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Eppur Si Muove: ferritin is essential in modulating inflammation

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Summary

Ferritin, which was only discovered in the last century, has stirred a formidable debate. Ferritin has long been appreciated as a non-specific acute-phase reactant. Several years ago, we hypothesized the contributory role of ferritin as a pathogenic molecule rather than being a product of inflammation. The latest emerging evidence provides support to this notion. Such revelation provides a step forward towards the understanding of disease conditions associated with hyperferritinaemia, and hence provide new targets for treatment modalities.

Keywords: acute phase reactant, ferritin, hyperferritenemic syndrome, macrophage activating syndrome, pro-inflammation

Commentary

In the last few decades, ferritin, a ubiquitous key protein in iron metabolism, has been shown to present a paradox. Ferritin is recognized widely as a non-specific acute-phase reactant and inflammatory marker, but it remains uncertain and debatable whether serum ferritin in itself is a perpetrator of inflammation.

Ferritin is an iron-binding molecule that stores iron in a biologically available form. Apoferritin (iron-free ferritin) is composed of 24 subunits that are arranged by their molecular weight into heavy (H-) subunits and light (L-) subunits [1]. The ratio between H- and L-subunits vary widely depending on the tissue type and physiological status of the cell. The production of ferritin is known to be under delicate control at several levels by various factors, among which are cytokines, oxidative stress, growth factors, hypoxia–ischaemia and others [1].

Recently, research has imparted a great deal of knowledge regarding the role of ferritin on the immune system. Accumulated evidence highlighted the role of ferritin as both a signalling molecule and a direct mediator of the immune system. Inflammation and oxidative stress has been proved to upregulate the synthesis of ferritin in multiple cells, including macrophages. It is proposed that FER-2, which is a regulatory element, acts as a binding site to nuclear factor kappa B (NF-κB), a prototypical proinflammatory signalling molecule. From another aspect, ferritin-treated cells activated a T cell immunoglobulin mucin 2 (TIM 2)-independent pathway that results ultimately in the activation of NF-κB, which enhances the production of proinflammtory mediators including, for instance, interleukin (IL)-1β among others, therefore resulting in a cycle of activation [2].

Another established concept in the biology of ferritin is its immunosuppressant role. The mechanism for the immunosuppression requires further elucidation, but it is believed that it probably occurs through the inhibitor of lymphocyte stimulations (i.e. CD2) or blockage of chemokine receptors involved in cell proliferation [3,4]. A dysregulation in these processes would probably counteract ferritin's immunosuppressant role [4]. Such an assumption led Recalcati *et al.* [2] to hypothesize the intricate role of ferritin in inducing autoimmunity.

The fine tune between the proinflammatory and anti-inflammatory capacity is hence proposed to be dependent upon the different signalling pathways activated, and the various contexts. To elucidate the last point more clearly, for ferritin to be pathogenic it would require another factor, for instance a proinflammatory environment, for example, on an infection background, hyperinflammation or genetic basis [5].

The pathogenic role of ferritin could also be appreciated further in the study conducted by Ruddell *et al.* [6], who set out to investigate the immunological role of H-ferritin on hepatic inflammation. Ferritin was shown to regulate an iron-independent signalling pathway that resulted ultimately in NF-κB activation and, hence, increased proinflammatory molecule release, thus proposing the role of ferritin as a cytokine regulating proinflammation.

In 2013, we hypothesized that elevated ferritin levels in hyperinflammatory conditions are not only a byproduct of the inflammatory process, but rather play an integral role in the pathogenic mechanism [5]. Hence, we identified four conditions that are characterized by hyperinflammation and hyperferritinaemia with closely similar clinical and laboratory, and coined the term 'hyperferritinaemic syndrome'. Hyperfertinaemic syndrome entails four distinctive conditions, including macrophage activation syndrome (MAS), adult-onset still disease (AOSD), catastrophic anti-phospholipid syndrome (cAPS) and sepsis. Not only do they share clinical and laboratory parameters, these conditions were proved to have a considerable similarity in response to therapies employed, such as corticosteroids, plasma exchange and intravenous immunoglobulin, thus supporting a common aetiological mechanism, with ferritin being a common link [5].

Our proposed hypothesis challenged the status quo and raises the question of whether ferritin is an innocent product of inflammation or if, itself, has a pathogenic role.

In the current issue of *Clinical and Experimental Immunology*, Ruscitti and colleagues [7] present interesting evidence that suggests the contribution of H-ferritin, M1 macrophages ($CD86^+$/H-$ferritin^+$) and proinflammtory cytokines in a vicious pathogenic loop. In their study they examined bone marrow (BM) samples from 10 adult patients with MAS. MAS is a hyperinflammatory disease referred to as secondary haemophagocytic lymphohistiocytosis, which in these cases occurs secondarily and in the context of a rheumatic disease, and is characterized by elevated proinflammatory cytokines, including IL-1β, tumour necrosis factor (TNF)-α, IL-6 and IL-18 [8].

In their study, H-ferritin was elevated in BM samples and was correlated positively with IL-1β and C-reactive protein (CRP). Additionally, a higher population of macrophages was shown to infiltrate the BM with up-regulated co-localization of H-ferritin and increased secretion of proinflammatory cytokines. Moreover, the state of hypercytokinaemia was shown to enhance the preferential differentiation and recruitment of classical (M1) macrophages (a cell subset that is linked closely to proinflammatory cytokine production), therefore fuelling the pathogenic vicious cycle. Interestingly, peripheral blood cytopaenia (characteristic for the disease) was shown to be correlated inversely with ferritin levels and $CD68^+$/$ferritin^+$-expressing cells, suggesting a possible role as biomarkers.

All this emerging evidence substantiates our preconceptualized viewpoint. We continue to believe that as a peptide, H-ferritin has wide array of functions, including a pathogenic role, and is not simply the product of inflammation. Additionally, ferritin is proposed to be a biomarker for the disease which could aid in early disease diagnosis, as well as in monitoring response to treatment modalities employed. The concept of understanding the role of a possible denominator in the pathogenesis of these diseases allows for the development of more targeted therapy. Accordingly, additional research is required to delineate further the molecular pathway of ferritin function, to study the clinical significance of ferritin as a biomarker and to develop targeted therapies that can help to manage disease cases.

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Disclosure

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