Hyperferritinemia in Autoimmunity

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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.

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 granulomonocytopeniesis [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 culprit 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 hyperferritinnemia (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 polyarthritis, 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.

**References**