The Hyperferritinemic Syndromes and CD163: a Marker of Macrophage Activation

Serena Colafrancesco MD, Roberta Priori MD PhD, Cristiano Alessandri MD, Elisa Astorri MD PhD, Carlo Perricone MD, Miri Blank PhD, Nancy Agmon-Levin MD, Yehuda Shoenfeld MD FRCP (Hon.) MaACR and Guido Valesini MD

1Department of Medicine, Rheumatology Unit, Sapienza University, Rome, Italy
2Zabludowicz Center for Autoimmune Diseases Sheba Medical Center, Tel Hashomer, Israel
3Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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 histioyte-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.

References


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

Correspondence

Dr. R. Priori
Dipartimento di Medicina Interna e Specialità Mediche, UOC Reumatologia, Sapienza Università di Roma, Policlinico Umberto I, Viale del Policlinico 155, 00161 Roma, Italy
email: roberta.priori63@gmail.com

Capsule

Reversion of advanced Ebola virus disease in non-human primates with ZMapp

Without an approved vaccine or treatments, Ebola outbreak management has been limited to palliative care and barrier methods to prevent transmission. These approaches, however, have yet to end the 2014 outbreak of Ebola after its prolonged presence in West Africa. Qiu et al. show that a combination of monoclonal antibodies (ZMapp), optimized from two previous antibody cocktails, is able to rescue 100% of rhesus macaques when treatment is initiated up to 5 days post-challenge. High fever, viremia and abnormalities in blood count and blood chemistry were evident in many animals before ZMapp intervention. Advanced disease, as indicated by elevated liver enzymes, mucosal hemorrhages and generalized petechia could be reversed, leading to full recovery. ELISA and neutralizing antibody assays indicate that ZMapp is cross-reactive with the Guinean variant of Ebola. ZMapp exceeds the efficacy of any other therapeutics described so far, and results warrant further development of this cocktail for clinical use.

“In matters of style, swim with the current; in matters of principle, stand like a rock”

Thomas Jefferson (1743-1826), American Founding Father, principal author of the Declaration of Independence (1776), and third President of the United States (1801–1809). He was a spokesman for democracy, embracing the principles of republicanism and the rights of the individual