The Hyperferritinemic Syndromes and CD163: a Marker of Macrophage Activation

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Ferritin is a key protein in iron metabolism. Its involvement in iron detoxification and iron storage is known, but recently, a new role in the pathogenesis of different autoimmune and autoinflammatory syndromes was hypothesized [1]. Four immune mediated conditions sharing the feature of marked hyperferritinemia have been gathered under the single term "Hyperferritinemic Syndromes" [1]. Such syndromes include macrophage activation syndrome (MAS), catastrophic antiphospholipid syndrome (CAPS), septic shock, and adult-onset Still's disease (AOSD). These conditions constitute the scenario of the so-called cytokine storm and share a marked hyperferritinemia as well as clinical and laboratory features.

As far as we know, with regard to its structure, ferritin is composed of two different subunits, H and L, whose ratio is not fixed as it varies among several inflammatory and infectious conditions. Ferritin in spleen and liver, as well as in serum, is largely composed of L-subunits (involved in iron storage), while in heart and kidney the H-subunits (involved in iron detoxification) are predominant. Recently, an increase in the H-subunit expression, driven by different inflammatory stimuli, was demonstrated [2]. Furthermore, a possible role for ferritin in the regulation of immune response was suggested by Recalcati et al. in 2008 [3]. Indeed, the H-ferritin subunit can inhibit lymphoid and myeloid cell proliferation; and a specific ferritin receptor named TIM-2, present on several immune effector cells in murine models, has been identified [4]. Ruddell et al. reported in 2009 [5] that ferritin may behave similarly to pro-inflammatory cytokines, binding to the TIM-2 receptor in hepatic cell media. In doing so it may activate the hepatic cells, inducing enhanced production of several cytokines such as interleukin (IL)-1β.

With regard to its production, ferritin synthesis is induced by several inflammatory stimuli including cytokines IL-1α, IL-1β, IL-18, tumor necrosis factor-alpha (TNFα), interferon-gamma (IFNγ), macrophage-colony stimulating factor (M-CSF) and IL-6. It was initially believed that the main passive source of ferritin was its leakage from damaged cells during inflammatory conditions. Ghosh et al. [6] later described an active production of ferritin L-subunit through a classical secretory pathway. More recently, Cohen et al. [7] reported the significant contribution of macrophages in ferritin production owing to the proven ability of these cells to actively secrete this protein through a non-classical secretory pathway. Such findings support the idea of active production of ferritin in the course of specific autoinflammatory conditions and, thus, a possible role other than second acute inflammatory reactant.

ADULT-ONSET STILL'S DISEASE

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory syndrome characterized by a typical triad of symptoms comprising a spiking fever, maculopapular rash and arthritis. Apart from laboratory features, marked neutrophilic leukocytosis and increased cytokine production (such as IL-18, one of the main cytokines driving the inflammatory response) [8], hyperferritinemia is one of the main findings. Indeed, over the course of AOSD, ferritin serum values are more than five times above the upper limit of normal, reaching extremely high levels in some cases (> 50,000 μg/L). For this reason, a fivefold increase in ferritin serum levels was noted to have a specificity and sensitivity for AOSD diagnosis of 41% and 80% respectively. Mehta et al. [9] speculated on the possible pathogenic function of ferritin in AOSD, suggesting the existence of a mutated form with defective iron release. A possible role has been proposed for the histiocyte-macrophagic system and/or increased release from damaged hepatocytes over the course of AOSD.

MACROPHAGES AND CD163

Macrophages are involved in the regulation of iron homeostasis which, during inflammatory conditions, leads to increased iron uptake and suppressed iron release [10]. Indeed, in the course of inflammatory conditions "M1 macrophages" execute

iron uptake and iron storage; on the other hand, during the resolution of inflammation, "M2 macrophages" are involved in iron release. These "M2 macrophages" usually express scavenger receptors, and CD163, involved in haptoglobin–hemoglobin complex uptake, is one of the best characterized. sCD163 represents the serum form of this molecule and it is released by shedding into the sera during inflammatory conditions. Its precise function has not yet been defined; however, different stimuli are responsible for its production including Toll-like receptor (TLR) activation [10]. This molecule was found over-expressed in several infectious conditions; nonetheless, it has been proposed as a biomarker for MAS. Over the course of MAS the sCD163 levels positively correlate with ferritin serum levels, suggesting a possible pathogenic relationship between these molecules. Thus, according to such findings, the sCD163 is considered one of the main markers of macrophage activation [10].

CD163 AND ADULT-ONSET STILL'S DISEASE

To determine the possible link between ferritin production and macrophage activation, sCD163 expression was recently evaluated for the first time by our group in patients with AOSD (in press). We evaluated the expression of sCD163, with the aim of defining its possible utility as a biomarker of disease activity as well as identifying a possible correlation with ferritin serum levels. Patients with sepsis and healthy subjects served as control groups. Despite the lack of specificity, sCD163 was significantly increased in active patients with AOSD when compared with non-active patients. Importantly, a positive correlation between sCD163 and ferritin serum levels supports the hypothesis of a possible role of macrophages in ferritin production.

Thus, in the unfinished puzzle of autoinflammatory diseases, new players have arrived on the scene and their exact role has still to be defined.

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References

1. Rosário C, Zandman-Goddard G, Meyron-Holtz EG, D'Cruz DP, Shoenfeld Y. The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. *BMC Med* 2013; 11: 185.
2. Torti SV, Kwak EL, Miller SC, et al. The molecular cloning and characterization of murine ferritin heavy chain, a tumor necrosis factor-inducible gene. *J Biol Chem* 1988; 263: 12638-44.
3. Recalcati S, Invernizzi P, Arosio P, Cairo G. New functions for an iron storage protein: the role of ferritin in immunity and autoimmunity. *J Autoimmun* 2008; 30 (1-2): 84-9.
4. Chen TT, Li L, Chung DH, et al. TIM-2 is expressed on B cells and in liver and kidney and is a receptor for H-ferritin endocytosis. *J Exp Med* 2005; 202 (7): 955-65.
5. Ruddell RG, Hoang-Le D, Barwood JM, et al. Ferritin functions as a proinflammatory cytokine via iron-independent protein kinase C zeta/nuclear factor kappaB-regulated signaling in rat hepatic stellate cells. *Hepatology* 2009; 49 (3): 887-900.
6. Ghosh S, Hevi S, Chuck SL. Regulated secretion of glycosylated human ferritin from hepatocytes. *Blood* 2004; 103 (6): 2369-76.
7. Cohen LA, Gutierrez L, Weiss A, et al. Serum ferritin is derived primarily from macrophages through a nonclassical secretory pathway. *Blood* 2010; 116 (9): 1574-84.
8. Priori R, Colafrancesco S, Alessandri C, et al. Interleukin 18: a biomarker for differential diagnosis between adult-onset Still's disease and sepsis. *J Rheumatol* 2014; 41 (6): 1118-23.
9. Mehta B, Efthimiou P. Ferritin in adult-onset still's disease: just a useful innocent bystander? *Int J Inflam* 2012; 2012: 298405.
10. Cairo G, Recalcati S, Mantovani A, Locati M. Iron trafficking and metabolism in macrophages: contribution to the polarized phenotype. *Trends Immunol* 2011; 32 (6): 241-7.