 10.15789/2220-7619-EOU-16874

AUTOIMMUNE DISORDERS IN PATIENTS WITH GRANULOMATOSIS DISEASES AFTER COVID-19: T AND B-CELLS SUBSETS FUNCTION

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 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

 10.15789/2220-7619-EOU-16874

АУТОИММУННЫЕ НАРУШЕНИЯ У БОЛЬНЫХ ГРАНУЛЕМАТОЗНЫМИ ЗАБОЛЕВАНИЯМИ ПОСЛЕ COVID-19: ФУНКЦИОНИРОВАНИЕ СУБПОПУЛЯЦИЙ Т- И В-КЛЕТОК

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 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

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ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

 10.15789/2220-7619-EOU-16874

Abstract

Sarcoidosis and tuberculosis are both granulomatous diseases that have many similarities, making the differential diagnosis of sarcoidosis and tuberculosis difficult, as well as leading to inappropriate treatment selection of both diseases. Autoimmune inflammation (AI) is one of the processes identified tuberculosis and sarcoidosis. Current evidences about the risk and clinical outcomes of COVID-19 infection in patient with sarcoidosis and *M.tuberculosis* co-infection are still not well understood. SARS-CoV-2 has direct damage to the epithelial cells of the respiratory system, and in-directly due to circulatory disorders. **Materials and methods.** In the study we analyzed characteristics of autoimmune response in patients with granulomatosis diseases (tuberculosis and sarcoidosis) after COVID-19. We have analyzed articles for the period of December 2019 to March 2023, published in international database ("Medline", "PubMed", "Scopus"). The keywords we used “COVID-19”, “SARS-CoV-2”, “tuberculosis”, “sarcoidosis”, “granulomatosis diseases”, “T cells”, “B cells”, “Treg", "follicular Treg" and "Treg subsets". The narrative review was carried out in accordance with the PRISMA protocol (http://www.prisma-statement.org) used for this type of study (ID -423604). **Results.** The influence of COVID-19 infection can also make a significant contribution to the violation of the T- and B-cell immune response, the violation of the nature of cellular metabolism, which will affect the course of granulomatous inflammation in various ways. According to the different researches, autoimmune inflammation can be an important protective mechanism in sarcoidosis and, at the same time, exacerbates the course of tuberculosis infection with the disease progression and pathogen drug resistance formation subsequently. The study of immune response features in patients with COVID-19 showed the presence of several similar characteristics in cellular components of the immune response. **Conclusion:** Evidence of the presence of autoimmune inflammation in patients with these granulomatous lung diseases, the development of patient immunotypes, including the transferred COVID-19, will be a significant contribution to the

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

 10.15789/2220-7619-EOU-16874

development of personalized patient management tactics, taking into account the identified violations of the immune response mechanisms.

Keywords: autoimmunity; tuberculosis; sarcoidosis, granulomatosis diseases, T cell, B cell, Treg, follicular Treg, Treg subsets, prognosis.

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

 10.15789/2220-7619-EOU-16874

Резюме

Саркоидоз и туберкулез являются гранулематозными патологиями, имеющими большое количество схожих черт, из-за которых возникают трудности в дифференциальной диагностике этих заболеваний, что в дальнейшем приводит к неправильному выбору тактики лечения пациентов. Аутоиммунное воспаление (АВ) является одним из процессов, выявленных как при туберкулезе, так и при саркоидозе. Текущие данные о риске и клинических исходах инфекции COVID-19 у пациентов с саркоидозом либо с сочетанной инфекцией *M.tuberculosis* все еще недостаточно изучены. SARS-CoV-2 оказывает как прямое патологическое действие на эпителиальные клетки дыхательной системы, так и опосредованное за счет нарушений кровообращения.

Материалы и методы. В этом исследовании мы изучили особенности аутоиммунного ответа у пациентов с гранулематозными заболеваниями (туберкулезом и саркоидозом) после COVID-19. Мы проанализировали статьи с декабря 2019 по март 2023 года, опубликованные в международных базах данных («Medline», «PubMed», «Scopus»). Ключевые слова, которые мы использовали: «COVID-19», «SARS-CoV-2», «туберкулез», «саркоидоз», «гранулематозные заболевания», «Т-клетки», «В-клетки», «Treg», «фолликулярный Treg» и «Подмножества Treg». Описательный обзор проводился в соответствии с протоколом PRISMA (http://www.prisma-statement.org), используемым для этого типа исследования (ID-423604).

Результаты. COVID-19 вносит существенный вклад в нарушение Т- и В-клеточного иммунного ответа. Коронавирусная инфекция может изменить и характер клеточного метаболизма, что отразится на течении гранулематозного воспаления. По данным различных исследований, аутоиммунный компонент может быть важным защитным механизмом при саркоидозе и, в то же время, он способен усугублять течение туберкулезной инфекции, приводить к прогрессированию заболевания с формированием в дальнейшем

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

 10.15789/2220-7619-EOU-16874
лекарственной устойчивости возбудителя. Изучение особенностей иммунного ответа у пациентов с COVID-19 и пациентов с интерстициальными заболеваниями легких показало наличие ряда схожих характеристик у клеточных компонентов иммунного ответа.

Заключение: Доказательства наличия аутоиммунного воспаления у пациентов с данными гранулематозными заболеваниями легких, определение иммунотипов пациентов, в том числе перенесших COVID-19, будут вносить существенный вклад в разработку персонализированной тактики ведения пациентов с учетом выявленных нарушений механизмов иммунного ответа.

Ключевые слова: Аутоиммунитет, туберкулез, саркоидоз, гранулематозные заболевания, Т-клетки, В-клетки, Treg, фолликулярные Treg, субпопуляции Treg, прогноз.

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

 10.15789/2220-7619-EOU-16874

1 Introduction

It is now known that the development of autoimmune diseases is multifactorial, and they follow regularities of additive polygenic inheritance with a threshold effect of a number of natural factors and sociocultural-anthropogenic epigenetic factors [34]. Currently, numerous studies demonstrated that a combination of many factors, including non-infection and infection triggers in individually special immunogenic predictors with special reactivity, activated autoimmune inflammation (AI) with development and progression of the disease [105, 118, 125, 127]. As we know, tuberculosis (Tbc) and sarcoidosis are similar to granulomatous disease. However, the AI has been diagnosed in both diseases with different etiologies [11, 27, 136].

Various T-cell subsets play an important part in the pathogenesis of autoimmune diseases, represented by Th1, Th17, regulatory T cells (Treg) and CD8+ T-cells [9, 99]. It is believed that the ratio of Th17 cells, stimulating the immune response, and Treg cells, that are suppressors of immune responses, can lead to the formation of autoimmune inflammation which is characterized by the presence of self-specific CD3+ T-cells and CD19+ B-cells [65, 61]. It is also known that uncontrolled chronic infections, including *M.tuberculosis* infection, are commonly accompanied by AI with violation of T- and B-cell link of the immune response, however, little attention is paid to this issue [4, 21].

The phenotypic assessment of B-cells is able to indirectly reflect the functions of certain subsets of B-cells [135]. Recent studies have shown that in the peripheral blood of patients with sarcoidosis, the subpopulation of ‘naïve’ B cells with the CD19+IgD+CD38- phenotype reduce and activate resting memory of B cells with CD19+IgD-CD38+ and CD19+IgD-CD38- phenotypes, respectively. There are few studies in tuberculosis [104, 149]. Furthermore, the theory of the development of vimentin autoantibodies has become widespread [126]. The role of vimentin, which is present in cells and extra cellular matrix of connective tissues, and is involved in different types of cell-to-cell interactions, as well as in immune response regulation, has been known for a long time [90]. Bagavant et al. found an increased titer of IgG

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

to vimentin in patients with sarcoidosis compared with healthy controls [10]. However, other researchers, despite the discovery of autoantibodies to vimentin, denied their significant impact on the pathogenesis of sarcoidosis in general [90]. Therefore, the part of autoantibodies in the pathogenesis of sarcoidosis is still open.

According to the results of our recent studies, it was noted that patients with tuberculosis had a significantly high level of autoantibodies in citrullinated vimentin [20, 90]. A number of clinical manifestations in tuberculosis indicated that the interaction of the host with mycobacterial antigens causes the subsequent development of an additional autoimmune inflammatory process, aggravating the pathology of tuberculosis. *M.tuberculosis* affects extensive destruction of the extracellular matrix and the breakdown of collagen and elastin which promote the release of new potentially autoreactive epitopes [122, 124]. At the same time, one of the most important ways to avoid the immune response of *M.tuberculosis* is the ability to destroy normal functioning of the cells of the immune system and their metabolism. For example, after PRR recognition that is responsible for endocytosis, *M. tuberculosis* is taken up by phagocytic host cells (macrophages, neutrophils and dendritic cells, DCs) and internalized into the phagosome [140]. Studies have shown that *M. tuberculosis* actually uses disruption of phagosome-lysosome fusion and blockade of acidification of the environment in the phagosome in order to avoid cell destruction and antigen presentation to acquired immune cells to trigger a specific immune response. The effectiveness of the approaches that is described above, it is an evidence that up to 70% of phagosomes, containing *M.tuberculosis*, do not fuse with lysosomes [48, 140].

The emergence of COVID-19 and the rapid spread of the SARS-CoV-2 virus in worldwide has revealed the dramatic changes in the immune response of infected patients, affected COVID-19 with varying degrees of severity [139]. The SARS-CoV-2 has now been shown to be able to suppress the innate mechanisms of the antiviral response [116]. The lymphopenia was described in many patients is mainly characterized by a decrease in CD4+ and CD8+ T-cells, which is a characteristic feature of coronavirus infections. This apparent change in T-cell populations

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demonstrates the significance of their role in the infection. SARS-CoV-2-specific CD4+ T-cells express IFNγ, TNF and IL-2, indicating that patients with SARS-CoV-2 infection exhibit Th1 cellular responses. The importance of CD4+ T-cells has been shown in murine models of infection, where T-cell depletion was accompanied with the development of more severe inflammation in the lungs [57, 151]. At the same time, immunization of mice with SARS-CoV-2 peptide-derived dendritic cells induced the formation of virus-specific CD4+ and CD8+ T-cells massively infiltrating the lungs, leading to increased survival [151]. Moreover, translocation of SARS-CoV-specific CD4+ and CD8+ T-cells into immunodeficient mice contributed to better protection against the mouse-adapted strain SARS-CoV-2 [38]. In addition to lymphopenia, patients with COVID-19 also showed increased T-cell depletion, decreased functional diversity, and correlation with disease progression. We hypothesise that COVID-19 would alter the immune status of tuberculosis [88] and sarcoidosis patients [129], but with different manifestations and consequences.

Thus, the review helps to understand key immunological points in pathogenesis of autoimmune inflammation in patients with the most frequent granulomatous lung diseases (sarcoidosis and tuberculosis), similar in clinical and radiological symptomatology and different in etiology, based on changes in T- and B-cell subsets after COVID-19.

The aim of our study was to determine characteristic of autoimmune inflammation in development and progression of the disease, and to analyze T- and B-cell subsets roles in patients with granulomatosis diseases (sarcoidosis and tuberculosis) after COVID-19.

The Methods of the Review

We have analyzed articles for the period of December 2019 to March 2023, published in international database ("Medline", "PubMed", "Scopus"). The keywords we used “COVID-19”, “SARS-CoV-2”, “tuberculosis”, “sarcoidosis”, “granulomatosis diseases”, “T cells”, “B cells”, “Treg", "follicular Treg" and "Treg subsets". Inclusion criteria were original research with observation of patients with sarcoidosis, TB and COVID-19, meta-analisis, review articles and research articles.

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

Exclusion criteria: books, result of clinical trials, clinical cases. Totally, 37 publications were processed. The narrative review was carried out in accordance with the PRISMA protocol (http://www.prisma-statement.org) used for this type of study (ID-423604).

2 **Autoimmune response in patients with granulomatosis diseases (sarcoidosis and tuberculosis) and COVID-19**

The clinical symptoms in patient with sarcoidosis and tuberculosis prone to chronic and generalized cause, based on tissue sites of chronic inflammation that are driven by delayed-type hypersensitivity (DSH) mechanisms are very similar [40]. Their course, degree of epidemiology danger, treatment management and prognosis are significantly different [34, 136]. The identification of the etiological factors and pathogenesis of the disease in such cases can be a key factor in the choice of management, determining its effectiveness [95]. The main proof of the tuberculosis etiology of the process is the isolation of *M.tuberculosis* using bacteriological diagnostic methods, which determines the basic principle of anti-tuberculosis therapy - exposure to the pathogen [34].

The interaction of the *M.tuberculosis* with the host organism is poorly understood and may results in the activation or the localization of the infection [118]. Despite two decades of an intensified research to understand and cure tuberculosis disease, biological uncertainties remain and hamper the progress. The problem of the spread and treatment of drug-resistant tuberculosis became even more urgent. With the rise of drug resistance, treatment failure rates have increased along with the use of more toxic therapies that are far more costly [138].

Recently, the interest and the research on the autoimmune aspects in tuberculosis have been increasing. It is widely accepted, that many autoimmune diseases could be promoted by inefficiently controlled and/or wrong targeted immune responses to different types of pathogens, including *M.tuberculosis* [118, 82]. *M.tuberculosis* infection is a multifaceted process and has many different outcomes and complications. Moreover, autoimmunity is one of the processes characteristics of *M.tuberculosis* infection [122]. The role of autoantibodies,

produced by self-reactive plasma cells, in the pathogenesis of Tbc is not quite clear and widely disputed [95]. However, autoantibodies production could be considered as the result of poorly controlled and imbalanced immune response, as well as a critical part of pathogenesis of tuberculosis. Autoantibodies during *M.tuberculosis* infection might be the markers of comorbid, or even might provoke and upregulate autoimmune inflammation in chronically inflamed tissues. However, there is an alternative point of view regarding increased titers of self-reactive antibodies as a part of protective mechanisms, helping in the clearance of damaged tissue debris [124].

Unlike tuberculosis, sarcoidosis is one of the few diseases similar in its characteristics but with an unspecified etiology, leading to a large number of diagnostic errors and a lack of personalized management [117, 119]. Many researchers have been looking for pathophysiological similarities between *M.tuberculosis* infection and sarcoidosis, based on mycobacterial components and/or specific to *M.tuberculosis* antibodies detection in patients with sarcoidosis [111, 115, 117]. Currently, the role of *M.tuberculosis* as one of the main etiological factors in sarcoidosis is still unconfirmed. But the concept of tuberculosis and sarcoidosis as two responses, whose differences are determined by various organism relativities and conditions, to closely related etiological factors - is still being developed [82]. The study of the Mbc role as a classic adjuvant factor of autoimmune inflammation, is also continuing in this context [84, 122].

It is well-known that the one of the key feature of sarcoidosis pathogenesis is granulomas formation in lungs, lymph nodes of different localization, spleen, skin, and other organs. In patients who are genetically predisposed to sarcoidosis, a contact of antigen-presenting cells (monocytes, macrophages, dendritic cells) with an unknown non-self antigen may result in imbalanced immune inflammation that may manifest in granulomas formation [113]. Unlike *M.tuberculosis*-mediated granulomas in sarcoidosis necrotic masses are not formed in granulomas and serum angiotenzin-converting enzyme hyperproduction occurs [123]. The central part of the epithelioid cell granuloma is composed of activated macrophages, epithelioid

cells and giant cells, as well as with CD4+ T-cells between them [6]. Furthermore, the peripheral area of a granuloma contains CD8+ T-cells, fibroblasts, macrophages, and fibrocytes, while CD19+ B-cells are not typical for granulomas in sarcoidosis [6]. Innate immunity macrophages and dendritic cells are the first immune cells to meet the non-self molecules due to the presence of pattern-recognition receptors (PRRs) [147]. Long-term exposure of PRRs to foreign molecules results in high rates of cells activation, proinflammatory cytokine production and epithelioid differentiation of tissue-resident macrophages and peripheral blood monocytes. Moreover, having recognized and internalized antigens, activated dendritic cells migrate to the nearest lymph node, where they present the antigens CD4+ and CD8+ T-cells [58, 150].

Currently, special attention is paid to the part of Th17 cells in the pathogenesis of sarcoidosis [81]. These CD4+ T-cells expressed IL 17A and IL-22, as well as showed many pro-inflammatory properties. Furthermore, it was showed that macrophages from granuloma in patients with sarcoidosis express CCL20, that unregulated Th17 cells migration to inflamed tissue, while IL-23 expression causes a significant increase in IL-17A production in the sites of granuloma formation during sarcoidosis [17]. Furthermore, in was shown that anti-inflammatory M2 phenotype was predominant for tissue macrophages in sarcoidosis granulomas, and their frequencies and activation status were linked with disease progression [17]. Moreover, *in vitro* and *in vivo* models also revealed that these cells play an important part in granuloma formation at the initial stages sarcoidosis. Recently, mTOR signaling pathway also takes part in sarcoidosis and important for macrophages during granuloma formation [78]. For instance, mTORC1 activation in murine macrophages resulted in disease progression and formation of granulomas [78]. Thus, metabolic adaptation of different tissue resident and peripheral blood cells to the inflammatory conditions in granuloma affected autophagy regulation, as well as influenced the effectively of antigen clearance and promoted the persistence/progression of granuloma in general [27]. To date, the diagnosis and treatment of *M.tuberculosis* infection remain a problem for the world community.

Vaccination with the use of BCG, the use of new drugs did not allow coping with the annual spread of infection and the formation of drug-resistant forms of tuberculosis [118].

Studies of the autoimmune response in Tbc have been conducted since the middle of the XIX century. Many scientists note the presence of clinical symptoms of autoimmune diseases in tuberculosis patients, the appearance of autoantibodies, the presence of a genetic predisposition [1, 34]. The existing assumptions have not yet found unambiguous evidence of the autoimmune inflammation in tuberculosis and its effect on the course of the disease, but research in this direction continues. Previously, the relationship between the development of autoimmune pathology after the introduction of an attenuated strain of *M. bovis* was shown. *M. bovis* is the main causative agent of tuberculosis in cattle and it is used for immunization in humans to date, both for the prevention of Tbc and for the treatment of oncological pathology and even severe COVID-19 [16]. In the experiment, Mtb is quite often used as an adjuvant, for example, in a complete Freund adjuvant in animal models of autoimmune diseases [11], which is presumably related to the fact that these antigens overcome tolerance to host antigens when co-administered. In experimental models, Mtb immunization can cause autoimmune joint lesions by the cross-reactivity with proteoglycan in cartilage [12].

Currently, there are evidences of the trigger role of *M. tuberculosis* in the development of different autoimmunity diseases, including systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, primary biliary cirrhosis and many others [35, 102]. No reliably known mechanisms for antibodies formation in tuberculosis which have been identified to date. There are assumptions about possible mimicry between the antigenic structure of mycobacteria and the host tissue's own antigens [14].

At the same time, a number of studies had shown that during *M. tuberculosis* infection approximately 40% of patients had increased titers of self-reactive antibodies, that were typically detected in patients with polyangiitis, systemic lupus erythematosus and other autoimmune diseases [34]. Statistically significant increase

in plasma concentrations of antibodies in tuberculosis patients was diagnosed to ribonucleoproteins (15%), anti-SSA (64%) and anti-ACA-IgM antibodies (59%) [53]. In some cases, high levels of autoantibodies to neutrophil cytoplasm, beta-2-glycoprotein (anti-b2GPI), cyclic citrullinated peptide, as well as anticardiolipin antibodies were found. Moreover, the serum levels of detection autoantibodies in some cases were very similar to patients with autoimmune diseases, while the effective anti-tuberculosis treatment led to down-regulation of some self-reactive antibodies levels [25].

Previously, Elkholy et al. reported that the frequency of CD19+ B-cell in peripheral blood samples from patients with active pulmonary tuberculosis was significantly lower than in control group [34]. In contrast, Wu et al. found that CD19+ B-cells were higher in patients with TB vs control group [143]. We noticed no differences in relative and absolute numbers on total CD19+ B-cell subset between *M. tuberculosis* infected patients and healthy controls, but we found dramatic alterations in B cell subsets composition. The presence of an autoimmune component is associated with an increase in the level of autoantibodies may be significant for the correction of therapy and serve as a criterion for considering the appointment of immunosuppressive therapy in the future. Probably, autoantibodies elevation could be linked with molecular mimicry, that could be on of the pathogens strategies of immune evasion during chronic infections and hyperactive immune response. For instance, some *M. tuberculosis* heat shock proteins, including Mtb-HsP60, Mtb-HsP65, and mKatG, could be considered as the mycobacterial candidate antigens with predicted involvement in cross-reactions [33]. The presence of antibodies in patients with tuberculosis may reflect the relationship between the pathogenesis of those diseases with the possibility of cross-reactivity between vimentin and *M. tuberculosis* peptides [130].

SARS-CoV-2 virus may exacerbate the course of the disease, which could be associated with increased autoimmune inflammation and altered immune response [15, 64]. SARS-CoV-2 is also able to suppress antiviral responses as the part of its immune evasion strategy. As it was shown previously, lymphopenia was described

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in many patients, mainly characterized by a decrease in the number of CD4+ and CD8+ T cells, which is a characteristic feature in a number of coronavirus infections as well [36, 45, 83].

Special form of hyper-inflammatory reactions in response to SARS-CoV-2 may develop in some patients, leading to autoimmune reactions [28, 100]. Apparently, the main role in this case is played by a genetic predisposition to this. In such cases, hyperinflammatory reactions in response to SARS-CoV-2 lead to the rapid formation of autoimmune and/or autoinflammatory dysregulation and, as a consequence, to the development of severe interstitial pneumonia [100]. One of the explanations for the development of autoimmune complications may also be the molecular similarity of SARS-CoV-2 Sproteins with surfactant proteins that Kanduc study showed [28]. The course of COVID-19 infection can be significantly influenced not only by factors of the genetic predisposition of the host organism, but also by existing diseases that affect the lung tissue. In this regard, the study of various forms of the course of COVID-19 in patients with tuberculosis is the particular interest. Immune response in patients with *M. tuberculosis* infection, sarcoidosis and SARS-CoV-2 infection are presented in table 1.

Recent studies have shown that the incidence of CD4+CD25+ T cells was higher in patients with active TB in contrary with latent TB. However, there were no differences in relative number of Treg cells, identified by flow cytometry as CD4+CD25+CD127lo, CD4+CD25+FoxP3+, or CD4+CD25+FoxP3+CD127lo [146]. A correlation analyzis revealed the close link between the stages of treatment in patients with tuberculosis and Treg cells. Prior to treatment, patients had higher frequencies of CD4+CD25high Treg and more pronounced expression of FoxP3 in peripheral blood compared to healthy controls [44]. Overall, on and tuberculosis show that this is not an unambiguous problem. In conditions of excessive inflammation regulatory T cells in Tbc may be useful [21].

In sarcoidosis, there was a decrease in the number of Tregs cells in bronchoalveolar lavage (BAL), while, oppositely, in the peripheral blood samples these cells increased. However, in the same group of patients, peripheral blood Treg

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

 10.15789/2220-7619-EOU-16874

cells were three times lower if compared to healthy donors [50]. In addition, many studies have noted a decrease in the level of the Treg transcription factor FOXP3 in BALF, which indicates a decrease in the functionality of these cells [30, 50, 88]. Recently, we noted that the relative numbers of central memory CD45RA-CCR7+ Tregs was decreased in patients with sarcoidosis, while the frequency of circulating effector memory and effector Tregs was increased if compared to healthy controls [66]. In our previous studies, we also noticed an evaluated CD39 expression on the surface of Treg cells in both acute and chronic sarcoidosis [51]. We have found that the content of CD39-positive cells increases in both chronic and acute sarcoidosis. In addition, the level of CD39+ cells among CD45R0+CD62L+ T-regulatory central memory cells in patients with both acute and chronic sarcoidosis significantly exceeded the values in the control group. CD45R0+CD62L- T-regulatory effector memory cells increased in peripheral blood only in the chronic sarcoidosis group. We have also shown that in chronic sarcoidosis the content of the total phenotype of T-regulatory cells in the peripheral blood is significantly lower than that in the control group [51]. Thus, alterations in Treg cell numbers in circulation, their phenotypes and/or functional activity could be associated with high risk of autoimmune diseases in numerous models and human autoimmune diseases [71].

2 Similarity of immune response in COVID-19, sarcoidosis and tuberculosis

It is considered that both for sarcoidosis and tuberculosis, an autoimmune damaging component of healthy lung tissue is involved (Fig 1).

For example, for acute respiratory distress syndrome while COVID-19 infection a neutralising auto-antibodies to type I IFNs were determined [133]. It is known that these types of interferons are responsible for MHC molecules' expression increment in infected cells and virus elimination from the organism [106]. Natural and adaptive immunity is also relevant in fibrogenesis for these pathologies [148]. This is why the research of immunocompetent cells separately and in combination is substantial. This could be the key for determination of prognosis for patients with

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

 10.15789/2220-7619-EOU-16874

comorbidity, as well as an assistance for further therapy correction. Nowadays it is possible to parallel Th1 in these pathologies. When recognizing a specific antigen in peripheral tissues effector Th1 cells produced IFNg, that activates various inntate and adaptive immunity cells, including CD8+ T-cells, ILC1 and macrophages, that take part in pathogen elimination [9]. Hyperproduction of IFNγ and TNFα by Th1 cells as the response for SARS-CoV-2, as well as mass virus infected cell death can lead to lung tissue damage and trigger acute respiratory distress syndrome. Thus, Th1 cells migration to inflamed tissues marginally specifies certain fraction decreasement of these cells in patients' peripheral blood when in the acute phase of infection. This Th1 cells migration was noted in several independent researches [72, 112]. Thereby an opportunity of revealing new data of immune variation for patients with tuberculosis and lung sarcoidosis and their impact on disease progress after COVID-19 is crucial and prompt. A practical application of received data can raise the effectiveness of curation and observation of patients with tuberculosis and sarcoidosis in future.

4 **Discussion**

SARS-CoV-2 has many harmful direct effects on various cell of different location, these effects could directly damage to the cells of the respiratory system, as well as could effect in-directly causing circulatory disorders. The direct cytotoxic effect of SARS-CoV-2 virus is due to the virus penetration to ACE2-expressing cells - alveolocytes, which leads to pneumonia development [77]. There is an unrestricted inflammatory infiltration of immune cells in the lungs which, in addition to direct viral damage, take part in self tissue damage due to excessive secretion of proinflammatory cytokines and chemokines, proteolystic enzymes and reactive oxygen species. Diffuse alveolar damage, characterized by desquamation of alveolar cells, the formation of hyaline membranes, and the development of pulmonary edema. Finally, microcirculation disturbance due to endothelial cell and vascular, as well as increased thrombus formation increase lung tissue damage and reduce the effectiveness of reparative processes in general [144].

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

In severe COVID-19, a cytokine storm develops, characterized by the production of vascular growth factor (VEGF), monocyte chemoattraction protein-1 (MCP-1), IL-8, and additionally IL-6 [49, 55, 59]. There is an activation of alveolar macrophages, the complement cascade along the lectin pathway, locally formed immune complexes that enhance pro-inflammatory processes. Activation of the complement system leads to damage to the endothelium, and also induces leukocytes through components C3a and C5a to produce pro-inflammatory cytokines interleukin (IL)-1, IL-6, IL-8, and IFNγ [8].

It should be noted that in patients with severe COVID-19 showed increase in serum CXCR9 and CXCR10. They together with increased levels of both cellular ("non-classical" monocytes, CD38+HLA-DR+ T cells and granzyme-B+/perforin+ T -cells) and serum (CXCL8, IL-6 and IL-10 levels) factors made it possible to differentiate mild and severe course of the disease [97]. The data obtained, according to the authors of the study, indicate the fact that polarization towards Th1 is associated with a high cytolytic profile of T cells in patients with severe COVID-19. Moreover, when analyzing BAL cells from patients with COVID-19, an increase in the proportion of IFNγ- and/or TNFα producing Th1 was noted, whereat the mRNA level an increase in the expression of chemokines CCL4 and CCL5 or CCL2, CCL18, CXCL9, CXCL10 and CXCL11 was noted, respectively, which contributed to the attraction of leukocytes to the focus and inflammation in the lung tissue [145].

The interaction of CXCR3 with ligands plays an important role in infectious, auto-immune, and oncological diseases, as well as in a number of pathological conditions associated with dysregulation of angiogenesis [13]. The chemokine receptor CXCR3 interacts with several ligands (chemokines), including CXCL9 or MIG (monokine induced by gamma-interferon), CXCL10 or IP-10 (interferon-induced protein of 10kDa), as well as CXCL11 or I-TAC [42]. All of the listed CXCR3-binding chemokines have a number of functional features [42]. Migration of CD4+ T-cells from peripheral blood to damaged tissues in sarcoidosis is possible due to the presence of the chemokine receptor CXCR3 on the cell surface. A number

of papers were devoted to the study of ligands for CXCR3 in sarcoidosis [73]. This was determined that CXCR3-expressing cells were involved in the formation of granulomas in sarcoidosis, and, on the other hand, the main inducer of the synthesis of all the studied CXCR3 ligands was IFNγ, which played an important pathogenetic role in the development of immune responses during sarcoidosis [19]. It was also noticed that in sarcoidosis CXCR3 ligands – CXCL9, CXCL10, CXCL11 – provide CD4+ T-cell and monocytes homing to the lesions for further formation of granulomas [73]. These chemokines are also involved in angiogenesis and cell proliferation in sarcoidosis. The typical adaptive immune response in sarcoidosis is characterized by the pres-ence of IFNγ producing CD4+ cells in inflamed tissues, which supports the idea that sarcoidosis is a T-helper cell type 1 (Th1) disease.

The literature data on the possible use of the levels of CXCL9, CXCL10, CXCL11 - chemokines in the peripheral blood of patients with sarcoidosis for clinical and laboratory generalizations. Some authors point the role of CXCL10 in the mechanisms of granuloma formation in both acute and chronic sarcoidosis [73]. Similarly, Arger et al indicated that increased the level of peripheral blood and BAL CXCL11 in patients with sarcoidosis correlated with a decrease in respiratory function, lung volumes, and, accordingly, with a worsening of the course of the disease.

In sarcoidosis, there is also local overproduction of Th1 profile cytokines such as IL-2 and (IFNγ) associated with high expression of macrophage-derived molecules such as IL-15, CXCL10, CXCL16, CCL5 and CCL20 [19]. The activity of Th1 is associated with the intensity of the process of granuloma formation, the nature of the clinical course of sarcoidosis and its outcome. It is worth remembering that Th17 lymphocytes are actively involved in the pathogenesis of most inflammatory processes in autoimmune and infectious diseases. The pro-inflammatory cytokines IL-1β, IL-6, and IL-23 play the most important role in the “polarization” of Th0 towards Th17 [146] and their attraction to the focus of inflammation, and IL-22, the main function of which is the activation of the protective functions of the cells of the epithelial layers [5]. With COVID-19, a

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decreased levels of Th cells carrying on their cell-surface key Th17 antigens – CD161 and CCR6 – were noted, compared with the control group [85]. It is worth remembering that Th17 lymphocytes are actively involved in the pathogenesis of most inflammatory processes in autoimmune and infectious diseases. The proinflammatory cytokines IL-1β, IL-6, and IL-23 play the most important role in the "polarization" of Th0 towards Th17 [85]. Next, Th17 migrated to the sites of inflammation, and produced IL-22, that played the initial role in activation of epithelial layers cells activation and increase of their protective functions [5, 85].

Similar results were obtained using methods of molecular biology, when it was shown that expression of Th17-associated genes were reduced in peripheral blood CD4+ T-cells of patients with severe COVID-19, for example, RORC, IL17A, IL17F, and CCR6 [85]. These cells migrated to the sites of infection, which was confirmed by studies of BAL. In bronchoalveolar lavage fluid during COVID-19 infection, Th17 had the phenotype of tissue resident memory T cells, and also expressed genes associated with cytolytic properties (SRGN, GZMB and GNLY) and cytokine genes - IL-21, IL-17F, IL -17A, IFNg and GM-CSF. Next, the lung tissues of COVID-19 patients were enriched in cells co-expressing CCR6 and IL17A, and high levels of IL-6, IL-17A, GM-CSF and IFNg were found in BALF, which may explain the volumetric inflammatory changes in severe patients. with pneumonia [54]. This subpopulation of CD3+CD4+ cells has also been considered in sarcoidosis. The frequency of T-cells producing IL-17 increased in the peripheral blood and lungs of patients with sarcoidosis compared with the control group [131]. Moreover, IL-17A was showed in mature granuloma formation in response to mycobacterial infections [94]. A recent large case-control study confirmed an association between genetic variants of the IL-23 receptor (which promotes the Th17 response) in different cohorts of patients with sarcoidosis [39].

Previously, we have already determined that in the chronic course of sarcoidosis, the number of Th17 lymphocytes in the peripheral blood is increased relative to the group of patients with an acute course of the same disease [39, 131].

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

This confirms the assumption that Th17 is mainly involved in the acute phase of inflammation, synthesizing a large number of pro-inflammatory cytokines.

In tuberculosis, the main role in the immune response is played by adaptive immunity, which is carried out mainly by T lymphocytes. Th1 cells contribute to protection against tuberculosis by secreting IFN-γ and activating antimycobacterial activity in macrophages [81]. There is a hypothesis that the balance between Th1 and Th17.1 lymphocytes with a higher content of Th1 cells compared to Th17.1 may contribute to the development of an effective immune response to the penetration of *M. tuberculosis* into the cell [81]. In some studies, the production of antigen-specific IFN-γ by Th1 cells correlated with a decrease in mycobacterial load [81]. Similarly, in bronchoalveolar lavage fluid there was an increased number of Th1 lymphocytes, as well as cytokines of the profile of the same cells - IFNγ and TNFα compared with healthy controls. However, the number of Th1 cells, IFNγ and TNFα did not differ from those in patients with sarcoidosis [23, 98].

In our previous studies, it was demonstrated that the level of Th17 cells in peripheral blood significantly decreased in patients with tuberculosis [68]. Similar results were obtained when subset composition of peripheral blood Th in TB was analyzed using *in vitro* nonspecific stimulation methods, when it was shown that the level of CD4+IL-17A+ cells decreased during infection [93]. Similarly, elevated levels of CD4+IL-17+ T-cells were found in the lungs, that process confirmed the migration of this subpopulation to the site of inflammation during acute infection [76] Effector antigen-specific Th17 in peripheral tissues produce effector cytokines (IL-17A, IL-17F and IL-22), which activate various immune and non-immune cells of connective tissues, increasing the efficiency of their defense reactions aimed at eliminating extracellular pathogens [76]. Moreover, a decrease in the level of IL-17 in the peripheral blood of patients with tuberculosis was closely associated with the low effectiveness of the therapy used and the poor outcome of this disease [24].

5 **Conclusion**

Current evidences about the risk and clinical outcomes of COVID-19 infection in patient with sarcoidosis and tuberculosis are still not well understood. COVID-19, sarcoidosis and tuberculosis share similar common pathogenetic pathways, and all three diseases affect primarily the lung tissue. Multiple sets of conflicting clinical data showed that patients with sarcoidosis and tuberculosis immune response correlated with decreasing pulmonary function and higher risk of adverse outcomes from COVID-19. In some respects, the immune responses during COVID-19 and two pulmonary conditions had some similarities, ranging from the Th-cell subsets imbalance, inflammatory cytokines production to altered B cell activation and excessive infiltration of inflammatory sites by highly activated peripheral blood cells, which could lead to excessive tissue damage. Therefore, the identification of new immunological features of sarcoidosis and tuberculosis during or following SARS-CoV-2 infection will provide us with a deeper understanding of the diagnosis and treatment of these pathological conditions.

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Acknowledgments

Government funding was obtained from Almazov National Medical Research Centre of the Ministry of Health of Russian Federation. This work was financially supported by the Ministry of Science and Higher Education of the Russian

 10.15789/2220-7619-EOU-16874

Federation (Agreement No. 075-15-2022-301) and carried out in the flames of the State Assignment of Institute of Experimental Medicine (FGWG-2022-0005, no. 122020300186-5).

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

 10.15789/2220-7619-EOU-16874

TABLES

Table 1. Features of the immune response in patients with Tbc, sarcoidosis and COVID-19.

Cells	COVID-19	Sarcoidosis	Tuberculosis
Th1	↑[54, 112]; ↓[43, 107, 109]	↑[91]; ↓[67]	↑[79, 132]
Th2	↑[31, 41, 43]	↑[67, 74, 91]	↑[62, 68]; not significant [79]
Th17	↑[96, 137, 142]; ↓[31, 37, 43, 54]	↑[101, 103]; ↓[131]	↓[62, 68]
Tfh	↑[41, 112]; ↓[43, 54, 56]	↑[29]; not significant [67, 65]; ↓[80]	↑[68]; ↓[68] not significant [62]
Treg	↑[22, 128]; ↓[63, 89]	↑[18,88]; ↓[47, 50, 51]	↑[23, 26, 44, 114, 146]
Th maturation			
‘naïve’ Th	↓[7, 86]	↓[32, 68]	not significant [68]
CM Th	↑[108, 121]	↓[68]	↓[68]
EM Th	↑[86]	↓[68]	↑[134]; not significant [68]
TEMRA Th	↑[31, 86]	↑[68]	↑[68]; ↓[134]
Tcyt maturation			
‘naïve’ Tcyt	↑[92]; ↓[31, 70, 141]	↓[75]	↓[134]
CM Tcyt	↑[46, 70, 141]; ↓[31, 92]	↓[75]	↓[134]
EM Tcyt	↑[3, 86]; ↓[46, 70, 86]	↓[75]	↓[134]

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

 10.15789/2220-7619-EOU-16874

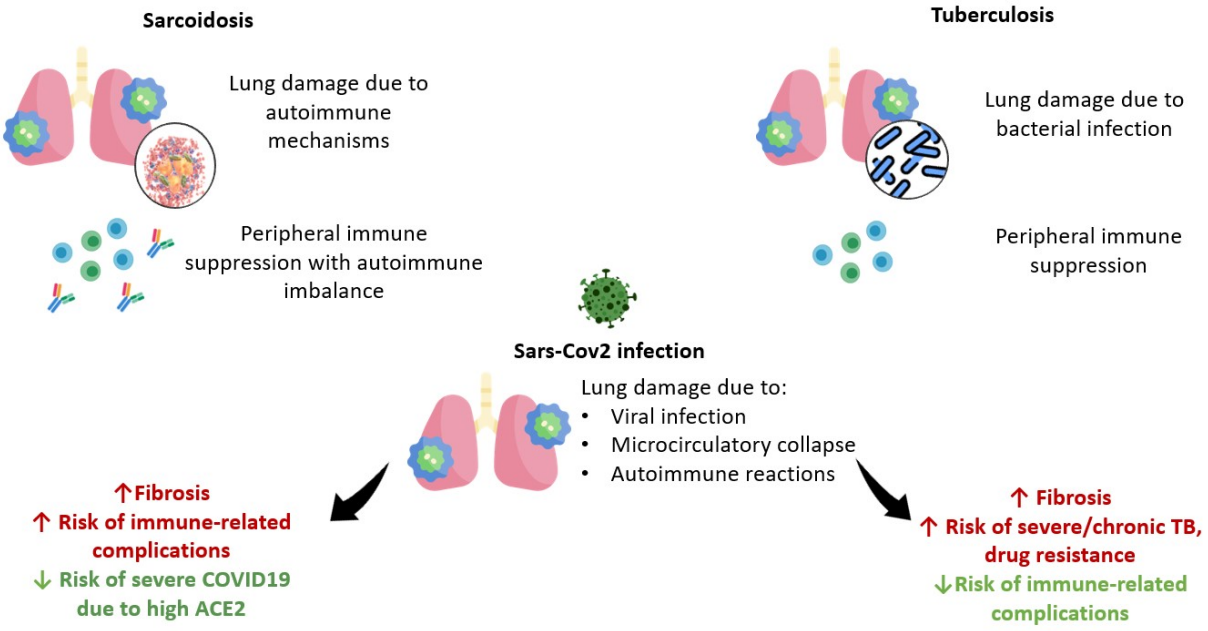
TEMRA Tcyt	↑[60, 86]; ↓[70]	↑[75]	↑[134]
B-lymphocytes			
‘naïve’ B-cells	↓[31, 69]	↑[65, 80, 110]	↓[52]
Memory B-cells	↓[31, 69]	↓[65, 80, 110]	↓[2]
Plasmablasts	↑[31, 56, 69, 120]	↑[65, 110]; not significant [80]	↓[2]

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

10.15789/2220-7619-EOU-16874

FIGURES

Figure 1. Scheme of immune response in COVID-19, sarcoidosis and tuberculosis.



ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

 10.15789/2220-7619-EOU-16874

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 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

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 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

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 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

 10.15789/2220-7619-EOU-16874

Блок 3. Метаданные статьи

AUTOIMMUNE DISORDERS IN PATIENTS WITH GRANULOMATOSIS DISEASES AFTER COVID-19: T AND B-CELLS SUBSETS FUNCTION

АУТОИММУННЫЕ НАРУШЕНИЯ У БОЛЬНЫХ ГРАНУЛЕМАТОЗНЫМИ ЗАБОЛЕВАНИЯМИ ПОСЛЕ COVID-19: ФУНКЦИОНИРОВАНИЕ СУБПОПУЛЯЦИЙ Т- И В-КЛЕТОК

Running head:

EXPERIENCE WITH THE USE OF GLUCAFERON

АУТОИММУННЫЕ РЕАКЦИИ ПОСЛЕ COVID-19

Keywords: autoimmunity; tuberculosis; sarcoidosis, granulomatosis diseases, T cell, B cell, Treg, follicular Treg, Treg subsets, prognosis.

Ключевые слова: Аутоиммунитет, туберкулез, саркоидоз, гранулематозные заболевания, Т-клетки, В-клетки, Treg, фолликулярные Treg, субпопуляции Treg, прогноз.

Reviews.

29 pages, 1 table, 1 figure.

04.10.2023

 ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

 10.15789/2220-7619-EOU-16874

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