Hyperferritinemia in Autoimmunity

Gisele Zandman-Goddard MD[1] and Yehuda Shoenfeld MD[2*]

[1]Department of Medicine C, Wolfson Medical Center, Holon, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel,
[2]Department of Medicine and Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: ferritin, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, thyroiditis, dermatomyositis

Abstract

Controlling iron/oxygen chemistry in biology depends on multiple genes, regulatory messenger RNA structures, signaling pathways and protein catalysts. Ferritin synthesis is regulated by cytokines (tumor necrosis factor-alpha and interleukin-1α) at various levels (transcriptional, post-transcriptional, translational) during development, cellular differentiation, proliferation and inflammation. The cellular response by cytokines to infection stimulates the expression of ferritin genes. The immunological actions of ferritin include binding to T lymphocytes, suppression of the delayed-type hypersensitivity, suppression of antibody production by B lymphocytes, and decreased phagocytosis of granulocytes. Thyroid hormone, insulin and insulin growth factor-1 are involved in the regulation of ferritin at the mRNA level. Ferritin and iron homeostasis are implicated in the pathogenesis of many disorders, including diseases involved in iron acquisition, transport and storage (primary hemochromatosis) as well as in atherosclerosis, Parkinson's disease, Alzheimer disease, and restless leg syndrome. Mutations in the ferritin gene cause the hereditary hyperferritinemia-cataract syndrome and neuroferritinopathy. Hyperferritinemia is associated with inflammation, infections and malignancies, and in systemic lupus erythematosus correlates with disease activity. Some evidence points to the importance of hyperferritinemia in dermatomyositis and multiple sclerosis, but further mechanistic investigations are warranted.

IMAJ 2008;10:83–84

Ferritin is nature's unique and conserved approach to the controlled and safe use of iron and oxygen, with protein synthesis in animals adjusted by dual genetic DNA and mRNA sequences that selectively respond to iron or oxidant signals and link ferritin to proteins of iron, oxygen and antioxidant metabolism [1]. It is well established that elevated ferritin levels are found in adult Still's disease, but hyperferritinemia has been scantily investigated in other autoimmune diseases. Acute-phase reactants such as C-reactive protein in rheumatoid arthritis are elevated and conducive of disease activity. However, in systemic lupus erythematosus, acute-phase reactants such as serum amyloid component P, C-reactive protein, and mannose binding lectin are not raised, indicating a possible mechanism of antibody production that blocks their function [2,3]. In this article, we report on hyperferritinemia in various autoimmune diseases.

* Incumbent of the Laura Schwartz-Kipp Chair in Autoimmunity, Tel-Aviv University, Israel.

IL = interleukin

TNFα = tumor necrosis factor-alpha

RA = rheumatoid arthritis

Ferritin structure, regulation and function

The structure, regulation and function of ferritin are extensively reviewed in a previous paper [4]. Briefly, ferritin is the major intracellular iron storage protein in all organisms; it shares a unique protein cage structure resembling spherical viruses and permits storage of up to 4500 Fe (III) atoms. Each apoferritin (iron-free ferritin) shell comprises a heavy subunit (H-subunit) and a light subunit (L-subunit) that are identified on chromosomes 11q23 and 19q13.3, respectively. H-ferritin plays a major role in rapid detoxification of iron and intracellular iron transport (found in the heart and pancreas), while the L-subunit is involved in iron nucleation, mineralization and long-term storage (predominately found in the liver and spleen) [1,5]. Ferritin's control of iron/oxygen chemistry depends on multiple genes, regulatory messenger RNA structures, signaling pathways and protein catalysts. The cellular response by cytokines to infection stimulates the expression of ferritin genes. Tumor necrosis factor-alpha and interleukin-1α alone or together induce the expression of the H chain of ferritin in mouse adipocytes, human muscle cells and other cell types. Translation of ferritin is induced by IL-1β, IL-6 or TNFα in the HepG2 hepatic cell line, and iron is required for this regulation [5]. Expression of ferritin is also regulated by hormones (thyroid, insulin), growth factors (insulin growth factor-1), second messengers, and hypoxia-ischemia and hyperoxia (nitric oxide) [6].

Ferritin and inflammation/infection/immune system

Macrophage ferritin accumulates during inflammation, when serum iron decreases and iron in specific cells increases, leading to ferritin with more iron/protein cage [1]. Ferritin exhibits different immunological activities, including binding to T lymphocytes, suppression of the delayed-type hypersensitivity to induce anergy, suppression of antibody production by B lymphocytes, reduction of the phagocytosis of granulocytes, and regulating granulomonocytopoiesis [4].

Hyperferritinemia in autoimmune diseases

Adult-onset Still's disease is a systemic inflammatory disorder characterized by fever, arthritis, rash, and elevated levels of glycosylated and basic ferritin in 89% of cases [7,8]. High concentrations of ferritin are found in the synovial fluid of RA patients [9], and in patients with juvenile RA correlates with disease activity [10]. In another study, the mean ferritin was higher in RA patients with active disease (utilizing the DAS28

score) when compared to controls [11]. In studies of SLE patients, serum levels of ferritin during the more active stage of SLE exceeded those of RA patients and patients at less active stages of SLE [4,12,13]. Serum ferritin was elevated especially in serositis and hematological manifestation [12]. Only one study found contrasting results [14]. Iron is essential for myelin formation and oxidative phosphorylation. Data indicate that free radicals participate in the pathogenesis of experimental allergic encephalomyelitis, and iron has been implicated as the catalyst leading to their formation [15]. In one study, apoferritin was injected into EAE mice and resulted in a reduction in disease activity [16]. In brain tissue from multiple sclerosis patients, the normal pattern of transferrin and ferritin binding distributions is disrupted. Ferritin binding is absent in the lesion itself and in the immediate periplaque region within the white matter but returns to normal as the distance from the lesion becomes greater. These data suggest that the loss of ferritin binding is involved in or is a consequence of demyelination associated with MS [17]. In MS patients, ferritin levels were significantly elevated in the serum and the cerebrospinal fluid only in chronic progressive active patients [18]. Thyroid hormone induces ferritin expression and, in one study, elevated ferritin levels in patients with subacute thyroiditis correlated with disease activity. These levels were higher when compared to patients with Graves' disease and Hashimoto's thyroiditis [20].

Ferritin as a novel biomarker

In our study, serum samples from 403 patients with various autoimmune diseases were evaluated for hyperferritinemia (levels are age and gender dependent). We utilized a two-site immunoluminometric assay (sandwich principle). Monoclonal antibodies were used for the coating of the solid phase (magnetic particles) and for the tracer. The tests were performed on the LIAISON-Analyser. Twenty-three percent of SLE patients had elevated ferritin levels (5 men/18 women), and a statistical significant correlation was found with disease activity using the ECLAM score (European Collaborative Lupus Activity Measure) ($P = 0.03$). Fifteen percent of dermatomyositis patients had elevated concentrations of ferritin, as did 8% of MS patients. Four percent of RA patients had hyperferritinemia that did not correlate with elevated titers of rheumatoid factor or anti-cyclic citrullinated peptide antibodies. In systemic sclerosis and polymyositis, hyperferritinemia was negligible [26].

Conclusions

Perturbations in ferritin function are not only detrimental for iron homeostasis, but can lead to disease states by mechanisms of inflammation, infection, injury and repair. Ferritin has been implicated in various diseases and may be important in autoimmune conditions. Hyperferritinemia is present in active SLE, and may play a role in dermatomyositis and MS. Further investigation into the mechanisms of ferritin in this group of diseases is warranted.

SLE = systemic lupus erythematosus
EAE = experimental allergic encephalomyelitis
MS = multiple sclerosis

References

1. Hintze KJ, Theil EC. Cellular regulation and molecular interactions of the ferritins. *Cell Mol Life Sci* 2006;63:591–600.
2. Zandman-Goddard G, Blank M, Langevitz P, et al. Anti-serum amyloid component P antibodies in patients with systemic lupus erythematosus correlate with disease activity. *Ann Rheum Dis* 2005; 64:1698–702.
3. Shoenfeld Y, Szyper-Kravitz M, Witte T, et al. Autoantibodies against protective molecules – C1q, C-reactive protein, serum amyloid P, mannose binding lectin, and apolipoprotein A1. *Ann NY Acad Sci* 2007;1108:227–39.
4. Zandman-Goddard G, Shoenfeld Y. Ferritin in autoimmune diseases. *Autoimmun Rev* 2007;6:457–63.
5. You SA, Wang Q. Ferritin in atherosclerosis. *Clin Chim Acta* 2005; 357:1–16.
6. Torti FM, Torti SV. Regulation of ferritin genes and protein. *Blood* 2002;99:3505–16.
7. Uppal SS, Al-Mutairi M, Hayat S, Abraham M, Malayiya A. Ten years of clinical experience with adult onset Still's disease: is the outcome improving? *Clin Rheumatol* 2007;26:1055–60.
8. van-Reeth C, Moel GL, Lasne Y, et al. Serum ferritin and isoferritins are tools for diagnosis of active adult Still's disease. *J Rheumatol* 1994;21:890–5.
9. Blake DR, Bacon PA, Eastham EJ, Brigham K. Synovial fluid ferritin in rheumatoid arthritis. *Br Med J* 1980;281:715–16.
10. Pelkonen P, Swanjung K, Siimes MA. Ferritinemia as an indicator of systemic disease activity in children with systemic juvenile rheumatoid arthritis. *Acta Paediatr Scand* 1986;75:64–8.
11. Yildirim K, Karatay S, Melikoglu MA, Gureser G, Ugur M, Senel K. Associations between acute phase reactant levels and disease activity score (DAS28) in patients with rheumatoid arthritis. *Ann Clin Lab Sci* 2004;34:423–6.
12. Lim MK, Lee CK, Ju YS, et al. Serum ferritin as a serological marker of activity in systemic lupus erythematosus. *Rheumatol Int* 2001;20:89–93.
13. Beyan E, Beyan C, Demirezer A, Ertugrul E, Uzuner A, The relationship between serum ferritin levels and disease activity in systemic lupus erythematosus. *Scand J Rheumatol* 2003;32:225–8.
14. Hesselink DA, Aarden LA, Swak AJG. Profiles of the acute-phase reactants C-reactive protein and ferritin related to the disease course of patients with systemic lupus erythematosus. *Scand J Rheumatol* 2003;32:151–5.
15. Levine SM, Chakrabarty A. The role of iron in the pathogenesis of experimental allergic encephalomyelitis and multiple sclerosis. *Ann NY Acad Sci* 2004;1012:252–66.
16. LeVine SM, Maiti S, Emerson MR, Pedchenko TV. Apoferritin attenuates experimental allergic encephalomyelitis in SJL mice. *Dev Neurosci* 2002;24:177–83.
17. Hulet SW, Powers S, Connor JR. Distribution of transferring and ferritin binding in normal and multiple sclerotic human brains. *J Neurol Sci* 1999;165:48–55.
18. Sfagos C, Makis AC, Chaidos A, et al. Serum ferritin, transferrin and soluble transferring receptor levels in multiple sclerosis patients. *Mult Scler* 2005;11:272–5.
19. Sakata S, Nagai K, Maekawa H, et al. Serum ferritin concentration in subacute thyroiditis. *Metabolism* 1991;40:683–8.
20. Orbach H, Zandman-Goddard G, Amital H, et al. Novel biomarkers in autoimmune diseases. *Ann NY Acad Sci* 2007;1109:385–400.

Correspondence: Dr. Y. Shoenfeld, Dept. of Medicine B, Sheba Medical Center, Tel Hashomer 52621, Israel.
Phone: (972-3) 530-2652
Fax: (972-3) 535-2855
email: shoenfel@post.tau.ac.il