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Invited Commentary

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Is it a high time to focus on iron-mediated pathology initiated by COVID-induced inflammation?

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The paper published in the current issue of Acta Biomedica by Duca et al. clearly demonstrate a link between deregulated of iron homeostasis (FeH) and hyperinflammation in non-treated COVID-19 patients. The authors found essentially altered physiologically critical parameters of FeH (serum ferritin, hepcidin, iron, NTBI and transferrin saturation) in concert with enhanced indexes of inflammation (IL6, CRP, chitotriosidase enzyme etc) and oxidative stress (MDA, LDH). Importantly, an essential alteration of the parameters which stay at a cross-road between inflammation and FeH (ferritin and hepcidin) are shown in their work. All these alterations were enhanced by disease severity. These observations are in line with other clinical reports (1-3) while Duca et al. applied quantitative analysis of interaction between two physiological systems – immune response and FeH. Notably, despite more than 240,000 publications related to COVID-19 are currently available in PubMed, the precise mechanisms of abnormal SARS-Cov2-induced pathogenesis still is not completely understood. Recently, it was hypothesized that deregulated FeH is a presumable core of Sars-Cov2-induced pathology (4,5). Nevertheless, just 0,01-0,02% of the papers related to COVID-19 demonstrated a significance of FeH disturbance for the SARS-Cov-2 pathology and the results of Duca et al. adjust to this pool of research. Among iron-related parameters serum ferritin is generally accepted as one of the additional markers of SARS-Cov-2 infection. Elevated ferritin levels are usually interpreted as a marker of inflammation (1). Mechanistically, an elevation of serum ferritin levels mainly results from inflammation followed by local ferroptosis while subsequent disturbance of local FeH amplifies both inflammation and the FeH deregulation. Data regarding serum hepcidin levels are a bit contradictory among publications. Basically, physiological role of hepcidin, a major FeH hormone, is protecting

(4). Mechanistically, hepcidin down-regulates the only iron exporter ferroportin to lock the iron inside cells, thus, blocking local iron recycling to prevent tissue injury. This hepcidin function makes local hepcidin levels extremely important and it may be expected to be as pronounced as other FeH parameters (ferritin, non-heme iron, hemoglobin, haptoglobin) shown in infected RDS patients in comparison to health subjects (6).

Intriguingly, Duca et al. also revealed a correlation between some parameters of the two systems (NTBI versus both transferrin saturation and chitotriosidase as well as hepcidin versus CRP). In addition, a correlation between lung ultrasound (LUS) and high-resolution CT scan of the chest (HRCT) opens a possibility to monitor the disease progression and treatment by LUS.

Importantly, a positive correlation between hepcidin and fibrinogen points on a third system linked to the cross-talk between inflammation and FeH. In patients with COVID-19 , fibrinolysis shutdown is accompanied with markedly elevated D-dimer concentrations, a marker of hyperfibrinolysis (7). Thus, stable fibrin clots persist despite activated fibrinolysis. This paradox can simply be explained, given that ferric ions are able to induce a formation of proteolytically insoluble fibrin clots (8) due to continuous local iron influx via ferroptosis. Despite some limitations of the research as mentioned by Duca et al., the authors should be prized for an attempt to consider a link between deregulated FeH and abnormal coagulation in patients infected by SARS-Cov-2. Surely, this work will inspirate researchers to extent the task and to look for updated designs of both experimental approaches and data analysis.

At least three directions may extend the research of Duca et al. to reveal the mechanism of iron-dependent pathology initiated by SARS-Cov-2 infection.

First, a correlation between local characteristics of inflammation and the FeH in SARS-Cov-2 infected lungs needs an evaluation as they could be more pronounced in compare to systemic one. Remarkably, Duca et al. operate with systemic parameters of the interacting physiological systems while they interpret their results at the level of local changes in iron metabolism mediated by tissue iron-sequestrating cells.

Second, as it is quite difficult to measure many parameters both in lavage and serum in statistically relevant cohort of patients, case reports regarding individual patients may reveal a link between local and systemic characteristics in the course of disease progression and a recovery during treatment.

Third, as abnormal coagulation seen as D-dimer levels enlargement in concert with ferritin may result from iron-induced fibrin clots stabilization (5,9), then, in line with a correlation between fibrinogen and hepcidin found by Duce at al. a correlation between D-dimer levels and local NTBI may be supposed. In tissues, even partial blocking of small vessels by fibrin clots suppress two main ways of iron efflux from the infected organs (4) and, thus, it may enhance the local ferroptosis and subsequent local NTBI elevation.

In lungs, free iron may catalyze stabilization of fibrin clots (8). This link between disturbed local FeH and abnormal fibrin clotting in COVID-induced pathology hypothesized earlier (5, 9) still needs clinical and experimental verification. Remarkably, a bit elevated levels of serum NTBI observed by Duce et al. illustrates the extension of the local FeH disturbance into systemic level and explains the abnormal fibrinolysis observed in blood of patients with COVID-19 as well as it presumably unravels the way how local FeH disturbance in respiratory tract may lead to post-COVID complications in cardiovascular and neurological systems, kidney failure and Kawasaki-like disease in children via iron-mediated fibrin clots formation in small vessels.

Finally, it should be noticed that covidin, recently identified by a computational approach, if its availability and hepcidin function mimicking is confirmed experimentally and clinically, could explain enormous amplification of iron-mediated COVID-induced lungs damage as well as the disease complications (10).

In conclusion, a cross-talk between SARS-Cov-2 induced hyper-inflammation, dysregulation of FeH and fibrin clots formation seems to be a key point of the pathogenesis of the coronavirus disease. More precisely, FeH

presumably stays at a cross-road between two generally accepted COVID-initiated pathological events: hyperinflammation and abnormal fibrin clotting. If so, intensive research is needed to look for interventions able to support and recover FeH in SARS-Cov-2 infected patients.

Conflict of Interest: Author declares that she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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