears to be dose-dependent, as it was not detectable at lower dosages (Müller et al., 2007). Furthermore, the anticancer effect was identified in an immunocompromised system by manipulation of Fpn expression, indicating that this therapeutic nanomaterial has even more potential for future applications (Trujillo-Alonso et al., 2019).

Although an excessively high quantity of iron in cancer cells can promote fast growth, it also poses a threat to their survival, because an increase in labile iron combined with increased oxidative stress is always harmful, and may make cancer cells more susceptible to ferroptosis. Since the introduction of the notion of iron age for cancer therapy (Tarangelo & Dixon, 2016), the ROS linked to ferroptosis in conjunction with iron has been increasingly popular and has been extensively explored in order to discover the most effective therapeutic forms. Even in inductive settings, cancer cells have a comprehensive mechanism to protect themselves against ROS and ferroptosis since they were born and grown in a highly oxidative environment. In a nutshell, system Xc-and glutathione peroxidase 4 (GPX4) work together to maintain the delicate ROS equilibrium (W. S. Yang et al., 2014). The cystine/glutamate antiporter system Xc-is a cystine/glutamate antiporter on the cellular membrane that allows cystine uptake by exchanging glutamate out of the cell under certain extracellular conditions, while also facilitating the cystine/cysteine redox cycle, which provides essential ingredients for the synthesis of the antioxidant glutathione (GSH) (Angeli, Shah, Pratt, & Conrad, 2017). GPX4 reduces hazardous lipid peroxidation by converting them to benign phospholipid alcohols with the help of GSH as an electron donor (Go & Jones, 2010). Breaks in any portion of this chain might reduce cancer tolerance to high levels of ROS and make them more susceptible to ferroptosis (Jiang et al., 2015; Sun et al., 2015; W. S. Yang et al., 2014; Wu et al., 2019). In this newly identified region, there is enormous promise for novel cancer treatments, and tremendous progress has already been achieved in targeting these enticing characteristics of cancer cells (Liang, Zhang, Yang, & Dong, 2019). Increased ROS can cause ferroptosis on its own. Iron-based IONPs have been regarded as a promising possibility for delivering iron to the target environment because of their low toxicity, which has been proven in a variety of methods. For cancer treatment, a new nano-system consisting of IONPs and linoleic acid hydroperoxide (LAHP) has been created (Zhou et al., 2017). Internalized by cancer cells through their hydrophobic ends and yet allowing hydration H+ to dissolve IONPs into Fe (II) inside the cell, NPs are terminated by a precisely developed surface with different hydrophilic and hydrophobic brushes. Under tumor acidic circumstances, a Fenton-like reaction between LAHP and released Fe (II) was created, which created reactive singlet oxygen and triggered ROS-mediated ferroptosis even in hypoxia. Additional inactivation of critical regulators in ferroptosis can also improve cell death induction. Following this strategy, a network-like corona of self-assembled Fe (III) and naturally generated tannic acid (TA) was produced on sorafenib (SRF) nanocores (SRF@FeIIITA) (T. Liu et al., 2018). The corona would disintegrate in acidic circumstances, releasing SRF into the cell to block GPX4 activities and initiate ferroptosis, but normal cells showed no toxicity. Free TA was designed to convert ferric ions to ferrous ions, providing a long-lasting catalytic action for lipid peroxidation in cancer cells, eventually leading to long-term cytotoxicity and ferroptosis. Ferroptosis is more usually detected in combination with apoptosis to destroy tumor cells. Induced ferroptosis boosted the impact of Dox-loaded, iron-saturated ferritin nanoparticles as a cancer therapeutic, according to a recent study (R. Yang et al., 2019). DOX and iron were delivered to cancer cells using ferritin as a carrier, and were released in acidic conditions. The anticancer impact has been boosted in this nano-delivery method by combining Dox-induced apoptosis with the excessive iron-induced ferroptosis cascade. A more refined approach to a similar composition is possible. A core-shell structure was developed for a nanolongan delivery system, with an up-conversion nanoparticle (UCNP) and Dox (as core) encased in an oxidized starch-based gel NP that was cross-linked by Ferric irons and adorned with polymers (as shell) (Bao et al., 2019). NIR light irradiation was used after the nanolongan was internalized and accumulated in the tumor cells due to the increased permeability and retention (EPR) effect and increased surface charge from functionalization. The energy was transformed into ultraviolet (UV) light by the UCNPs, which reduced ferric ions to a ferrous state, causing system rupture and medication release. Through the formation of reactive oxygen species (ROS), the iron and Dox triggered cell death in both forms. Apoptosis and ferroptosis were also detected in other chemotherapeutic treatments. The system's nanoparticle was created by loading cisplatin (IV) prodrugs onto IONPs with a second PEG coating (Fe-PtNP2) (Ma et al., 2017). Following internalization, the iron and Pt drugs not only performed their initial functions in cancer cells, but also collaborated to produce even more ROS, lipid peroxidation, and DNA damage, resulting in exceptional anticancer action.

To treat orthotopic brain tumors, a similar technique was devised by combining cisplatin with IONPs (Shen et al., 2018). Nanoparticles were hybridized with lactoferrin (LF) to traverse the BBB and RGD (arginine-glycine-aspartic acid) dimer (RGD2) to induce tumor-specific v3-mediated endocytosis. The NPs can also be used as an MRI agent to assess the therapeutic impact because of their intrinsic superparamagnetic characteristics. In addition, ferroptosis-inducing properties have been observed in a few noniron-based nanomaterials, such as ultrasmall silica NPs in nutrient-reprieved cancer cells (S. E. Kim et al., 2016) and Low-density lipoprotein docosahexaenoic acid nanoparticles (LPL-DHA) in liver cancer (Ou et al., 2017), providing an even There were just a few cases that incorporated more than one iron-related approach for cancer therapy strategic development. It's conceivable to include distinct target directions in a joint therapy or figure out some deeper reasons to target in their common edges because of their common affiliations with iron control.

4 CONCLUSIONS

Iron is found in almost all forms of life, though its distribution is typically restricted to certain areas. Local allocations, which are practically regulated by cellular iron metabolism, are coordinated to maintain systemic iron homeostasis. Iron problems have been linked to a growing number of refractory illnesses, raising questions about whether iron is the essential link in their etiologies and pathologies. Variations in iron regulator expression can disclose not only the mechanisms by which the system adapts to diverse surroundings and difficulties, but also the methods by which the system adapts to diverse environments and difficulties. Iron status is typically a long-term indicator, although its regulators usually respond quickly to a variety of events.

We may be able to identify some illnesses long before clinical signs appear if we study those important markers that connect to iron status on a regular basis. Nanotechnology's application in this industry will undoubtedly expand the possibilities for building point-of-care diagnostic tools for determining iron status. Additionally, locally enhanced iron absorption and retention have been employed to administer nano-therapy into specific regions, either to directly bring back the iron to a normal level or to have a lethal impact on sick tissues medically or immunologically. Nanomaterials have been changed into numerous shapes with functionalization targeting distinct internalization processes, inspired by the many paths of cellular iron absorption. Their nanoscale scale allows drugs to access cells or the extracellular milieu, while the original iron enrichment in specific places may be used to combat illnesses, including cancer.

Despite the fact that iron homeostasis has been fully investigated and the entire iron metabolic system has become clearer than ever before, there are still many more details to be discovered and validated. Despite the fact that those essential iron regulators have been studied for decades, the indices used in clinical studies have remained relatively unchanged. Because of their diurnal swings and sample variability, several innovative indices are challenging to apply in systemic analysis. However, using nanotechnology to examine local iron metabolism can give useful information for diagnostic optimization. The nanoprobes can get a better picture of both systemic and local iron status through multiplexed sensing and real-time analysis, which may be used to follow illness development and provide clinical input. The data may be used to create valuable patterns for forecasting illness risk and taking preventative measures. In terms of therapy development, the ubiquitous occurrence of iron overload in numerous lesion locations has created a possible barrier to therapeutic intervention. Simple iron chelation therapy may give short-term relief, but the question of how to scavenge iron out of the region (and the body) rather than leaving the chelated complex in place may necessitate more research. Drug administration via the iron uptake mechanism has also been underutilized. Higher specialized cellular uptake routes, such as Lipocalin-2 and its receptor mediated iron binding and transport in cancer cells, obviously have more specificity and provide considerable promise for designing novel delivery strategies. Furthermore, the influence of IONPs and intracellular iron load on macrophages is little known, leaving room for future manipulation of macrophage phenotypes based on various circumstances. Last but not least, while iron-based nanomaterials have shown considerable promise in biomedical applications with minimal toxicity, it is important to remember that systemic iron has no active export mechanism. To compensate for the increased iron that has been injected into the body, the passive routine loss will not rise. The long-term and undetectable stress that iron causes in cells and tissues does not induce acute toxicity, but rather long-term damage that is rarely included in toxicity assessments. The nano-sensing technology that discloses iron regulating circumstances might bring new insights into iron-based nanomaterial safety evaluation. In conclusion, a better knowledge of iron homeostasis will lead to additional diagnostic and therapeutic applications using nanotechnology, which may have greater clinical value and promote improved safety and accuracy for future therapies.

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