Severe COVID-19 and related hyperferritinaemia: more than an innocent bystander?

The catastrophic outbreak of acute respiratory distress syndrome induced by SARS-CoV-2 (the coronavirus disease 2019, COVID-19) has strongly confirmed the important role of systemic hyperinflammation, independently of the trigger, as a major cause of death.[1] In fact, accumulating evidence suggests that a subgroup of patients with severe COVID-19 is burdened by a cytokine storm syndrome, an overwhelming systemic inflammation with a massive release of pro-inflammatory cytokines. As reported in 150 patients in Wuhan, China, a subset of patients with COVID-19 are characterised by raised levels of ferritin, which identified those patients at higher risk of poor outcome (1297.6 ng/mL in non-survivors compared with 614.0 ng/mL in survivors).[1] Although the amplitude of ferritin elevation is not comparable, this finding may resemble what is observed in diseases included under the umbrella of the hyperferritinaemic syndrome.[2] This syndrome includes macrophage activation syndrome (MAS), systemic juvenile idiopathic arthritis, adult-onset Still's disease (AOSD) and catastrophic anti-phospholipid syndrome, which are burdened by severe clinical picture and high mortality rate.[2] Ferritin, the common denominator of all these diseases, is an iron storage protein comprising 24 subunits of two types, heavy (FeH) and light (FeL) subunits, differently expressed in tissues.[2] After specific injuries, pro-inflammatory cytokines activate the liver to produce several defence proteins, such as pentraxins (ie, C reactive protein) and ferritin, multifunctional proteins at the crossroads of immunity and inflammation. Ferritin transcription responds to interleukin (IL)-1β, IL-6 and molecules of interferon (IFN)-γ signature, which upregulate the ferritin gene transcription through the increased binding of nuclear factor-κB (NF-κB) to FER2 upstream of the iron responsive element and coding region.[2] Furthermore, during inflammation, other sources of ferritin include both secretion by macrophages and release from damaged cells. Interestingly, ferritin may actively play a pathogenic role in enhancing the inflammatory burden in the context of a pro-inflammatory milieu, characterised by high levels of IL-1β and IL-6 (figure 1). Once endocytosed, after binding to different receptors according to the FeH:FeL ratio, independently of its iron content, ferritin stimulates pro-inflammatory pathways, which ultimately culminates in activation of NF-κB, resulting in the increased expression of pro-inflammatory mediators, as shown on the hepatic stellate cells.[3] Intriguingly, in inflammatory infiltrate of AOSD and MAS, FeH and FeH+/IL-12+ pro-inflammatory macrophages are hyper-represented, suggesting that the pro-inflammatory properties of ferritin are mainly related to FeH.[4] The latter is released following inflammatory stimuli and binds a specific receptor on immune cells.[2] Furthermore, in an experimental model of sepsis, the deletion of FeH leads to a blunted activation of NF-κB, with a consequent reduction of pro-inflammatory cytokines, including IL-1β, IL-6, IL-12 and IFN-γ, and improving survival.[5] It has been shown that SARS-CoV-2 RNAs, acting as pathogen-associated molecular patterns and sensing toll-like receptors, trigger downstream cascades, which activate NF-κB, resulting in the production of pro-inflammatory mediators.[6] In this setting, ferritin may further and repeatedly stimulate these signalling pathways, acting as enhancer of the inflammatory process in more severe COVID-19. Thus, a vicious loop is induced by ferritin and pro-inflammatory cytokines, including IL-1β, IL-6 and IFN-γ, activating NF-κB and contributing to the development of a cytokine storm syndrome. Finally, the inhibition of these cytokines leads to a reduction of ferritin levels, as reported in other inflammatory diseases burdened by a cytokine storm syndrome.[2]

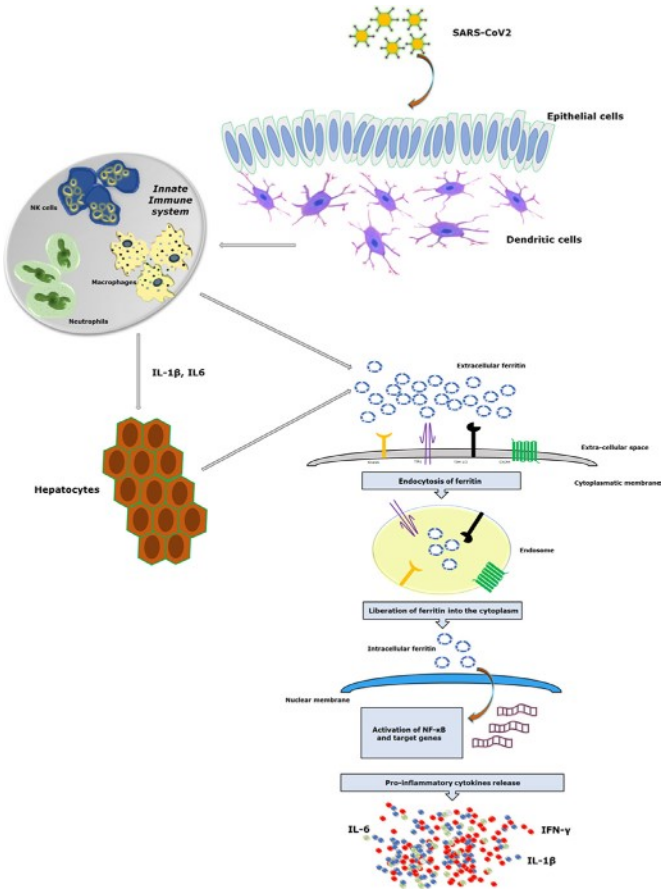

Figure 1 Inflammatory loop induced by high levels of ferritin. SARS-CoV-2 RNAs act as pathogen-associated molecular patterns and sense toll-like receptors, triggering downstream cascades in cells of innate immune system resulting in the production of pro-inflammatory mediators, which induce the production of ferritin. Once endocytosed, independently of its iron content, ferritin stimulates pro-inflammatory pathways, which ultimately culminates in activation of NF-κB, thus enhancing the expression of pro-inflammatory mediators, including IL-1β, IL-6 and IFN-γ. Although not all the receptors are simultaneously required for endocytosis of ferritin, the figure shows that all of the receptors have been found in the endosome since the binding of ferritin to different receptors is dependent on the FeH:FeL ratio. CXCR4, C-X-C chemokine receptor type 4; FeH, heavy ferritin subunit; FeL, light ferritin subunit; IL, interleukin; NF-κB, nuclear factor-κB; Scara5, scavenger receptor class A member 5; TfR1, transferrin receptor protein 1; TIM, T-cell immunoglobulin and mucin domain.

In conclusion, SARS-CoV-2 and consequent COVID-19 are a new great challenge for the health systems worldwide, needing a multidisciplinary approach and a large body of knowledge. Severe COVID-19 displays many common aspects with the other disorders included in the hyperferritinaemic syndrome, and ferritin could enhance the inflammatory burden, thus contributing to a vicious pro-inflammatory loop.

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