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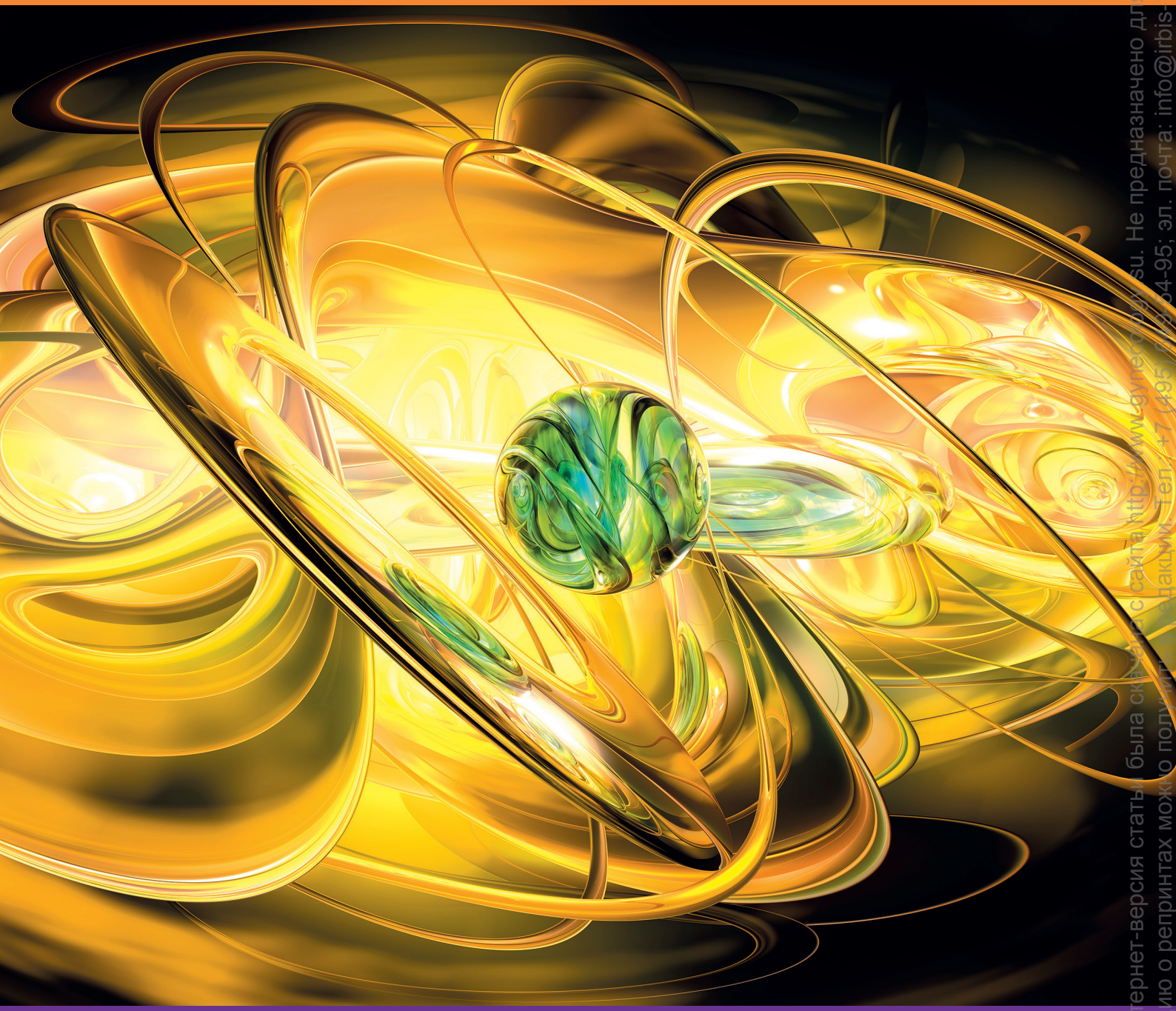

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Macrophage activation syndrome in COVID-19

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Abstract

The novel coronavirus epidemic is characterized by high rates of morbidity and relatively high mortality. Laboratory test results in patients include leukopenia, an increase in liver function tests and ferritin levels reaching hundreds, and sometimes thousands of units. These data remind us about the macrophage activation syndrome (MAC). Secondary hemophagocytic lymphohistiocytosis syndrome, MAC, which pathogenesis is based on a defect in the mechanisms of T-cell cytotoxicity and decreased level of natural killer cells associated with the defect in the perforin-encoding gene as well as hyperproduction of a number of cytokines – interleukin (IL)-1β, tumor necrosis factor-α, etc. by T-lymphocytes and histiocytes, indirectly leading to the activation of macrophages and production of proinflammatory cytokines, in particular IL-6 hyperproduction. MAC is one of "hyperferritinemic syndromes". These disorders have similar clinical and laboratory manifestations, and they also respond to similar treatments, suggesting that hyperferritinemia may be involved in the overall pathogenesis and is characterized by elevated ferritin level and cytokine storm. Despite the fact that data on the immune and inflammatory status in patients with COVID-19 have only started to appear, it is already clear that hyperinflammation and coagulopathy affect the disease severity and increase the risk of death in patients infected with SARS-CoV-2. Hence, understanding the pathogenesis of the novel coronavirus infection can help in its early diagnostics and treatment.

Keywords: macrophage activation syndrome, MAC, hyperferritinemic syndrome, SARS-CoV-2

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Синдром активации макрофагов при COVID-19

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Резюме

COVID-19 – инфекционное заболевание, вызываемое бета-коронавирусом SARS-CoV-2, которое получило распространение по всему миру в 2020 г. Эпидемия нового коронавируса характеризуется высокими показателями заболеваемости и относительно высокой смертностью. В большинстве тяжелых случаев клиническая картина характеризуется не только лихорадкой, кашлем и другими конституциональными симптомами, но также гиперцитокинемией, дыхательной недостаточностью и в конечном итоге может привести к смерти. Среди лабораторных данных можно выделить лейкопению, повышение функциональных проб печени и уровень ферритина, достигающий сотен, а иногда и тысяч единиц. Совокупность этих данных напоминает нам о синдроме активации макрофагов (САМ). Синдром вторичного гемофагоцитарного лимфогистиоцитоза, САМ – это состояние, которое развивается у пациентов с инфекционными и ревматологическими заболеваниями, а также у пациентов со злокачественными новообразованиями. Основу патогенеза составляет дефект механизмов Т-клеточной цитотоксичности и снижение уровня естественных киллеров, сопряженных с дефектом в гене, кодирующем перфорин, а также гиперпродукция Т-лимфоцитами и гистиоцитами ряда цитокинов – интерлейкина (IL)-1β, фактора некроза опухоли альфа и др., опосредованно ведущих к активации макрофагов и продукции провоспалительных цитокинов, в частности гиперпродукции IL-6. САМ входит в комплекс «гиперферритинемических синдромов», также как катастрофический антифосфолипидный синдром, болезнь Стилла и септический шок. Эти расстройства имеют сходные клинические и лабораторные проявления, и они также отвечают на аналогичные методы лечения, предполагая, что гиперферритинемия может быть вовлечена в общий патогенез. Все вышеперечисленные состояния характеризуются повышенным уровнем ферритина и цитокиновым штормом.

Ключевые слова: синдром активации макрофагов, САМ, гиперферритинемический синдром, SARS-CoV-2

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COVID-19 as hyperferritinemic syndrome / COVID-19 как гиперферритинемический синдром

In March 2020, the World Health Organization declared a pandemic that resulted from the spread of the novel coronavirus infection, COVID-19 [1–4]. Currently, COVID-19 is included in the list of "hyperferritinemic syndromes" due to exerting a number of clinical and laboratory features common with macrophage activation syndrome (MAC), catastrophic antiphospholipid syndrome (CAPS), Still's disease, and septic shock [5, 6]. One of the main laboratory parameters assessed is hyperferritinemia [7–9]. In recent years, we have noted an increasing body of evidence supporting the hypothesis that high levels of circulating ferritin may not only reflect the acute phase response, but also play a critical role in developing inflammation [10]. Ferritin appears to exhibit not only an immunosuppressive effect [11], but also pro-inflammatory activity associated with the expression of various inflammatory mediators, including interleukin (IL)-1β [12]. Various mechanisms can inhibit ferritin-mediated suppression of immune cells, and in turn, such altered immunosuppression can contribute to the loss of tolerance and development of autoimmune diseases [10]. Moderate levels of hyperferritinemia are associated with autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis [5, 13–16], and antiphospholipid syndrome (AFS) [17, 18]. It is important to remember that ferritin in inflammatory reactions can be actively secreted by hepatocytes [19] and macrophages [20]. Pro-inflammatory cytokines can induce the expression of ferritin, which in turn may elicits expression of the former. In addition, induction of the anti-inflammatory cytokines (IL-10) by ferritin is an impor-

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Highlights

What is already known about this subject?

- COVID-19 is an infectious disease caused by the beta-coronavirus SARS-CoV-2, which is characterized by leukopenia, increased liver function tests and ferritin levels.

What are the new findings?

- COVID-19 is included in the list of "hyperferritinemic syndromes" due to exerting a number of clinical and laboratory features common with macrophage activation syndrome (MAC), catastrophic antiphospholipid syndrome, Still's disease, and septic shock because it has a number of common clinical and laboratory manifestations of the above four states.
- Severe hyperferritinemia in the presence of systemic signs and symptoms, along with negative infectious and rheumatologic examinations, should raise suspicion of MAS.

How might it impact on clinical practice in the foreseeable future?

- Understanding the pathogenesis of the novel coronavirus infection can help in its early diagnostics and treatment.

Основные моменты

Что уже известно об этой теме?

- COVID-19 – инфекционное заболевание, вызываемое бета-коронавирусом SARS-CoV-2, которое характеризуется лейкопенией, повышением функциональных проб печени и уровня ферритина.

Что нового дает статья?

- COVID-19 включен в перечень «гиперферритинемических синдромов», также как синдром активации макрофагов (САМ), катастрофический антифосфолипидный синдром, болезнь Стилла и септический шок, так как имеет ряд общих клинических и лабораторных особенностей с четырьмя указанными выше состояниями.
- Выраженная гиперферритинемия при наличии системных признаков и симптомов наряду с отрицательными инфекционным и ревматологическим обследованиями должна вызывать у врачей подозрение на САМ.

Как это может повлиять на клиническую практику в обозримом будущем?

- Понимание патогенеза новой коронавирусной инфекции может помочь в ранней диагностике и лечении заболевания.

tant mechanism underlying its immunosuppressive action. Therefore, a complex interplay seems to exist between ferritin and cytokines in controlling pro-inflammatory and anti-inflammatory mediators. Hence, ferritin may exert a context-dependent immunosuppressive or pro-inflammatory activities.

Currently, it is generally accepted that the level of circulating ferritin reflects the acute phase reaction, but still no explanation of why and how the level of serum ferritin increases is available. C. Rosário et al. in their article "The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome" suggested that the marked ferritin levels observed in MAC, Still's disease, CAPS, and septic shock are not solely a secondary product of the inflammatory process, but rather a part of the pathological mechanism [8]. In one recently published study describing a cohort of 39 hospitalized patients with confirmed diagnosis of COVID-19, S. Dahan and his colleagues found a correlation between the serum ferritin levels and disease severity [21]. Many people with diabetes also had elevated serum ferritin levels [22–24], who are known to more likely experience serious complications from COVID-19 [25]. However, it is not completely clear whether ferritin is just an epiphenomenon that can be used for diagnostic purposes, or whether it is involved in a vicious cycle by enhancing the inflammatory response.

Role of macrophage activation syndrome during pregnancy / Роль синдрома активации макрофагов во время беременности

Diagnosis of MAS during pregnancy is challenging due to the rarity of this condition, variability of clinical manifestations and laboratory data. Difficulties in making a diagnosis can delay effective treatment and lead to unfavorable outcome both for mother and fetus. Hence, it is so important to timely diagnose this condition. Severe hyperferritinemia in the presence of systemic signs and symptoms, along with negative infectious and rheumatologic examinations, should raise suspicion of MAS [26].

Unfortunately, by now the pathophysiological mechanism of MAS development has not been fully understood, especially in during pregnancy. It is important to remember that MAS can develop at any stage of pregnancy. It is believed that abortion in the first trimester can alleviate the course of this syndrome, but no consensus on it has been achieved. A. Shukla et al. noted that the patient's condition markedly improved next day after spontaneous abortion [27]. However, there are other data, particularly those by J.M. Giard et al. reporting about death of one patient on day 48 after spontaneous abortion, despite appropriate treatment with etoposide and dexamethasone [28]. While reviewing publications, we noticed that most cases of MAS in the second trimester (12–27 weeks of gestation) treated appropriately had favourable outcome. However, in the third trimester (28–40 weeks), mothers may die sometimes due to developing multiple organ failure.

J. Cheng et al. suggested that in most cases the cause of emerging MAS during pregnancy was due to previous infections (including Epstein-Barr virus, cytomegalovirus, herpes simplex virus type 2, human immunodeficiency virus and parvovirus B19), and one patient had a malignant neoplasm (B-cell lymphoma), and other 3 patients had a history of autoimmune diseases (systemic lupus erythematosus, adult Still's disease and autoimmune hemolytic anemia) [29].

As mentioned earlier, it is very difficult to diagnose

MAS: a prolonged or intermittent fever is often the main symptom upon hospitalization, which may also be accompanied with atypical laboratory results. Thus, MAS must be differentiated from other diseases such as infections, adult Still's disease , HELLP syndrome (hemolysis, elevated liver enzymes and low platelets), thrombotic thrombocytopenic purpura (TTP), aplastic anemia, etc. The "gold diagnostic standard" in diagnostics is based on bone marrow biopsy.

The standard MAS treatment for high-risk patients has been proposed by the Pediatric Histiocyte Society (HLH–2004) and consists of dexamethasone, etoposide, and cyclosporine plus intrathecal methotrexate and hydrocortisone. Steroids formed an integral part of the protocols from 1994 to 2004 and have been used in the treatment of MAS regardless of the trigger. Corticosteroids are anti-inflammatory drugs which dampening immune system activity and are classified as Category C according to the FDA (Food and Drug Administration) [30–32].

Ferritin and its main function / Ферритин и его основная функция

Ferritin is the main protein of the intracellular iron supply in all organisms, and its structural properties are largely preserved in different species. Each shell of apoferritin (ferritin containing no iron) includes 24 subunits of two types: H-subunit and L-subunit. Depending on the type of tissue and the cell physiological status, the ratio of H- and L-subunits in ferritin can vary widely from ferritin containing a high L-subunit content in tissues such as the liver and spleen to H-subunit–rich ferritin found in the heart and kidneys [33, 34]. The amount of cytoplasmic ferritin is regulated by the translation of H- and L-ferritin mRNA in response to intracellular pool of "chelated" or "free" iron. In addition to iron, ferritin synthesis is regulated by cytokines at various levels (transcriptional, post-transcriptional, and translational) during development, so that cellular amount is also regulated by oxidative stress, thyroid hormones, growth factors, secondary messengers, as well as hypoxia-ischemia and hyperoxia. Lipopolysaccharide (LPS, endotoxin), a component of the outer membrane of Gram-negative bacteria, causes various reactions involving ferritin. When LPS was administered experimentally in animals, upregulated ferritin expression was observed. In addition, cyclopentenone prostaglandins, which are involved in inflammatory and febrile reactions, as well as in viral replication, induce L-chain ferritin in human monocytes [35]. When released, ferritin "loses" part of the internal iron, which leads to an extremely high level of "free iron" in the blood serum. An excess of circulating "free iron", found in severe inflammatory conditions can worsen host condition and induce activity of vascular-platelet and coagulation arms of the hemostatic system. This feature is associated with changes in the morphology of red blood cells and fibrin influenced by "free iron", resulting in hydroxyl radical formation [36]. Oxidized phospholipids were found in the lungs of patients with COVID-19, which also play a role in the development of fatal outcomes. Oxidized phospholipids are produced after oxidative stress; they promote tissue factor expression and inflammatory programs in monocytes, and stimulate endothelial cells to interact and bind to monocytes [37, 38]. Intervention in activating monocytes and/or endothelial cells by oxidized phospholipids can help to prevent thrombotic complications, especially in patients with COVID-19 already suffering from cardiovascular and associated metabolic pathologies [39].

N-ferritin and macrophage activation syndrome / H-ферритин и синдром активации макрофагов

Serum ferritin contains low iron amount and mainly consists of L-subunits [10]. Until now, iron incorporation has been considered as a sole function of L-ferritin found in *in vitro* studies, but more recent studies have shown that L-ferritin can have a stimulating effect on cell proliferation, regardless of available iron [40].

Moreover, still there is paradox that circulating ferritin is mainly composed of L-subunits, whereas most of the evidence supporting the existence of ferritin receptors indicates specificity for H-subunits. The ferritin H-chain promotes macrophage activation, which in turn leads to excessive cytokine release. Hemophagocytic lymphohistiocytosis (HLH) is a prototype of cytokine storm syndrome, characterized by a hyperinflationary reaction that leads to organ damage. HLH traditionally consists of a primary (caused by an inherited genetic defect in the mechanisms of cellular cytotoxicity and other mechanisms regulating immune response) and secondary form (due to impaired immune response in the context of infectious, oncological or rheumatic disease). Secondary HLH or macrophage activation syndrome (MAS) is a severe and potentially fatal condition, which is based on altered regulation of the immune response, leading to abnormal activation of T-lymphocytes and monocytes/macrophages, their accumulation in the affected organs and the developed systemic inflammatory response syndrome, in most cases against various infectious agents [41, 42]. HLH is characterized by a long-term fever, hepatosplenomegaly, cytopenia, high levels of ferritin, triglycerides, transaminases and bilirubin, as well as low fibrinogen levels [43]. Hemophagocytosis is often absent at the disease onset, but is usually detected upon its progression. The soluble IL-2 receptor is a valuable disease marker due to its continuously elevating levels during active HLH [44]. MAS is a prototype underlying prominent activation of the immune system, characterized by a huge level of ferritin and severe hypercytokinemia: IL-1β, IFN-γ (interferon gamma), TNF-α (tumor necrosis factor alpha), IL-10, IL-6, IL-18, IL-2 and IL-12 [45]. The pathogenesis of this condition is poorly understood, but both genetic and acquired causes manifest by altered or lacked functioning in natural killer (NK) and cytotoxic T-cells. In the secondary MAS, cytopenia

may initially be less prominent, whereas severe heart failure is more common with more pronounced coagulopathy, C-reactive protein level tends to increase, and while comparing the cytokine profile, pro-inflammatory IL-1β is increased, whereas level of IL-6 and TNF-α is markedly elevated [46]. Thus, it is important to understand that higher values of serum inflammatory markers (including C-reactive protein, ferritin, and D-dimer), a difference in the neutrophil/lymphocyte ratio [39, 40], and increased amount of inflammatory cytokines and chemokines, are associated with the disease severity and a higher risk of death [47–50]. In patients with COVID-19, elevated production of IL-6, IL-7, IL-9, IL-10, TNF-α, as well as several inflammatory chemokines (CCL2, CCL3, and CXCL10) are observed [51]. According to F. Zhou et al., the main role in the developing "cytokine storm" is played by IL-6 anyway, which causes a cytolytic dysfunction. In fact, exposure to high levels of IL-6 as noted in severe COVID-19 inhibits the cytotoxicity of NK cells and downregulated expression of perforin and granzyme. This results in inability of cytotoxic T-lymphocytes or NK cells to kill target cells by perforin/granzyme-induced apoptosis, thus ensuring the survival of target cells and enhancing antigen stimulation, followed by overproduction of the pro-inflammatory cytokines [38, 52]. Enhanced antigen presentation leads to repeated and constant IFN-γ-dependent activation via toll-like receptors, which, in turn, further suppresses cytolytic function and increases activity of cytotoxic T-lymphocytes and macrophages (**Fig. 1**) [53, 54].

It is believed that the excessive inflammatory response occurring against SARS-CoV-2 is the main cause of severe course and death in such patients, which is associated with high levels of circulating cytokines, profound lymphopenia, and significant infiltration of mononuclear cells in the lungs, heart [54], spleen, lymph nodes, and kidneys [55–59] as noted in postmortem examination.

Recently, J.A. Tetro put forward a hypothesis about differences in the outcomes of COVID-19 in patients who were exposed to another coronavirus, due to developing type II hypersensitivity reaction [60]. Indeed, previous contact with other coronaviruses responsible for enhancing immune response prior to COVID-19 infection may play a role in the disease severity.

Conclusion / Заключение

The data on the immune and inflammatory status of patients with COVID-19 have begun emerge only now, but it is already clear that hyperinflammation and coagulopathy affect the severity of the disease and increase a risk of death in SARS-CoV-2-infected patients. Understanding pathogenesis of the novel coronavirus infection can help in its early diagnostics and treatment.

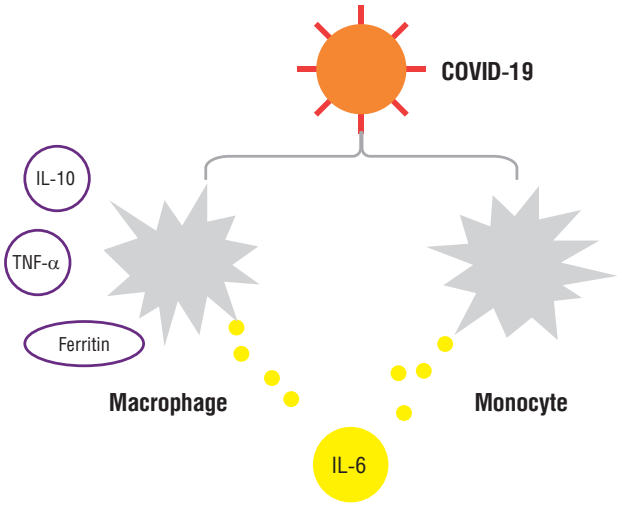

Figure 1. Impaired regulation of the immune response in COVID-19 [53, 54].

Рисунок 1. Нарушение регуляции иммунного ответа при COVID-19 [53, 54].

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