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The clinical applications of ferritin

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Abstract

Ferritin is the main iron storage protein that plays an important role in iron homeostasis and is concerned with many physiological functions and pathologic disorders. Clinically, ferritin is mainly used as a biomarker for total body iron stores. Serum ferritin has a critical function in both iron deficiency and overload that related to the diagnosis and treatment. High levels of both serum and tissue ferritin are related to the coronary artery disorder, cancer, and bad results after stem cell transplantation. Less commonly, ferritin is related to other human diseases like the neurodegenerative complaints, sideroblastic anemias, and hemophagocytic disorder. Moreover, up to date research explains a novel function of ferritin that not related to the iron storage.

Keywords: Ferritin; Iron Homeostasis; Iron storage; Ferroxidase activity

1 Introduction

The ferritin main function as iron storage protein, made of twenty four polypeptide chains of two forms, the heavy H chains and the light L chains, with different ratios of both, forming a hollow sphere shape that retain more than 4000 ferric iron inside it. So, the ferritin performs iron sequestration, ferritins rich with heavy H chains catalyse the oxidation of iron II, while the ferritins rich with light L chains stimulate the nucleation and storage of iron III. The ferritin hollow interior cavity supports a reaction vessel in which different reactions are carried out away from the exterior environment. naturally, the hollow cavity is used for sequestration of the iron molecules and also for bio-mineralization to make iron inactive and nontoxic from the external environment (1,2).

The H and L subunits connected in different ratios that forming the ferritin with twenty four subunit protein shell, In human, the ratio of H and L subunits is depend on the type of the tissue in which the ferritin is synthesized (3). These subunits have different functions, the H subunit catalyzing the oxidation of ferrous iron. The L subunit lay on the site of nucleation and storage of iron (4). So, the ratio of H subunits to L subunits is higher in tissues with high activity of iron oxidation and detoxification, as in brain or in the heart (5). In other tissues, as in the spleen, ferritin is used mostly for storage, so it has a lower H subunits to L subunits ratio. While in the liver the ferritin formed from 50% H subunits and 50% L subunits.

The transferrin as a transport protein brought the ferrous ions to the ferritin for storage. The entry of these ions across one of the symmetric three-fold channels or one of the symmetric four-fold channels that formed by the different subunits of ferritin structure (3).

The three-fold channels are hydrophilic because they lined with the polar side chains of acidic amino acids the aspartate and glutamate (6). The hydrophilic character of these channels allows the transport of water in addition to cations and

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hydrophilic molecules of an suitable size into inside and outside the ferritin molecule. The major of the studies shows that the three-fold channel is mainly channel for ferrous ions for both in and out of the ferritin molecule(7).

The four-fold channels lined with non-polar side chain of the basic amino acid leucine that make the hydrophobic channel. These four-fold channels are responsible for the diffusion of oxygen and hydrogen peroxide, to inside and outside the ferritin molecule (8).

At the ―ferroxidase site‖ on the heavy H-chain, the ferrous ions are oxidized, converted to ferric ions, the storage of the iron as a crystalline iron/oxy mineral(6), the mineral are collected on the light L-chain(4).

Apoferritin is a protein usually present in the membrane of the intestinal mucosa. The biological activity of apoferritin is related to its ability for binding and storage of iron, the binding of apoferritin with a ferric hydroxide–phosphate compound forming ferritin, as shown in (figure: 1)(9)

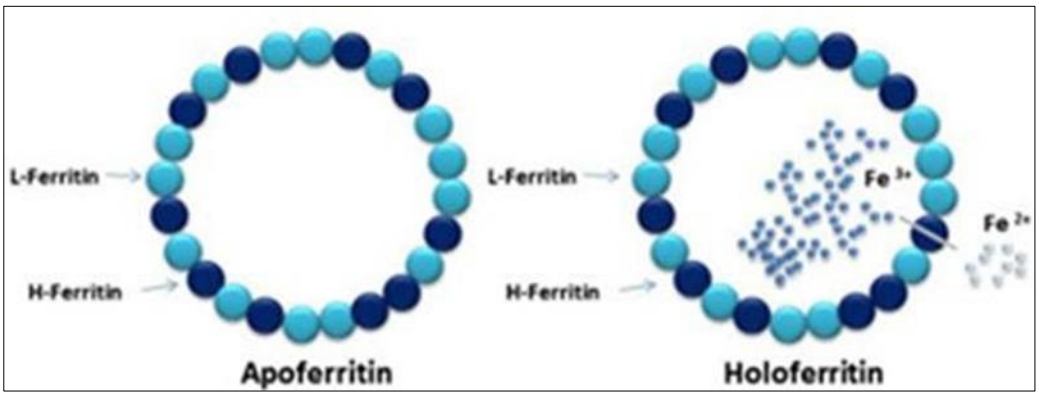

Figure 1 The Structure of Ferritin: Apoferritin forms approximately spherical vessel in which iron ions are stored. Apoferritin shows iron-free protein, while the iron-containing apoferritin is the ferritin. The apoferritin shell formed from twenty four subunits of both heavy H subunit of 182 amino acids and light L subunit of 174 amino acids

2 Biosynthesis of ferritin

The biosynthesis of ferritin is controlled both translationally and transcriptionally. The increased or decreased translation of the ferritin subunit mRNA is related to the labile iron pool that regulated by an iron-responding element that present on the 5′-untranslated region with ferritin subunit mRNA. The transcription of the ferritin subunits genes is regulated by cytokines and hormones, may leads to a change in the pool of the translatable mRNA. The balance between the synthesis of ferritin and its degradation will determine the concentration of intracellular ferritin. The complete release of iron from the ferritin is by the degradation of ferritin in the cytosol, while its degradation in secondary lysosomes forming the hemosiderin that protect against iron toxicity. Most of the ferritin is established in the cytosol. Though, ferritin that established in the organelles like in nuclei and mitochondria have slightly different properties. Most of the ferritin that formed intracellularly is utilized for the control of the iron bioavailability; on the other hand, some of the ferritin is secreted and take on by other cells. Ferritin may also participate in the control of the myelopoiesis and immunological reactions (10).

2.1 The role of ferritin on iron homeostasis

Mainly the iron is integrated within the globin proteins that facilitate the transport of oxygen through the body. The iron plays a vital role in respiration process by converting oxygen into useable cellular energy as a key constituent in the electron transfer chain. Iron is also utilized as an enzymatic co-factor in numerous other reactions. Like the conversion of ribose nucleotides to deoxyribose nucleotides which is important for DNA replication and also for cell division. In addition, the iron may be with a high toxic influence through the production of free radicals.

A controlled mechanisms should be developed for transporting iron across the biological membranes for its distribution throughout the body, and should be stored in the inactive form until it needed, so ferritin has the central role in iron homeostasis.

Regulation of systemic iron balance occurs at the site of absorption and this due to the absence of any physiologic process for excreting the excess iron (11) . Some of the absorbed iron reside inside the enterocyte in form of ferritin, while the major part is transported to different parts of the body. Before the transport of iron to the outside the cell, it should be converted to the ferric ions, this conversion may be accelerated by the hephaestin or by the ceruloplasmin, both have the ferroxidase activity ($Fe2+ \rightarrow Fe3+$). Inside the intestine, both of hephaestin and ceruloplasmin are active, while in the liver (the main storage site of iron) only the ceruloplasmin is active.

For the transporting of iron throughout the body, it is loaded onto transferrin, which is the main transporter of iron in the circulation. When it bound to transferrin, in form of ferric ions it is soluble and unreactive, to enter the circulation (12).

The bone marrow is the primary consumer of iron, where red cells needs a large quantities of the iron for the making of iron-containing hemoglobin. Inside the bone marrow, the precursors of erythroid, express the transferrin receptors on their surface. When the iron-saturated transferrin is bind to its receptor, the resulting complex is endocytosed. Acidic PH of the endosome leads to the release of iron from transferrin. Unbound iron is then reduced to its ferric/ferrous form ($Fe2+$) and next transported from the endosome into the cytoplasm. Later on, the empty transferrin with the transferrin receptors both are resumed to the cell's surface and then are dissociate at a neutral pH, and after that re-enter the circulation (13).

Due to the constant turnover of red cells, this requires the recycling of the iron content inside hemoglobin, and this recycling practice is accomplished mainly inside the macrophage, that phagocytosing erythrocytes, which then are lysed. The iron content is liberated from the phagolysosome heme by the hemoxygenase.

Transporting, distribution and recycling of the iron are controlled inside the body of human. While much remains to be determined about the control of iron balance, hepcidin, which is a recently discovered twenty five amino-acid protein, is assumed to be serious to this process. Hepcidin act as a negative regulator, when elevated, lead to the reduction in both intestinal iron absorption and macrophage iron liberation. Hepcidin frequently elevated with inflammation, a process that is assumed to be accountable for much of the iron defects that indicates anemia of chronic disease (14). The impact of inflammation on hepcidin, is by reducing obtainable iron for attacking pathogens and tumor cells to replicate. On the other hand, a deficient hepcidin may cause obvious and toxic iron overload (15).

2.2 Physiological Functions of Ferritin

2.2.1 Iron storage

The main function of ferritin is to store iron in to nontoxic form, to accumulate it in a safe form, and to transport it to where it is required. The structure and function of the ferritin protein changes in many different types of cells. This is organized mainly by the quantity and constancy of mRNA, furthermore by changes in what way the mRNA is stored and how effectively it is transcribed. One main cause for the formation of several ferritins is the existence of iron (16).

The toxicity of free iron to the body cells is due to the formation of free radicals from reactive oxygen species, by the Fenton reaction. Inside the body cells, iron is stored within ferritin or hemosiderin. Free ferrous iron is binds to apoferritin and stores it inside it as ferric cation. When ferritin aggregates within the cells of the reticuloendothelial system, the formed protein aggregates forming a hemosiderin. Iron that present in ferritin and hemosiderin can be extricated to be released by the reticuloendothelial system, while hemosiderin is less freely accessible. The level of ferritin in the blood is relates to the total body stores of iron; thus, the serum ferritin is very convenient laboratory test to estimate iron stores.

Ferritin degradation cause the release of iron from ferritin to be used where required, and this performed primarily by lysosomes (17).

2.3 Ferroxidase activity

The ferritin molecule formed from two or three subunits which are based on their molecular weight: L the light chains, H the heavy chains, H subunits of ferritin associated with ferroxidase activity as shown in (figure 2) (18), the conversion of ferrous iron to ferric forms. This prevents Fenton reaction between ferrous iron and hydrogen peroxide which leads to the formation of the highly damaging hydroxyl free radical. The ferroxidase activity take place at a diiron binding site in the center of each H- subunits (19). The oxidation of Ferrous iron to Ferric iron, the product stays metastable in the ferroxidase and is relocated by Ferrous iron, The L light subunit of the ferritin has no ferroxidase activity, however, it may be liable for the electron transport throughout the protein cage (20).

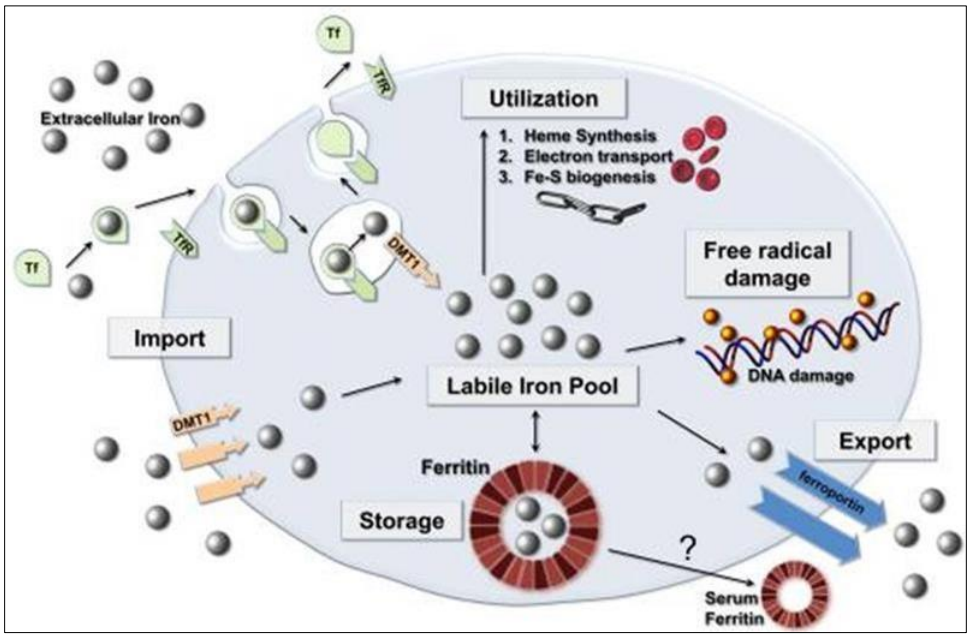

Figure 2 Iron Intracellular Homeostasis: Ferritin as a ferroxidase, converting Ferrous to Ferric iron , is assumed and impounded in the ferritin mineral core. Free radicals can directly damage DNA and proteins. DMT1 = divalent metal ion transporter 1, Tf = Transferrin, TfR = Transferrin receptor

2.3.1 Immune response

In the presence of an infection or malignant, ferritin level will increase significantly. Endotoxins up-regulate of the gene coding for ferritin, and this leads to increase the ferritin level. Therefore, the iron stores of the infected body are blocked to the virulent agent, so inhibit its metabolism (21).

2.3.2 Stress response

In response to stresses such as anoxia, the concentration of ferritin has been proved to be raise , this indicates that it is an acute phase protein (22).

2.3.3 Mitochondria

Mitochondrial ferritin has many jobs relating to molecular function. It contributes with ferroxidase enzyme activity, oxidoreductase activity, binding, ferric iron binding , metal ion binding ,iron ion binding, as well as transition metal binding, that need for biological processes in which it participates in oxidation-reduction, for sustaining the respiratory chain and kreb's cycle(23).

2.4 Pathological aspects that related to ferritin

Many diseases are associated with iron overload or iron deficiency. Serum ferritin is widely used in diagnosing and monitoring these diseases.

2.5 Clinical Aspects of Ferritin

Even though ferritin being a cytosolic protein, it has also been observed in the mitochondria (24), the nucleus, also found extracellularly in serum and cerebrospinal fluid (18). Ferritin different subcellular localization paved the way for trying to understand its role and function for a variety of cell types. Nuclear ferritin binding and protecting DNA from UV and iron Induced damage is one example (25). Studying ferritin present in nuclei of cancer cells showed that ferritin increased the sensitivity to chemotherapy and radiation in these cells. While in the mitochondria, ferritin uses ferroxidase activity to sequester potentially harmful free iron (26).

The regulation of iron delivery throughout the body is very important. Iron deficiency may result in longstanding and severe anemia (27). on the other hand, hemochromatosis may result from excess iron in the body leading to organ failure or inflammatory conditions (28). Furthermore, iron dyshomeostasis in the brain tissues may lead to serious neurodegenerations (29).

2.6 Iron Deficiency

The clinical estimation of the iron status for a certain patient is frequently made by measuring serum ferritin in combination with other iron parameters. Serum ferritin being the most useful in the diagnoses of iron deficiency. Apart from two clinical conditions that lower serum ferritin; ascorbate deficiency and hypothyroidism, A low level of serum ferritin is highly specific for iron deficiency. Most of the time ferritin is considered to be not sufficient alone to make a definite diagnosis, and further blood test are required, for example in the cases of inflammatory response that modifies iron regulations (18).

Soluble transferrin receptors (sTfR) are up regulated in the case of iron deficiency, therefore, measuring the amount of sTfR may help better to differentiate between iron deficiency anemia, and anemia of chronic disease. Using the transferrin receptor – ferritin index, a value more than 2 is suggestive of iron deficiency cause for the anemia, on the other hand anemia of chronic disease is more consistent with values lower than 1 (19).

As discussed, earlier ferritin is a useful tool in the evaluation of iron-deficiency anemia, it is less reliable in the case of end-stage kidney disease where Iron status must be evaluated thoroughly (31). In the cases of anemic patients on hemodialysis iron demand is not sufficiently met in theory even if the ferritin level is greater than 200 ng/L. The absence of bioavailable iron versus plentiful iron storage is termed ―functional iron deficiency‖, this can be estimated by calculating transferrin saturation (TSAT), by dividing serum iron by the total iron-binding capacity, the result will aid in predicating response to iron therapy. Studies have shown that TSAT values of less than 20% in end-stage kidney disease patients, suggesting and chance of good response to intravenous iron infusion (32).

2.7 Iron Overload Conditions

Iron overload is another clinical area were ferritin play important role in the identification and in the treatment. Most cases of iron overload happen as consequence of either abnormal iron absorption or excess administration for example in the case of repeated red blood cells transfusion, knowing that primary regulation of iron occur at the site of absorption and the lack of physiologic process to eliminate excess iron. Excess iron over time may lead to injury and progressive heart and liver failure with the result of significant morbidity and early mortality due to deposition of iron in these organs causing chronic free radical induced injury. Other manifestations of iron deposition in tissues and organ may include arthropathy, changes in the skin, and endocrine dysfunction (33).

2.8 Hereditary Hemochromatosis

Hereditary hemochromatosis is disorder that causes the body to absorb too much iron from the diet. As mentioned earlier excess iron will be stored in other tissues and organs and will lead to a damage in these organs and tissues. Human body is not able to increase the excretion of excess iron leading to overload due the deficiency of an iron regulatory protein call hepcidin (34).

Environmental and lifestyle factors such as iron in the diet, plus alcohol use and infection; all affect the presence and severity of symptoms associated with hereditary hemochromatosis. Symptoms in the early run may include fatigue, pain the joints, weight loss, loss of sex drive, and abdominal pain. As the disorder progress patient may experience more serious manifestations such as arthritis, liver cirrhosis or even liver cancer, poor glycemic control, abnormal skin pigmentation and heart abnormalities. Phlebotomy is the mainstay of treatment that may reduce liver complications, improving the function of the heart and improving skin discolorations. While some patient may require liver transplantation (34).

2.9 Transfusional Iron Overload

Thalassemia major is an inherited blood disorder where the mainstay of management is based on chronic transfusion therapy. As the body inability to excrete excess iron, this will lead to build up iron from the repeated blood transfusions. Excess iron then deposit in the reticuloendothelial cells prior to parenchymal iron loading within the heart and liver. Morbidity and mortality eventually result from progressive heart and liver failure. Another hypothesis is that excess iron led to ineffective erythropoiesis, resulting in many marrows failure disease that also need require chronic transfusions. In this case phlebotomy is not an option as these patients are dependent on the chronic transfusions. Chelation therapy is the favored choice for treatment of iron overload, for example using deferoxamine as iron chelator and administered either intravenously or subcutaneously (35).

2.9.1 Ferritin as a Marker for Inflammation

For long time elevated serum ferritin has been considered to be clinical marker in acute phase inflammation, as Elevated serum ferritin have been associated with increased levels of pro-inflammatory cytokines (36). One of the sources of high levels of serum ferritin in inflammatory process is its secretion by the macrophages, or release from cells due to tissue damage (37).

The correlation between iron deficiency anemia or hemochromatosis with serum ferritin level decreased in the first one or elevated in the later, were examined in many studies. However, infection and inflammation were also known to affect the level of ferritin drastically. In Patients with chronic or acute inflammation the degree of change in serum ferritin level may reflect the inflammation and may also give a reflection for the total store of iron the body. The serum ferritin in disease setting may be more indicative for underlying pathophysiology as in organ damage of infection. Also, intercellular ferritin has also been linked with the host response to infection (38).

2.9.2 Ferritin as a Neurological Disease Biomarker

The amount of iron in the human body increases normally with age, yet abnormal iron homeostasis may result in dangerous diseases. Ideally, increased levels of iron in the body are paired with an increase in levels of ferritin also (39). Normal physiology is affected by increased levels of ferritin that come along of elevated level of iron and may led pathological response as a result of iron mediated oxidative stress. Some examples like Still's disease and sideroblastic anemia (18).

Ferritin also has been reviewed as bio indicator for cancer (40). a recent meta- analysis found that serum ferritin acts as a bio marker for renal cell carcinoma, head and neck cancer, pancreatic cancer and lung cancer where levels of serum ferritin where higher in these patients when compared to healthy individuals, and also served as sensitive biomarker for the detection of advance stages of tumors (41).

Neuroferritinopathy

Neuroferrininopathy (NF) was first discovered in 2001, an autosomal dominant disease as a result of mutations in the ferritin coding gene (42). NF is included with other group of movement disorders called neurodegeneration with brain iron accumulation (NBIA), as characterized by focal accumulation or iron and ferritin (43). Also, it is characterized by excessive iron accumulation in the basal ganglia. Barebito et al., in 2010 found that fibroblasts in NF patient increased the level of total iron stores (44). NF progress gradually where the age of onset is around 39 years (45). These mutations results in decreased or even abolished iron storage, subsequently iron mediated damage, as the mutation lead to the formation of ferritin with larger than normal pores, the high oxygen and glucose consumption of the brain cell will likely results in the increased level of iron utilization leading to the oxidative stress. With no normal functional ferritin, brain cells cannot withstand the oxidative damage of iron (46). Neuronal cells in NF patients will try to process the excess of the free iron by producing even more ferritin leading to the formation of ferritin aggregates in the neuronal cells. These ferritin aggregates where also found in tissues other than the brain such as the muscles in patient with NF (45).

Parkinson's Disease

Parkinson's disease (PD) is one of the common neurodegenerative diseases that is characterized with neurodegeneration in combination with excessive iron accumulation in the substantia nigra pars compacta (SNpc). The buildup of iron in the SNpc is increased as the person ages, but extra iron is accumulated in the SNpc occur as a consequence of PD and depends heavily on the stage and severity of PD. Studies also demonstrated an elevation the serum ferritin level in patients with PD when compared to healthy individuals. (42)

Alzheimer Disease (AD)

AD is progressive neurodegenerative disease affecting the cognitive function by causing generalized dementia such as memory impairment and executive dysfunction, and also leading to changes in personality and behavior. The formation senile plaques (SP) is one of the major pathological features associated with AD. The hippocampus and the cortex of AD content of iron is significantly higher when compared to healthy individuals, also iron is deposited in SP and neurofibrillary tangles on the neurons. Ferritin is also involved in the pathogenesis of AD where studies had shown that large quantities of ferritin existed in and around the SP (45).

Restless Legs Syndrome (RLS):

RLS is disorder characterized by and irresistible urge to move the limbs and unpleasant sensation in the legs. A low-level of brain iron despite normal peripheral iron levels is a well-known neurobiological abnormality. Ferritin may contribute to the progression of the disease and the development of symptoms (48).

Amyotrophic Lateral Sclerosis (ALS)

ALS is a progressive and overwhelming disease, which is characterized by the loss of motor neurons in brainstem, cortex, and spinal cord. The exact mechanism for ALS is still unknown, but many factor may play a role in the pathogenesis like oxidative stress and genetic factors. There is abnormal iron homeostasis in patient with ALS; that higher levels of iron are found in cerebral spinal fluid and spinal cord. Many studies also found increase in serum ferritin level in ALS patients (49).

3 Ferritin as a predictive biomarker in COVID-19

According to systematic review in 2022, increased levels of serum ferritin were noticed in patients with COVID-19 patient versus healthy people, where very high level was associated with even more intense and sever diseases. The level of serum ferritin in COVID-19 patients my aid in the management. Yet, the level of serum ferritin might be affected by many variables such as gender and age, while other co-morbid conditions may also affect the results (50).

3.1 Ferritin as an Emerging Drug Delivery System:

Ferritin poses unique ability to encapsulate and deliver many molecules other than iron. Due to ferritin precise cage alignment, self-assembly properties, and the capability to modify the surface of the fully formed protein with various conjugates increasing specificity and functionality, all of this made ferritin a preferred molecule in the field of nanotechnology. Ferritin structure is rigid under normal physiological conditions, but it can be disassembled when the pH becomes highly acidic (pH 2–3) or highly basic (pH 11–12). The rigid structure of ferritin is formed again into the full 24-mer spontaneously when the pH is set back to neutral conditions (51).

The assembly properties of ferritin are utilized by many researchers to install different compound within the ferritin core. The molecular weight of ferritin is (~474 kDa) but when assemble into the 24-mer the total diameter is about 12 nanometer. Making the ferritin smaller in diameter than many other nanoparticles that nowadays in development as drug delivery vehicles; allowing for wide movement capabilities of ferritin across membranes, even into the nucleus and probably out of the endosomes (52).

The fact that cancer cells need a much more iron than normal, made many researchers' studies and use ferritin as nanocage with encapsulated chemotherapies as delivery agent both in vitro (53, 54) and in vivo (54). The chemotherapeutic agent doxorubicin for example is modified by forming a complex of the drug with a transition metal like Cu (II) or adding a charged accessory molecule such as poly-L-aspartic acid. This complex serves two purposes the first one is enhancing the entry into the ferritin core, the other is allowing the transition of metal or accessory molecule to remain associated with the ferritin molecule where the drug is gradually released from ferritin (55). there is strong evidence that the delivery of cytotoxic agent via ferritin molecule is in effective method that may result in the reduction of non-specific cytotoxicity (56). Ferritin can transport across the blood brain barrier through Tim-1 based on evidence in the past few years, making ferritin nanocage representing an exciting and novel delivery route (57). With the potential of the delivery therapeutics agents directly into the brain parenchyma especially in diseases like neuroblastoma or glioblastoma where the disease is very aggressive, with severe phenotypes and limited treatment options. Chen et al., in 2017 proved that apoferritin loaded with doxorubicin can cross the blood brain barrier and achieving chemotherapy deposition within the tumor cells in a mouse model that result in higher survival rate (58).

Ferritin nanoparticles is currently used also in the vaccine development for many infectious diseases for example HIV-1, SARS-CoV-2, Rotavirus A, and influenza viruses. Ferritin-based vaccines carry several advantages such as safety, low cost and are easily produced (59).

3.2 Ferritin as a Mineralization Chamber:

Magnetic resonance imaging (MRI) is important and powerful diagnostic tool in many diseases such as the detection of tumors (60). Contrast agent are typically used to enhance the visual interpretation of the MRI scans. Gadolinium (Gd) is on of the common contrast agents and used in different formulations, owing to it is strong paramagnetism from seven unpaired electrons. The problem with Gd that it labels all high vascularized tissues nonspecifically, leading sometimes to false positive results and significant reduction of spatial resolution (61).

Ferritin represents a possible alternative to Gd labeling in MRI. Both endogenous and exogenous ferritin have found excellent utility in enhancing MRI contrast capabilities and disease monitoring (62). Some studies showed that Gd can also be loaded within the ferritin molecule and utilized as a more prominent imaging agent. This function of enhanced contrast has many uses, particularly in the diagnosis or monitoring of cancer management (63).

4 Conclusion

In clinical medicine, ferritin is primarily measured as a serum marker of total storage of iron in the body, as in cases of iron overload or deficiency, where serum ferritin play an significant role in the diagnosis of the disease and also help to guide the management.

Today researchers found that the estimation of serum ferritin is important biomarker for several different diseases, as in the case of neurodegenerative diseases (like Alzheimer disease, neuroferritinopathay and others), also ferritin may play as a marker for inflammation, infection, and recently also found to play a significant role in COVID-19 pandemic both to detect seriousness of infection and monitor response to treatment.

The unique criteria of ferritin molecule to encapsulate and then deliver many micro molecule other than iron, due to the precise cage alignment and self-assembly properties and many other properties made ferritin an interesting area for research in the field of nanotechnology to be used as a drug delivery system as in the case of cancer treatment to increase the selectively of drugs and reduce the non-specific cytotoxicity. Moreover, ferritin nanoparticle is currently used in the vaccine development for many infectious diseases. So, different additional applications of ferritin may be expected in the future.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest, financial or otherwise.

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