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The similar expression of both ferritin and scavenger receptors activation genes in patients with COVID19 and AOSD support their role in the pathogenesis of these diseases and identify a common mechanism at the basis of the "hyperferritinemic syndromes"

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ABSTRACT

A role for COVID19 in "hyperferritinemic syndromes" has been proposed based on its clinical and serological characteristics and its similarities with AOSD. To better understand the molecular pathways responsible of these similarities, we evaluated in the PBMCs of 4 active AOSD patients, 2 COVID19 patients with ARDS, and 2 HCs the expression of genes associated with iron metabolisms, with monocyte/macrophages activation, and finally with NETs formation.

Dear Editor,

Here we report for the first time the results of the comparison among peripheral blood mononuclear cells (PBMCs) RNA-seq from: I. adult-onset Still's disease (AOSD) patients, a polygenic autoinflammatory disease; ii. COVID19 patients, an emerging disease associated with novel coronavirus SARS-CoV2 infection; iii. Healthy controls (HCs), focusing on iron metabolism and peripheral monocyte/macrophage activations. In fact, both these diseases are part of the so-called "hyperferritinemic syndromes" [1–4] in which ferritin probably play an active role in immune response [1,5–7].

We already know that Sars-CoV-2 infects cells *via* ACE2, binding pulmonary and intestinal epithelial cells [8,9] and induces the activation of different transcription factors resulting in the secretion of pro-inflammatory cytokines by monocytes, macrophages, neutrophils, and dendritic cells (DCs) [8–12]. This secretion is amplified by type I interferons (INF) and interferon-stimulated genes (ISGs) [8–12]. Clinically, the disease course is characterised by 3 distinct phases: i) fever, cough, and myalgia during the viral replication; ii) high fever, hypoxiemia, and progression towards pneumonia; iii) progression towards acute respiratory distress syndrome (ARDS), which could result in the death of the patients [12–15]. The clinical picture is the results of the interconnection between SARS-CoV-2 and the host immune system, being the progression to the most severe form driven by the exuberance of the immune response [9,10]. Hyperferritinemia is a well-known marker of severity during COVID19, and ferritin has been suggested to be involved in the immune system activation. It has been reported that, serum ferritin enriched in light (L) subunit may have a possible pro-inflammatory role when compared to ferritin rich in heavy (H) subunit, for which an immunomodulatory role is postulated [1,7]. Lastly, a new role for ferritin has been suggested, has promoter of the formation of neutrophil extracellular traps (NETs), an emerging new pathogenetic mechanism in AOSD [16]. We have already shown some clinical and pathogenic similarities between AOSD and COVID19. To better understand the molecular pathways responsible of these similarities, we evaluated in the PBMCs of 4 active AOSD patients, 2 COVID19 patients with ARDS, and 2 HCs the genes expression, associated with iron metabolisms, with monocyte/macrophages activation, and finally with NETs formation. As far as genes involved in iron uptake and transport pathway (reactome pathway identifier: R-HSA-917937) are concerned we observed a different expression between HCs and patients (both AOSD and COVID19), the latter displaying similar cluster of genes activation (Fig. 1A). Of note, an increased RNA expression of the ferritin L subunit together, with a reduction of the ferritin H subunit RNA expression was observed (Fig. 1F-G). We furtherly explored the genes involved in the binding and uptake of ligands by scavenger receptors (reactome pathway identifier: R-HSA-2173782), as CD163, a molecule associated with macrophage activation, whose increase has been found on cell surface of active AOSD patients, and correlated to serum ferritin levels (Fig. 1B) [17]. Again, patients with COVID19 and AOSD clustered together when compared to HCs, suggesting a similar macrophages activation profile in the peripheral blood of patients with these 2 diseases. The interferon (INF) signalling (reactome pathway identifier: R-HSA-913531) was additionally analysed (Fig. 1C). Again, COVID19 and AOSD patients clustered together with a similar expression of cytokines involved in virus response and type I and type II INF signalling. Also, the interleukin (IL)-1 (reactome pathway identifier: R-HSA-9020702) and the IL-6 (reactome pathway identifier: R-HSA-1059683) signalling were explored, mirroring what already observed with COVID19 and AOSD patients clustering together with a remarkably similar gene expression (Fig. 1D-E). Finally, also the neutrophil extracellular trap formation pathway (KEGG: hsa04613), showed similar pathways activation in AOSD and COVID19 (Fig. 1F). Taking together all these data, new and unexplored therapeutic targets may be identified opening new perspectives in these 2 severe diseases.

To our knowledge this is the first report showing a very close similarity on the ferritin related genes expression in AOSD and COVID19 patients, thus reinforcing the hypothesis of its pro-inflammatory function in these diseases. Furthermore, our results contribute to explore the role of monocytes/macrophages in the pathogenesis of the hyperferritinemic syndromes. Interestingly, we also confirm what recently published on the role netosis in AOSD and COVID19, suggesting that this

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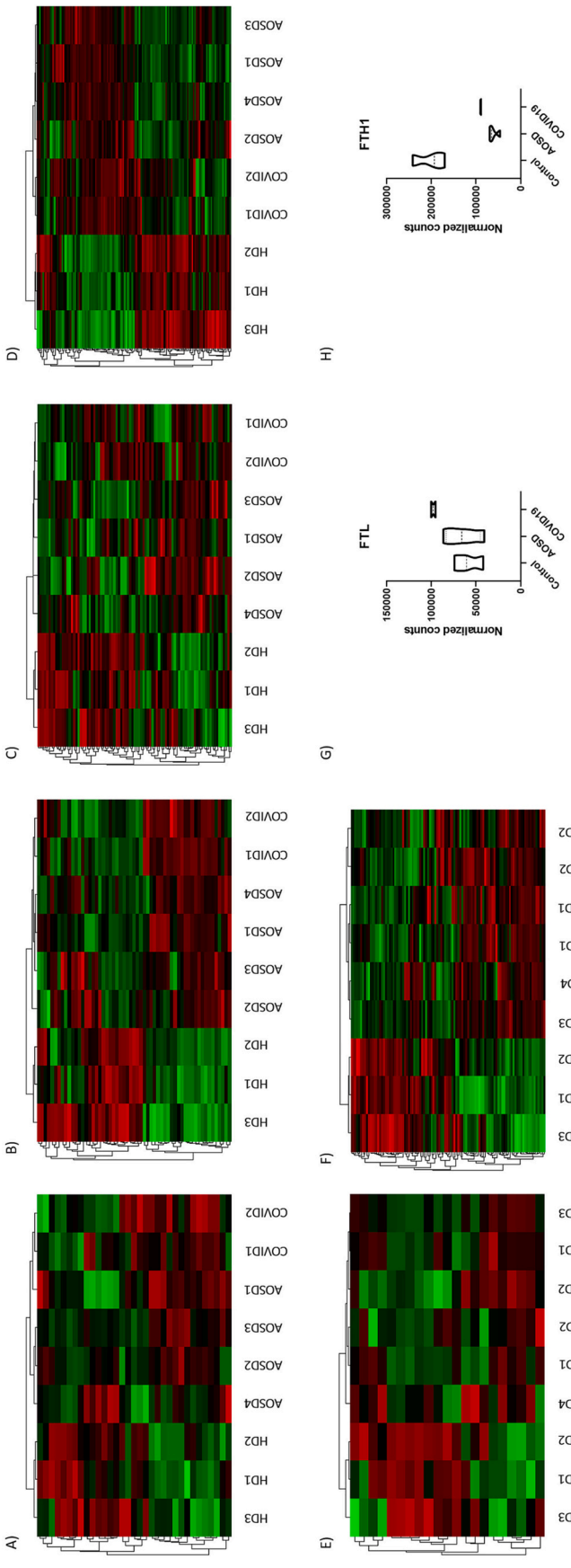

Fig. 1. Heatmap analysis combined with hierarchical clustering analysis of iron uptake and transport (A), binding and uptake of ligands by scavenger receptors (B), interferon signalling (C), IL-1 (D), IL-6 (E), neutrophil extracellular trap formation pathway (F) pathway. Violin plot representations of ferritin light subunit (FTL) (G) and ferritin heavy subunit (FTH1) (H).

pathway is crucial during hyper/auto-inflammatory diseases. In conclusion, our data suggest that ferritin serum levels during auto-inflammatory diseases are more than a simple biomarker of inflammation, but also play a pathogenic role due to its interconnections with cytokines production, monocyte/macrophages activation and NETs formation. These data, when confirmed in larger cohorts and *in vitro* studies, may suggest the possibility to target these pathways for future therapies in the hyper-inflammatory diseases.

Ethics

The study complies with the Declaration of Helsinki and informed consent has been obtained from the subjects.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Data availability

The data that has been used is confidential.

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