

Review

Role of Ferritin in Immunity, Inflammation and Malignancy

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Abstract

Since it has been used as the principal iron storage protein in cells for over 70 years, ferritin has been the subject of ongoing research. Recently the multifunctional role of ferritin protein has been observed with potential involvement in proliferation, angiogenesis, immunosuppression, and iron transport, as per several studies and evidence. Ferritin may promote tumour growth, promote angiogenesis, and suppress the immune system of the host. A higher ferritin level in cancer cells is linked to disease progression, therapy resistance, and a worse prognosis. Additionally, certain cancer cells have the ability to generate ferritin, which allows them to be partially independent of external iron supplies, or they can rob iron from nearby cells and tissues and retain it as ferritin to maintain their accelerated multiplication. The purpose of this research is to review the available information about the role of ferritin in immunity, inflammation and malignancy. Elevated ferritin levels are among the significant factors affecting defence mechanism during infection, which deprive bacterial growth of iron and safeguard immune cell function. Additionally, it might be protective by reducing free radical generation and regulating immunomodulation. With levels that reflect the severity of acute and chronic inflammation in infectious, rheumatologic, hematologic, and neoplastic disease, serum ferritin is a well-known acute-phase reactant. While it is well established that ferritin levels and inflammatory activity are correlated, and ferritin has a direct causative role in mediating inflammatory diseases. However further research is needed to elaborately study the role and mechanism of ferritin in inflammation, immunity and malignancy.

Keywords: *ferritin, inflammation, immune, iron, marker, biomarker*

Introduction

Major iron storage protein ferritin is engaged in a variety of physiologic and pathologic processes and is vital for maintaining iron homeostasis. Ferritin is primarily used as a serum marker of total body iron reserves in clinical medicine. Serum ferritin plays a crucial role in diagnosis and treatment of iron overload and insufficiency. Poor results after stem cell transplantation and elevated serum and tissue ferritin are associated with coronary artery disease, cancer, and other diseases. Hemophagocytic syndrome, sideroblastic anaemias, and neurological diseases are only a few less frequent but potentially fatal human diseases that ferritin is directly linked to (1). Age-related increases in serum ferritin levels appear to be more pronounced in males than in women (2).

Widely acknowledged as an acute phase reactant and marker of acute and chronic inflammation, serum ferritin is non-specifically elevated in a variety of inflammatory conditions, including chronic kidney disease, rheumatoid arthritis and other autoimmune disorders, acute infection, and cancer. The higher total body iron storage reflected by the raised ferritin in these conditions is paradoxically sequestered and unavailable for haematopoiesis, a mechanism that contributes to the well-known anaemia of inflammation. It is thought that this relative iron deficit in inflammation and cancer development acts as a defence mechanism to prevent microbes and tumours from utilizing serum iron (3). The liver, spleen, and bone marrow have substantial concentrations of ferritins which belongs to a class of isometric proteins with a key role in iron storage and metabolism. Acidic iso-ferritins, also referred as carcino-ferritins, are present in the human fetal liver, gastric, and pancreatic carcinomas. Serum ferritin levels have been reported to be elevated in people who suffer from Hodgkin's disease, chronic myeloblastic, granulocytic, and lymphatic leukaemia, myeloblastosis, breast cancer, multiple myeloma, malignant lymphoma, gastrointestinal tract carcinoma, and germinal cell cancers of the testis (4).

Numerous pathological diseases have been linked to increased serum ferritin levels. Iron and iron-binding proteins have significant effects on immune systems and immune system cells can help prevent potential tissue damage caused by iron build-up. Generally, ferritin is thought of as an intracellular iron storage protein. The physiological function of serum ferritin is still unknown, despite the fact that modest levels of ferritin are present in the serum of healthy people. The significance of ferritin in hematopoiesis and the immune system has

received attention for years, despite the fact that ferritin's activity is inextricably related to iron metabolism. Human hematopoietic progenitor cells and T lymphocyte proliferation are both inhibited by ferritin during *in vitro* growth. Ferritin may directly inhibit human B lymphocyte development into cells that produce antibodies in culture (5).

Initial presentations of ferritin included a variety of acute bacterial and viral illnesses, indicating an immediate reaction to inflammation. The development of the hyperferritinemic syndrome, which links four serious pathological conditions including adult-onset Still's disease, macrophage activation syndrome, catastrophic antiphospholipid syndrome, and septic shock added another dimension to ferritin where it might play a pathogenetic role rather than simply serving as an elevated protein. Coronavirus disease-19, in addition to the previously described four disorders, is a new member of the hyperferritinemic syndrome spectrum (6). The inflammatory response is closely linked to iron and its homeostasis which perhaps is the most evident link of anaemia of inflammation or chronic disease, which is caused by the adaptation to iron deficiency, which confers resistance to infection and enhances the inflammatory condition. Iron homeostasis during the inflammatory response needs to be precisely controlled by the integration of a variety of stimulatory signals (7). The purpose of this research is to review the available information about the role of ferritin in immunity, inflammation and malignancy.

Methodology

This study is based on a comprehensive literature search conducted on October 10, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about role of ferritin in immunity, inflammation and malignancy. There were no restrictions on date, language, participant age, or type of publication.

Discussion

Since low ferritin levels indicate insufficiency and high levels indicate primary or secondary hemochromatosis, understanding of ferritin biology has historically focused

on its role in iron storage and homeostasis. However, more recent research has revealed an unbreakable connection between inflammation, redox biology, and iron. An important host defence mechanism during infection is elevated ferritin levels, which deprive bacterial growth of iron and safeguard immune cell function. Additionally, it might be protective by reducing free radical generation and regulating immunomodulation. Clinicians frequently use hyperferritinemia as a marker for therapeutic intervention targeted at reducing inflammation in high-risk patients. Hyperferritinemia, is an innocent bystander biomarker of unchecked inflammation that can be used to assess the efficacy of intervention. Also, ferritin induction might function as a protective negative regulatory loop. Ferritin plays a significant role in immunological dysregulation, particularly in cases of severe hyperferritinemia, by directly suppressing the immune system and promoting inflammation. Further research is clearly needed to better understand the role of ferritin as a biomarker and disease mediator in uncontrolled inflammatory diseases, as its existence indicates patients at high mortality risk and its resolution indicates improved survival (8).

Role in immunity

The immunoregulatory functions of iron and the proteins it binds to can be altered by iron excess or shortage, which can have serious, harmful physiological implications. Reduced antibody-mediated and mitogen-stimulated phagocytosis by monocytes and macrophages, changes in T-lymphocyte subsets, and altered lymphocyte distribution in various immune system compartments are all consequences of iron overload. Both in vitro and in vivo studies have shown the significance of iron in controlling the expression of T-lymphocyte cell surface markers, impacting the expansion of various T-cell subsets, and modifying immune cell functions. The immune system complications in people with iron overload may be explained by lymphocytes' poor capacity to bind excess iron in ferritin. When compared to treated hereditary hemochromatosis patients or controls, iron overload as seen in patients with hereditary hemochromatosis significantly increases suppressor T-cell counts and activity, reduces the proliferation rate, numbers, and interaction of helper T cells with increases in CD8/CD4 ratios, hinders the generation of cytotoxic T cells, and changes immunoglobulin secretion (9).

Complex polypeptide ferritin primarily serves as an iron-storage protein. The control of immunological function

may also involve ferritin. It is well recognized to suppress a number of overall immune response parameters. Specifically, cell surface molecules necessary for T-cell activation and effector functions may be hidden from view or have their production downregulated by ferritin. When there is severe hyperferritinemia, such as in cancer and the acquired immunodeficiency syndrome, these interactions may take on pathogenic significance (10). Gupta, Imam and Licorish suggested in their study that serum ferritin levels rise as immunological dysfunction worsens and may contribute to the development of cell-mediated immune dysfunction in acquired immunodeficiency syndrome (11). Levina et al. demonstrated in their study that patients of chronic diffuse diseases of liver reported a high plasma ferritin concentration, which causes antibodies to this protein to develop and then produce circulating immune complexes that cause metabolic abnormalities that worsen the pathologic process. A decrease in ferritin and the amount of circulating immune complexes in the plasma spurred on by plasmapheresis and deferoxamine therapy has a positive impact on the patients' condition (12). The notion that extracellular ferritin is selectively released is supported by the revelation of a cell surface H-ferritin receptor, and several studies point to the involvement of macrophages in the synthesis and secretion of extracellular ferritin. Extracellular H-ferritin mediates an immunosuppressive signalling cascade by binding to a receptor expressed on several cell types, according to evidence from in vitro tests (13).

Association with inflammation

Ample evidence points to serum ferritin's potential active involvement in chronic inflammatory illnesses. Serum ferritin is a known acute phase protein that measures the severity of acute and chronic inflammation. Accordingly, a number of research indicate a connection between mild chronic inflammation and serum ferritin levels (14). Serum ferritin poses a conundrum since while not being synthesized in serum; ferritin is present there. Also, it is a well-known inflammatory marker, but it is not apparent if serum ferritin represents or contributes to inflammation or if it participates in an inflammatory cycle. Serum ferritin is a sign of cellular injury since it is produced by injured cells. Although the protein in serum ferritin is thought to be innocuous, the majority of its usual iron complement has been lost or dumped, which is severely hazardous when unliganded. On the basis of basic chemical kinetics, it implies that serum ferritin levels can be related to both disease and

body iron reserves (15). A rising incidence of iron deficiency occurs in patients with inflammatory diseases such as inflammatory bowel disease, chronic heart failure, and chronic kidney disease, which has negative clinical effects. Serum ferritin levels are a sensitive indicator of iron status under normal conditions, but because ferritin is an acute-phase reactant that rises in reaction to inflammation, the diagnosis is made more difficult. Hepcidin levels rise in response to proinflammatory cytokines, which also encourages the accumulation of iron by ferritin inside storage sites and limits dietary iron intake. Although normal or increased levels of serum ferritin, patients with inflammatory diseases may have limited iron availability for erythropoiesis and other cell processes because of elevated hepcidin expression (16).

It is well known that inflammation and elevated circulating ferritin levels are associated with chronic liver injury; however, elevated ferritin levels may not only be a result of inflammation but also be involved in mediating the injury-related processes. Circulating ferritin levels are raised with inflammation in chronic liver injury and represent body iron reserves. Although its function in hepatic inflammation and fibrogenesis is uncertain, H-ferritin demonstrates a number of extrahepatic immunomodulatory features. In response to liver damage, hepatic stellate cells produce proinflammatory mediators that promote fibrogenesis. On active hepatic stellate cells, a particular ferritin receptor has been found, albeit its identity and significance in stellate cell activation are unknown. It is hypothesized that ferritin regulates proinflammatory function in hepatic stellate cell biology by acting as a cytokine through nuclear factor kappa B regulated signalling. Hepatic proinflammatory mediators are activated and significantly increased in expression as a result of ferritin's activation of an iron-independent signalling cascade (17). Findings of a retrospective review study concluded that severely raised ferritin levels may be linked to rheumatological diseases, they are more frequently detected in people with other illnesses including infection or cancer. Additionally, people with chronic inflammation or diseases that appear to be indolent might have exceedingly high ferritin levels (18). Khan et al. concluded in their study that in overweight and obese individuals, ferritin is a measure of inflammation rather than iron status. Complete iron profiles that include transferrin are more accurate at predicting iron deficit in such individuals than serum ferritin alone (19).

Relation with malignancy

Many cancer patients have elevated ferritin levels in their serum, and these higher levels are associated with progressive disease and unfavourable clinical outcomes. Furthermore, tumour-associated macrophages, which have recently been discovered as playing crucial roles in tumour growth and therapeutic resistance, express ferritin at high levels. These traits imply that ferritin would be a desirable target for cancer therapy since its downregulation might affect the favourable tumour microenvironment, eliminate cancer cells, and improve chemotherapy sensitivity (20). Due to its prooxidant activity, which can result in oxidative DNA damage, iron has been implicated as a risk factor for several malignancies. Additionally, it has been demonstrated that those with hemochromatosis or iron overload are more likely to develop liver cancer. Globally, a larger intake of heme iron has demonstrated a tendency toward a positive connection with cancer risk, based on the findings of the systematic review and the meta-analysis. High blood ferritin levels and other biomarkers of iron storage have been linked to an increased risk of cancer (21).

Although serum ferritin has been implicated as a potential cancer biomarker in a number of research studies, the findings are conflicting. In particular, serum ferritin was higher in cancer patients with head and neck, lung, pancreatic, and renal cell carcinoma. Ferritin levels were also greater in the latter phases stages III and IV than in healthy persons. Serum ferritin is a sensitive biomarker for the detection of advanced stages of cancers and functions as a biomarker for head and neck cancer, lung cancer, renal cell carcinoma, pancreatic cancer, and renal cell carcinoma (22). Ferritin is present in breast cancer patients' serum and tumour lysates at higher levels, and its rise is associated with a poorer clinical prognosis. Increased tumour histological grade was associated with decreased ferritin expression in cancer cells but increased ferritin-rich CD68-positive macrophage infiltration. It's interesting to note that the stroma around the tumours stained with ferritin, suggested local release within the breast. Macrophages were able to secrete ferritin in cell culture, but not breast cancer cells, and this secretion was amplified in response to pro-inflammatory cytokines. The proliferation of the epithelial breast cancer cell lines MCF7 and T47D was induced by ferritin. Additionally, this proliferative effect was unrelated to ferritin's iron content and did not raise intracellular iron levels in cancer cells, pointing to a novel iron-independent activity for this protein. All of

this point to a possible inflammatory effector mechanism whereby ferritin directly promotes tumorigenesis: the generation of ferritin by infiltrating macrophages in breast cancers (23). Significance of ferritin in cancer is illustrated in (Figure 1).

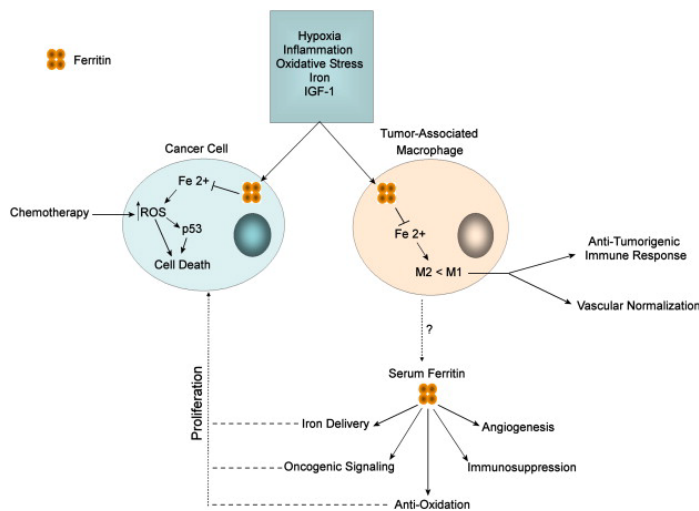


Figure 1: Significance of ferritin in cancer (28)
*ROS: reactive oxygen species

Results of a prospective study concluded that higher serum iron levels or transferrin saturation have been linked to an increased risk of both non-skin cancer and cancer death. Conversely, lower incidence of non-skin cancer was linked to higher serum iron concentrations in men. Uncertainty surrounds the molecular underpinnings of the observed variations in the relationship between serum iron and the risk of non-skin cancer (24). Findings of a case-control study concluded that high levels of serum ferritin may be a risk factor for pancreatic cancer, making it a potential novel tumour marker for pancreatic cancer diagnosis (25). Contradictory to this Quintana et al. demonstrated inverse relationships between ferritin levels and cancer mortality and breast cancer risk (26). Similarly, Kim et al. discussed in their study that despite evidence from experimental studies that iron may contribute to the production of oxidative stress, epidemiological research on the correlation between body iron store markers and cancer or cardiovascular disease is still debatable. There was no link between serum ferritin and all-cause, cancer, or cardiovascular death (27). Further research is however needed to elaborately study and define the role of ferritin in malignancy, immunity and inflammation since the available literature is limited to past times and clinical studies are scarce.

Conclusion

In addition to its homeostatic function, ferritin may be a significant marker and pathogenic factor in inflammatory pathology through its signalling as part of the innate immune response and regulation of lymphocyte activity although research in future can be beneficial in defining the role and mechanism of ferritin in malignancy and immunity.

Disclosure

Conflict of interest

There is no conflict of interest

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Ethical consideration

Non applicable

Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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