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Article

Ferritin as an Inflammatory and Prognostic Biomarker in Solid Tumors: A Narrative Review

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Abstract: Ferritin, a highly conserved intracellular iron-storage protein, has emerged as a multifunctional biomarker beyond its classical role in iron homeostasis. Increasing evidence indicates that ferritin acts as a key mediator at the intersection of iron metabolism, inflammation, oxidative stress, and tumor biology. In solid tumors, elevated serum ferritin levels have been consistently associated with tumor progression, systemic inflammation, immune dysregulation, and poor clinical outcomes. Mechanistically, ferritin contributes to tumor growth by modulating iron availability, promoting reactive oxygen species (ROS) generation, enhancing angiogenesis, and influencing immune cell polarization within the tumor microenvironment. Pro-inflammatory cytokines such as IL-6 and TNF-α upregulate ferritin expression, further linking chronic inflammation to carcinogenesis and tumor aggressiveness. Clinically, hyperferritinemia has been reported in various solid malignancies, including hepatocellular carcinoma, breast cancer, lung cancer, colorectal cancer, and pancreatic cancer, where it correlates with advanced stage, metastasis, chemoresistance, and reduced overall survival. Furthermore, ferritin has shown potential utility as a prognostic indicator and as a complementary marker alongside established tumor biomarkers. This narrative review synthesizes current evidence on the biological functions of ferritin in cancer-related inflammation and evaluates its diagnostic and prognostic value across major solid tumors. Understanding the dual role of ferritin as both an inflammatory mediator and a tumor-associated biomarker may provide new insights into risk stratification, therapeutic monitoring, and potential iron-targeted treatment strategies in oncology.

Keywords: Ferritin; Inflammation; Solid tumors; Prognostic biomarker; Iron metabolism

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1. Introduction

There is ferritin in every cell in the body. It stores iron and keeps the molecules that make up cell structures from getting damaged. Inflammation is a key part of many diseases and conditions, such as cancer, neurodegeneration, and infections. It has become a sign for these conditions as well as iron-related disorders. Antioxidative stress, which can harm cells, is caused by reactive oxygen species that are made during the Fenton reaction. These species set off signaling pathways that help tumors grow and spread. This review mostly focuses on basic studies that try to figure out what ferritin is and how it works. It also talks about ferritin's important role in iron metabolism, its role in

inflammatory diseases, and its potential as a key biomarker for cancer diagnosis and prognosis [1].

Mammals store most of their iron in ferritin, which is made up of up to 4500 atoms of ferric iron surrounded by protein groups. Apoferritin is a protein that is made up of 24 unique polypeptide chains, each with a molecular weight of 18500. That's what ferritin does: it stores iron in a form that is easily dissolved and used. Recently discovered information about the structure of the protein is shared, and progress in understanding how iron is added to apoferritin and taken out of ferritin is talked about [2].

Ferritin has generally been thought of as an iron-storing protein in the cytoplasm. But, over the last 20 years, several studies have shown that H-ferritin, a type of ferritin, is found in the nucleus of growing neurons, hepatocytes, corneal epithelial cells, and some cancer cells. These findings gave us a new way to think about ferritin that goes beyond just storing iron. For example, ferritin may play a part in controlling how iron gets to nuclear parts, protecting DNA from oxidative damage caused by iron, and controlling transcription [3].

2. Materials and Methods

This narrative synthesis was performed via a comprehensive and structured literature-based narrative approach to identify the available literature relevant to ferritin as an inflammation or prognostic biomarker in solid tumors. METHODS: Key scientific databases were used to identify all relevant peer-reviewed articles from the literature dealing with ferritin biology, iron metabolism, tumor-associated inflammation, and clinical outcome in solid malignancies. We have prioritized more modern scientific perspectives by including original research articles, systematic reviews, and mechanistic studies published in recent years. The filtering criteria have prioritized investigations on the molecular structure, physiological functions, and regulation of ferritin molecules, particularly the well-established acute-phase reactant function and the interaction of ferritin with inflammatory cytokines including IL-6, and TNF-α. A critical review of evidence underlying altered iron metabolism in cancer cells, tumor microenvironment interactions, and ferritin-mediated signaling pathways was performed to elucidate mechanistic associations between hyperferritinemia and tumour metastasis. METHODS: We surveyed clinical investigations of serum ferritin in different solid organ malignancies (hepatocellular, breast, lung, colorectal and pancreatic cancer) for associations with disease progression, metastases, treatment response, and overall survival (OS). Thereafter, data were narratively synthesized to allow identification of consistent themes, biological plausibility, and translational relevance. A strong focus was given for conjunction of experimental data and clinical data to determine the diagnostic and prognostic significance of ferritin. In addition, the review discussed possible therapeutic relevance focusing on the iron-targeting strategies and on ferritin-based drug delivery systems. By means of this multi-dimensional analytical paradigm, the current study offers a holistic overview regarding the multi-faceted part of ferritin in oncogenesis.

3. Results and Discussion

Biological Structure and physiological function of ferritin

Molecular Structure of ferritin

Ferritin is a spherical, hollow protein nanocomplex that serves as the primary intracellular iron-storage molecule, capable of sequestering up to 4,500 iron atoms (Fe^{3+}) within a non-toxic, bioavailable mineral core. Ferritin is made up of 24 subunits, which are heavy (H) and light (L) chains. These subunits self-assembly into a very symmetrical protein shell that is about 12–13 nm wide. The assembled structure contains hydrophilic channels that facilitate iron uptake and release, as well as hydrophobic pores that contribute to structural stability and controlled iron mineralization [4].

The ferritin protein shell, referred to as apoferritin in its iron-free form, is composed of 24 subunits, each with a molecular weight ranging between 19 and 21 kDa. These subunits assemble into a highly ordered quaternary structure exhibiting octahedral symmetry. Each monomer consists of a four-α-helix bundle (helices A, B, C, and D)

accompanied by a shorter inward-directed C-terminal helix (E), which contributes to stabilization of the overall structure [5]

Role of ferritin in Iron Homeostasis

Iron balance depends on ferritin, a protein that stores iron. Ferritin is the main way that iron is stored. It keeps lipids, DNA, and proteins safe from iron's harmful affects while still letting important biological processes use iron. In clinical practice, changes in ferritin are widespread and usually mean that iron homeostasis or metabolism is off. It is becoming clearer that ferritin is involved in many other conditions as well, such as inflammatory, neurodegenerative, and cancerous illnesses. In people, most of the iron they have is stored in globin proteins, which help oxygen get to all parts of the body. As an important part of the electron transfer chain, iron is also needed to turn oxygen into energy that cells can use. Iron is not only used in respiration, but it is also a co-factor for many enzymes in other processes. Changing ribose nucleotides to deoxyribose nucleotides is one of these reactions. This process needs iron and is sped up by ribonucleotide reductase. It is needed for DNA replication and cell division. Iron is also very good for you, but it can be very bad for you because it helps make free radicals. To move iron across biological barriers, spread it around the body, and store it until it is needed, carefully controlled systems have grown up. The body doesn't have a way to get rid of extra iron at the site of absorption, so that's the only place where the iron balance is kept in check. Most of the iron is absorbed by enterocytes in the middle part of the small intestine. Iron can move across the cell membrane with the help of the divalent metal transporter DMT1. Iron and other divalent metals can move across the apical membrane and into the cell through a process that is related to protons. DMT1 is a member of the N ramp family. Before the iron can be moved, it needs to be in the ferrous state (Fe^{2+}). With the help of brush border ferrireductases, added non-heme iron from food can be changed into Fe^{2+}. But heme carriers have been found, and we now know a little more about how heme iron is taken in. When the body doesn't have enough iron, DMT1 levels rise, which makes it easier for cells to take iron in. Some of the iron that is taken stays in the enterocyte as ferritin, but most of it is moved to other parts of the body. The recently discovered ferroportin is an iron efflux pump that helps iron leave the enterocyte. Intracellular iron must be changed to Fe^{+3} before it can be moved outside of the cell. One or both of hephaestin or ceruloplasmin can help with this because they are ferroxidase enzymes (Fe^{2+} to Fe^{3+}). Both of these proteins are active in the intestine, but ceruloplasmin is the main worker in the liver, which is a big place where iron is stored [6].The iron is then put on transferrin, which is the main iron carrier in the blood. Fe^{3+} is soluble and nonreactive when it is linked to transferrin. This lets it get into the bloodstream. The bone marrow is the main place where iron is used. When red blood cells make hemoglobin, they need a lot of iron to meet their needs [7].

On the outside of erythroid progenitors in the bone marrow, you can find transferrin receptors (TfRs). When the iron-saturated transferrin binds to its receptor, the complex goes inside the cell. The acidity of the endosome makes the iron from transferrin come out. The free iron is then changed by Steap 36 to its ferric/ferrous form (Fe^{2+}), and DMT1 moves it from the endosome to the cytoplasm. The empty transferrin and transferrin receptors are sent back to the cell's surface, where they break apart at a pH of 7. They then circulate again [8].

It's interesting that the transferrin receptor is not needed for iron to get into cells that are not hemopoietic. In studies with mice, a messed-up TFR gene causes fatal anemia very early in development, even though other organs that aren't blood cells have normal amounts of iron inside them. Because red blood cells are always being replaced, the iron in hemoglobin has to be recycled. The macrophage is mainly responsible for this recycling process because it can take in erythrocytes and break them down [9]. Through hemoxygenase, the iron is freed from the phagolysosome heme. The macrophage then sends out the iron that it hasn't stored yet. This process is thought to depend on ferroportin. The way that iron moves, is distributed, and is recycled is tightly controlled in people. Hepcidin is a new 25-amino-acid protein that is thought to play a big role in iron balance. However, there is still a lot to learn about this process. Hepcidin is a negative

regulator that stops macrophages from releasing iron when it is high and stops the gut from taking iron in. Hepcidin levels often rise during inflammation, which is thought to be the cause of many of the iron problems that are typical of anemia caused by long-term illness. Because inflammation changes hepcidin, some people think that hepcidin developed as a way for the host to protect itself by reducing the amount of iron that invaders and cancer cells can use to reproduce. On the other hand, not having enough hepicidin, like in young hemochromatosis, can cause a strong and harmful iron overload [10].

Ferritin as an Acute-Phase Reactant

The acute phase reaction is what the body does when it has an infection, tissue damage, cancer, or any other problem with the immune system. It is part of the innate immune system because it is an early and general defense system. There are acute phase proteins inside and outside of cells that make up the acute phase response. This response affects the liver and other organs [11]. the inflammation response and the cytokines that are made as part of it are important parts of the acute phase reaction. Both cytokines that cause inflammation and cytokines that stop inflammation help control the production of acute phase proteins. They make the "positive acute phase" proteins go up and the "negative acute phase" proteins go down. Some cytokines, like interleukin-1β (Il-1β) and interleukin-6 (Il-6), which cause inflammation, and interleukin-10 (Il-10) which stops inflammation can change how acute phase proteins are made [12]. Genetic regulation that goes up or down controls how many acute phase proteins are made. The body responds to cytokines that start or stop inflammation in a certain way. One of these proteins is called acute phase response factor (APRF), and it is part of the process of making acute phase proteins. Because more cells are being released, a positive acute phase protein called ferritin is turned up inside many types of cells and in the plasma outside of cells. One important thing that ferritin does during the acute phase response is lock up iron in the ferritin protein shell so that it can't be used. In addition, ferritin can change a lot of immune system processes, work in pathways that either promote or prevent cell death, and is linked to the development of cancer. A lot of oxygen radicals, which are molecules with single electrons, are made when there are infections or inflammations [13]. As a result, the phagosomes in neutrophils and macrophages break down the material that they take in by reacting with proteins, lipids, and nucleic acids. But a lot of these harmful chemicals leak into the fluids and tissues around the inflammatory reaction, where they can do a lot of damage by reacting with cell parts. Iron, because it plays a part in Fenton-type chemistry, can make oxygen radical production worse. When there is too much iron in the body, it can cause unwanted oxygen radicals to be made. This can happen in people with chronic inflammatory diseases. There is a strong link between the amount of thiobarbituric acid-reactive material (a lipid peroxidation result), the amount of iron in the synovial fluid, and how inflamed the disease is [15]. For example, people with rheumatoid arthritis have more iron in their synovium [14]. Giving people with anemia who have rheumatoid arthritis extra iron also speeds up lipid peroxidation, which makes the joint inflammation worse [16].

In general, lowering the solubility of iron will protect cells from damage caused by hydroxyl radicals, which are made from superoxides released by neutrophils and macrophages[17]. So, cells in the area of inflammation may be able to protect against the free radical attack by storing iron [18]. Researchers have found that cells are more likely to be killed by pro-oxidants when their ferritin levels are low, and cells that are attacked by oxidants are less likely to produce reactive oxygen species (ROS) when their ferritin levels are high [19]. These results back up the idea that ferritin helps host cells handle a rise in free radical damage. Macrophages help make ROS, but they can also protect against it by dropping the iron level. How many reactive oxygen species are made depends on how much bio-available iron is present during illnesses and inflammation. Keeping germs from getting bio-available iron can also stop them from spreading, which can help stop infections. There is a lot of iron that most germs need to stay alive. They use many drugs and tools to get iron from host ferroproteins, such as transferrin, haemoglobin, and ferritin [20]. More iron in macrophages is linked to infections like tuberculosis that are more

serious and have worse results [21]. On the other hand, taking iron pills may make you more likely to get malaria in places where it is common [22].The host reacts by storing iron to stop the pathogen from growing. This is shown by the fact that ferritin levels rise during the chronic phase of trypanosomiasis [23].

Ferritin and inflammation

Because the body doesn't have a way to actively get rid of iron, it can have a positive iron balance and, finally, iron overload if the homeostatic systems are harmed or bypassed. Too much iron in the body can be harmful because it can overload the iron-binding ability of transferrin. This creates non-transferrin-bound iron, which can be taken up without being managed, causing damage to the endocrine system, heart, and liver [24].When there is an acute inflammatory or infectious event, blood ferritin levels can rise dramatically [25].

Inflammation and iron metabolism in solid tumors

Chronic inflammation in the Tumor microenviroment

A major cause of cancer growth is long-term inflammation. You can find cancer cells engaging with nearby cells and non-cells in the inflammatory tumor microenvironment (TME). These include pro-inflammatory cells, innate immune cells, stromal cells, and more. Cells can talk to each other thanks to cytokines like interleukin 6 (IL-6), MIF (a macrophage migration inhibitory factor) and immune checkpoint factors. These are made by intrinsic immune cells in the TME. They link long-term inflammation to cancer by turning on different signaling pathways that support cancer growth and making it easier for the immune system to get rid of dangerous substances, which helps the cancer grow. As well, cancer cells take over the normal tolerogenic functions of monocytes, T regulatory cells (Tregs), and B regulatory cells (Bregs). This can make the immune system weaker in certain areas or all over the body. It's been a few decades since cancer treatments like chemotherapy and radiation therapy got better. Not good enough, though, because the drugs used to treat some types of cancer don't work or have bad side effects. There is new hope for people with cancer thanks to immune checkpoint therapy (ICT), but it's still not very good because it weakens the immune system. New data shows that the best treatments should get rid of tumor cells, stop the immune system from being slowed down by tumors by targeting suppressive TME, and turn on anti-tumor T cells again using ICT [26].

When cells and soluble messengers, like cytokines of the innate and adaptive immune systems, sense pathogens or tissue damage, they start a chain of events that make the immune system work. The main goal of this inflammatory reaction is to get rid of the foreign substance that is upsetting the balance of the tissue [27]. In a healthy body, inflammation goes away after tissue repair or pathogen removal, and the homeostatic state is restored [28]. It is now generally agreed that chronic inflammation that isn't properly resolved may raise the chance of cancer. Several diseases, like endometriosis, chronic prostatitis, chronic gastritis due to Helicobacter pylori, inflammatory bowel diseases (IBD), and primary sclerosing cholangitis (PSC), show this link. Inflammation can raise the risk of cancer by releasing bioactive molecules from cells that enter the tumor microenvironment. These molecules include cytokines, growth factors, chemokines that keep the cell proliferation rate steady, proangiogenic factors, and extracellular matrix-modifying enzymes like metalloproteinases that help the epithelial-mesenchymal transition (EMT) and other cancer-related processes, such as genome instability, reprogramming of energy metabolism, and immune evasion.

Many people think that long-term inflammation helps cancer grow, spread to other parts of the body, become resistant to drugs, and weaken the immune system by creating an environment that supports the tumor, which is called the tumor microenvironment (TME) [29]. The TME is made up of cancer cells, adaptive immune cells, stromal cells, and intrinsic immune cells. Intrinsic immune cells include TAMs, MDSCs, neutrophils, mast cells, DCs, and NK cells. Adaptive immune cells include TAMs, MDSCs, neutrophils, mast cells, DCs, and NK cells. When defense cells and cancer cells talk to each other, they make a place where cancer can grow. As we look at more than one part of the TME at the same

time, we might be able to figure out how this conversation works and improve treatments and outcomes for patients.

Dysregulation of iron metabolism in cancer

In many ways, iron is an important part of how cancer starts. However, iron can also play a key role in cell death through ferropotosis, a type of planned cell death.As a result, iron may help stop tumors from growing. Iron's ability to change between oxidized and reduced forms does, in fact, help make free radicals that speed up the start of tumors. Ferroptosis is a way for cells to die that seems to be caused by two things happening inside the cell: the antioxidant system getting weaker and the amount of iron inside the cell rising. Through iron metalloproteases, iron also helps with the growth of metastases and blood vessels. Iron can change the microenvironment by breaking down the iron framework and helping cancer cells spread. Finally, iron can also help tumor cells start to multiply. On the contrary, cancer cells need more iron because they divide and make DNA more quickly. Because of this, changes have been seen in the iron metabolism routes in cancer cells. Cancers may also get worse with iron because it can change genes and the way they are controlled. Cancer is actually a condition of both genes and epigenetics, and iron plays a role in controlling both the genome and the epigenome. As we've already seen, iron controls the transcription of many proteins that are directly or indirectly connected to iron balance through the IRE/IRP system. In addition to the IRE/IRP system, it's important to remember that iron also affects epigenetics through Fe-S clusters. It's true that Fe-S clusters are needed to make stable and active complexes like DNA polymerases and enzymes that fix DNA [31]. It has also been shown that Fe-S clusters are important for changing how histones and tubulins are acetylated. So, when Fe-S clusters' biogenesis and/or iron regulation are changed in cancer, changes happen at both the genome and epigenome levels [32].

Iron is involved in a number of processes that are often changed in cancer cells. For example, it helps tumor cells stay alive and changes the way the environment around the tumor works. Loss of Fe homeostasis can happen at different times of cancer development, such as when the tumor starts growing, when it spreads, and when it metastasizes. Some changes in the mRNA or proteins of important Fe metabolic players have been seen in cancer [33]. These differences might be useful factors for diagnosing or predicting cancer. So, using them as regular clinical tests could improve the way doctors treat cancer, which would eventually lead to better care for patients.

A lot of diseases, including cancer, mess up the way iron is used in the body. Cancer cells need more Fe, and changes in Fe balance help them keep growing quickly. This reliance on Fe is, however, also a weakness for cancer cells, and targeting Fe metabolism is an important and promising way to fight cancer. Depending on the type of cancer, the amounts of different actors in Fe metabolism that are higher or lower may be useful biomarkers for predicting or predicting the outcome. As we learned more about the processes that cause Fe dysregulation, new treatments were created that target Fe. In clinical studies, some of the most advanced drugs are even given to people with cancer. Combining Fe-targeting drugs with chemotherapy molecules is best because it may have anti-proliferative effects that build on each other or work together [34].

Ferritin as an inflammatory biomarker in Solid Tumors

mechanisms linking ferritin to tumor-associated inflammation

In several ways, ferritin is linked to inflammation in tumors. It does this by acting as a Damage-Associated Molecular Pattern (DAMP) that turns on the NLRP3 inflammasome and prompts macrophages to make pro-inflammatory cytokines (IL-1β, IL-6, and TNF). It is a protein that holds iron and is made more of by cytokines that are made when there is inflammation or cancer.

Additionally, tumor-Immune System Activation: TNF, IL-1β, IL-6, and IL-12 are pro-inflammatory cytokines that are released by the NLRP3 inflammasome when extracellular ferritin functions as a DAMP.

TAM-Derived Inflammation: The main source of ferritin in tumor settings is tumor-associated macrophages (TAMs), which aid in the development of tumors and chronic inflammation.Ferritin is secreted by associated macrophages (TAMs) to stimulate tumor

growth and angiogenesis, and its capacity to accumulate iron allows tumor cells to survive and proliferate in hypoxic environments. Pro-angiogenic Activity: Serum ferritin associates with High Molecular Weight Kininogen (HK/HKa) to stimulate angiogenesis, facilitating the formation of new blood vessels in the tumor. Positive Feedback Loop: Inflammatory cytokines (such as IL-1α/β) stimulate macrophages to produce ferritin, and the rise in ferritin amplifies inflammation, creating a self-sustaining loop. Iron-Independent Signaling: In addition to iron storage, ferritin interacts with receptors like TfR1, triggering intracellular pathways such as NF-κB to promote inflammation. Immune Suppression: Increased ferritin aids in the polarization of TAMs towards a pro-tumourigenic M2-like phenotype and diminishes the functionality of cytotoxic T cells [35]. In cancer patients, increased serum ferritin, commonly known as hyperferritinemia, indicates an inflamed microenvironment and correlates with worse prognosis [36].

Clinical Evidence of Elevated Ferritin in Solid Malignancies

Because of these features, ferritin is a very interesting target for cancer treatment because lowering it can mess up the environment around the tumor, kill tumor cells, and make the tumor more vulnerable to chemotherapy. Based on the information we have so far, we can guess that higher levels of ferritin in cancer patients' blood may be related to the point at which their cancer is spreading and may be a useful tool for predicting their prognosis and identifying their tumors[37]. In medicine, ferritin is used for treatment. For instance, because of the way its structure is built, it is used to carry drugs that kill cancer cells [38].

Prognostic Value of Ferritin in Solid Tumors

Higher levels of L-ferritin than normal in some tumor tissues have been linked to tumors being more aggressive, cancer cells multiplying more quickly, and a part in protecting against chemotherapy, which leads to a worse prognosis[39]. The amount of serum ferritin (SF) may also be able to show how active certain children cancers are, such as leukemias, Hodgkin and non-Hodgkin lymphomas, and solid tumors. Multiple SF levels were looked at during cancer treatment, and a return to normal concentration was linked to a good reaction to treatment[40]. When measuring serum ferritin levels in cancer patients, it's important to think about the many roles ferritin plays and how it changes under different circumstances, such as when the disease gets worse, when there are inflammatory processes going on at the same time, when the patient gets multiple blood transfusions and their iron levels rise, or when the patient responds to therapy [41]. In Hodgkin lymphomas (HLs), B-symptoms show that the inflammatory reaction is a big part of the disease[42]. Because iron metabolism is out of whack and ferritin is overexpressed in cancer cells, SF levels in HL patients are thought to be a good indicator of disease activity and return. Blood product transfusions are mostly done on people in the later stages of HL because they need special care. They are not common in the earlier stages [43].

Ferritin and survival outcomes

Elevated serum ferritin levels in solid tumor patients are strongly associated with poor prognosis, aggressive disease, and decreased survival outcomes, acting as a biomarker for tumor progression and, in some cases, immunotherapy resistance. High ferritin often indicates iron overload or inflammation, contributing to tumor-associated macrophage activation [44].

4. Conclusion

Ferritin has evolved from being recognized solely as an iron-storage protein to a clinically relevant inflammatory and prognostic biomarker in solid tumors. Accumulating evidence indicates that elevated serum ferritin reflects tumor-associated inflammation, altered iron metabolism, and oxidative stress within the tumor microenvironment. Its association with advanced disease stage, metastasis, therapeutic resistance, and reduced survival highlights its potential value in risk stratification and disease monitoring. Mechanistically, ferritin contributes to cancer progression by modulating iron availability, supporting angiogenesis, and influencing immune responses. Although not tumor-

specific, ferritin may serve as a complementary marker alongside established oncologic biomarkers. Further large-scale prospective studies are warranted to clarify its predictive utility and therapeutic implications in oncology.

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Declaration of Competing Interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

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