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ETIOLOGY OF SARCOIDOSIS — EMPHASIS ON *CUTIBACTERIUM ACNES* (LITERATURE REVIEW)

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Abstract. Sarcoidosis is a multisystem disease with an unknown etiology, characterized by the formation of epithelioid cell non-caseifying granulomas with the most frequent lesions of the lungs, peripheral lymph nodes, skin, eyes and liver. Previously, it was believed that sarcoidosis is only one form of pulmonary tuberculosis. Patients with sarcoidosis were observed in tuberculosis dispensaries, and Mycobacterium tuberculosis was often found in their sputum. However, it was later established that tuberculosis joined sarcoidosis a second time as a result of patients staying in tuberculosis network facilities. Sarcoidosis was excluded from the competence of phthisiologists, which made it possible to solve the problem of iatrogenic tuberculosis infection. However, since then, statistics on sarcoidosis have become extremely limited. Currently, the opinion is gaining popularity again that sarcoidosis can be caused by a bacterial infection, but not at all the one that was previously assumed. Convincing evidence has been presented for the involvement of the commensal bacterium *Cutibacterium acnes* in the pathogenesis of this disease. This view of sarcoidosis corresponds to modern views on all autoimmune processes. In this regard, completely new treatment regimens for sarcoidosis have been proposed, including antibiotics that have already proven themselves well. This article will present a generalizing scheme of the pathogenesis of sarcoidosis in connection with *C. acnes*, which will allow us to take a fresh look at this familiar, but still mysterious disease.

Keywords: *Cutibacterium acnes,* sarcoidosis, granuloma, delayed-onset hypersensitivity, circulating immune complexes, immunomodulatory effect, mitogens, Hamazaki–Wesenberg bodies, latent infection

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ЭТИОЛОГИЯ САРКОИДОЗА: АКЦЕНТ НА *CUTIBACTERIUM ACNES* (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме. Саркоидоз — мультисистемное заболевание с невыясненной до конца этиологией, характеризующееся образованием эпителиоидноклеточных неказеифицирующих гранулем с наиболее частым поражением легких, периферических лимфоузлов, кожи, глаз и печени. Ранее считалось, что саркоидоз является лишь одной из форм туберкулеза легких. Пациенты с саркоидозом наблюдались в противотуберкулезных диспансерах, и в их мокроте действительно часто обнаруживались микобактерии туберкулеза. Однако позднее было установлено, что туберкулез присоединялся к саркоидозу вторично в результате пребывания больных в учреждениях противотуберкулезной сети. Саркоидоз был исключен из компетенции врачей-фтизиатров, что позволило решить проблему ятрогенного инфицирования туберкулезом. Однако с тех пор статистические данные по саркоидозу стали крайне ограниченными. В настоящее время вновь набирает популярность мнение, что саркоидоз может быть вызван бактериальной инфекцией, но совершенно не той, которая предполагалась ранее. Были представлены убедительные доказательства участия комменсальной бактерии *Cutibacterium acnes* в патогенезе данного заболевания. Такое представление о саркоидозе соответствует современным взглядам на все аутоиммунные процессы. В связи с этим были предложены и совершенно новые схемы лечения саркоидоза, включающие антибиотики, которые уже успели хорошо себя зарекомендовать. В данной статье будет представлена обобщающая когнитивная схема патогенеза саркоидоза в связи с *C. acnes*, которая позволит по-новому взглянуть на это знакомое, но все еще загадочное заболевание.

Ключевые слова: *Cutibacterium acnes*, саркоидоз, гранулема, гиперчувствительность замедленного типа, циркулирующие иммунные комплексы, иммуномодулирующий эффект, митогены, тельца Хамадзаки–Везенберга, латентная инфекция

BACKGROUND

Sarcoidosis is a multisystem disease of unclear etiology, characterized by the formation of non-caseating epithelioid cell granulomas. It most frequently affects the lungs, peripheral lymph nodes, skin, eyes, and liver [1, 2].

Sarcoidosis occurs worldwide in both sexes, with a predominance in women. Individuals of working age, up to 40–50 years, are most often affected, and the peak incidence occurs at 20–29 years of age [1, 3]. Its prevalence ranges from 1 to 40 cases per 100,000 population. The prevalence of sarcoidosis in Moscow in 2001 was 11.5 per 100,000 population [1, 4]. Modern epidemiological data on sarcoidosis in other Russian regions are insufficient and heterogeneous. However, there is a common trend towards an increase in the incidence and prevalence of this pathology [4]. The overall mortality rate from sarcoidosis is 1–5%. Death usually occurs due to progressive respiratory failure or myocardial involvement [1].

Currently, etiological therapy for sarcoidosis has not been developed. All treatments methods for such patients are based on the suppression of inflammation and the prevention of fibrous transformation of granulomas. Currently, the most effective drugs fir treatment of sarcoidosis are glucocorticosteroids (GCS) [5, 6]. Antimetabolites (methotrexate), immunosuppressants, tumor necrosis factor-alpha (TNFα) inhibitors, and protein kinase inhibitors (nintedanib) are also used. High doses of vitamin E are recommended for patients without symptoms and functional disorders [1, 5, 7]. Despite the relatively high frequency of spontaneous remissions, sarcoidosis remains a serious health problem. It requires further study of causes and pathogenesis, as well as the development of new methods of therapy, which emphasizes the relevance of this topic.

ETIOLOGY OF SARCOIDOSIS

Traditionally, the following factors are identified that can lead to the formation of granulomas [2, 5]:

- infections (viral and bacterial as a cause of continuous antigenic stimulation);
- environmental non-infectious factors (haptens and semihaptens);
- medicines;
- heredity [2, 5, 8].

However, none of these factors acts independently. A combination of several of them is necessary for the development of the disease. Nevertheless, it is foreign antigens (AG) that are a prerequisite for the formation of granulomas, which is dictated by the very logic of their pathogenesis. In this regard, *Cutibacterium acnes* appears to be an extremely attractive object for research [5, 9].

Cutibacterium acnes

Cutibacterium acnes (formerly *Propionibacterium acnes*) is a pleomorphic, non-spore-forming, Gram-positive, aerotolerant anaerobe belonging to the phylum *Actinomycetota* [10]. Bacteria of this species are representatives of the normal human skin microbiota and are localized mainly in the sebaceous glands and hair follicles, as well as on the mucous membranes of the oral cavity, gastrointestinal tract and genitourinary system [11, 12]. *C. acnes* suppresses growth of *Staphylococcus aureus* and *Streptococcus pyogenes.* However, in some cases *C. acnes* can also contribute to the development of a wide range of inflammatory processes, such as acne and prosthetic joint infections (due to the active formation of biofilms) [11, 13]. Intracellular proliferation of *C. acnes* in the epithelium of the prostate gland is associated with prostate cancer prostate cancer. In addition, *C. acnes,* due to its pronounced effect on the immune system, can apparently participate in the pathogenesis of SAPHO syndrome, which includes synovitis, acne, pustulosis, hyperostosis and osteitis [11], and sarcoidosis, and can also be used as an adjuvant in vaccination and stimulate antitumor immunity [10, 12, 13]. *C. acnes*-associated diseases and effects are presented in Figure 1.

C. acnes as the causative agent of sarcoidosis

The etiology of sarcoidosis is still unknown, but there are several compelling arguments for the involvement of *C. acnes* in the pathogenesis of this disease. Below we will briefly consider some of them [9, 13, 14].

Indirect evidence for this hypothesis may be the fact that sarcoidosis most often affects the lungs and

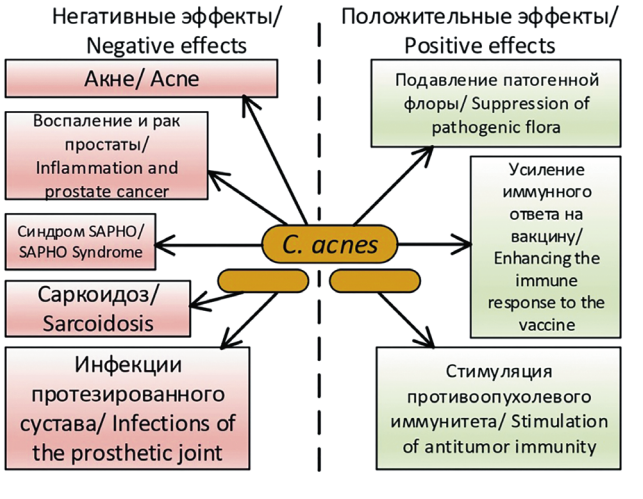

Fig. 1. ***C. acnes*-related diseases and effects. SAPHO syndrome — synovitis, acne, pustulosis, hyperostosis, osteitis**

Рис. 1. Связанные с *C. acnes* заболевания и эффекты. Синдром SAPHO — синовит, акне, пустулез, гиперостоз, остеит

associated intrathoracic lymph nodes (ITLNs), therefore, it may be caused by inhaled microorganisms or airborne pollutants [13, 15]. At the same time, it is proven that *C. acnes* is the most common bacterial species found intracellularly in the human lungs and intrathoracic lymph nodes [9].

Antigens (haptens) implicated in sarcoidosis may also include:

- **infectious agents:** *Mycobacterium tuberculosis* [16], *Borrelia* [17], *Aspergillus nidulans*, *Chlamydophila pneumoniae*, fungi [13], hepatitis C virus, herpes virus [2];
- **non-infectious environmental factors (haptens, semihaptens):** beryllium, aluminum [18], silica, copper, titanium [19], talc, quartz, wood combustion products [13], plant pollen, fungal spores [2];
- **autoantigens:** vimentin [20].

Since granulomatous inflammation requires the presence of an antigen in the granuloma, it is in them that the cause of the disease should be sought [13].

C. acnes is the one microorganism that is consistently detected in sarcoid granulomas. In cultures and immunohistochemical studies of lymph node homogenates from patients with sarcoidosis, *C. acnes* is detected in 78–92% of cases, depending on the research method [9, 21]. In the same studies of material taken from healthy individuals in the control group, the frequency of detection of *C. acnes* was only 25% [14, 21]. Moreover, molecular genetic methods allow us to obtain not only qualitative but also quantitative results. In samples taken from patients with sarcoidosis, using real-time PCR, significantly more copies of *C. acnes* DNA are detected than in controls [22].

It was assumed that sarcoidosis may be caused by *Mycobacterium tuberculosis*, but acid-fast bacteria have never been detected in sarcoid granulomas [23], and the QuantiFERON test gives negative results [24].

The Kveim reaction is another proof of the role of *C.acnes* in the development of sarcoidosis. A patient suspected of having sarcoidosis is given a subcutaneous injection of a homogenate of a lymph node affected by sarcoidosis. The formation of specific granulomas, detected by biopsy, confirms the presence of the disease [25]. Thus, it can be concluded that something that causes

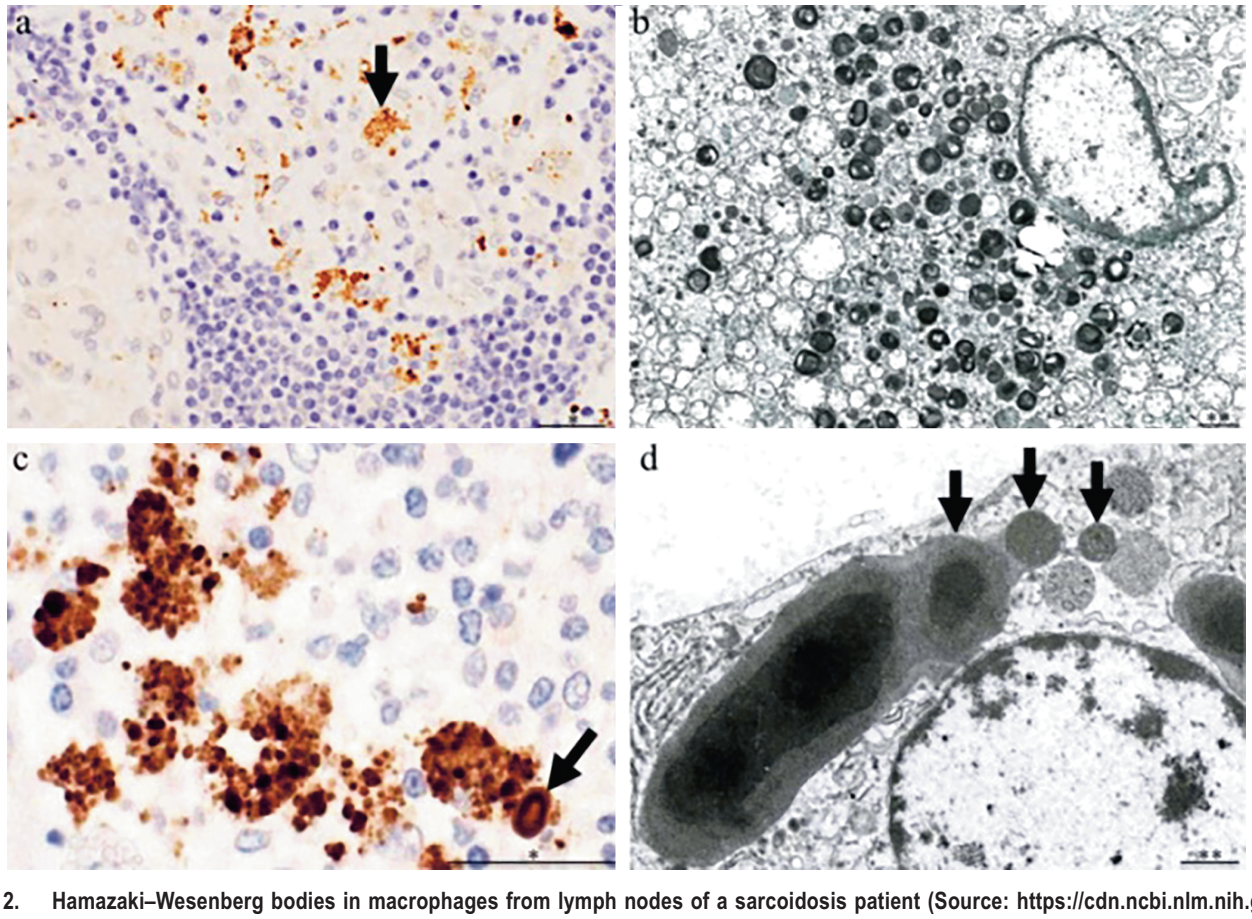

Fig. 2. Hamazaki–Wesenberg bodies in macrophages from lymph nodes of a sarcoidosis patient (Source: https://cdn.ncbi.nlm.nih.gov/pmc/blobs/03b5/9964181/8e148df1f939/microorganisms-11-00289-g002.jpg)

Рис. 2. Тельца Хамадзаки–Везенберга в макрофагах из лимфатического узла больного саркоидозом (Источник: https://cdn.ncbi.nlm.nih.gov/pmc/blobs/03b5/9964181/8e148df1f939/microorganisms-11-00289-g002.jpg)

sarcoidosis (*C. acnes* antigens) is contained within these lymph nodes [26].

The next proof is the detection of Hamazaki-Wesenberg bodies in macrophages during immunoelectron microscopy using antibodies to *C. acnes* antigens [27]. It was proven that Hamazaki-Wesenberg bodies are *C.acnes* without a cell wall and located intracellularly (Fig. 2) [28]. The loss of the cell wall, as well as the secretion of catalase, allows *C. acnes* to persist and multiply within the cells of the macroorganism. The phenomenon of incomplete phagocytosis is observed, similar to that in tuberculosis [9].

When bacterial culture is performed, *C. acnes* returns to its normal form, which, however, requires special nutrient media and a longer cultivation time [14].

Specific IgG and IgA to *C.acnes* antigens were detected in bronchoalveolar lavage (BAL), taken from patients with sarcoidosis [29].

In patients with sarcoidosis, mononuclear cells of peripheral blood stimulated with viable *C. acnes* exhibit increased IL-2 production (Th1-dependent cellular immune response) compared to peripheral blood mononuclear cells obtained from healthy controls [30].

An experimental model of subcutaneous immunization of mice with *C. acnes* using Freund's adjuvant showed that granulomas developed only in animals with latent *C. acnes* infection in the lungs [31]. That is, for the formation of granulomas, the presence of both a target antigen and allergization of the macroorganism is necessary [9]. When mice were pre-treated with antibacterial drugs against *C. acnes*, granulomas did not form [31].

Thus, sarcoidosis cannot be regarded as a simple infectious disease, since for its development the presence of *C. acnes* in the macroorganism is not enough. The presence of certain external and internal factors is also necessary [2, 14]. Koch's postulates (criteria developed to establish a causal relationship between microbes and disease) are not observed in this case (Fig. 3) [32, 33].

So, the infection caused by *C. acnes* can be named endogenous. Endogenous infections are infections that develop without the participation of transmission factors (the pathogen is initially localized in the patient's body) under certain conditions [14].

It has been proposed to divide endogenous infections into **three types:**

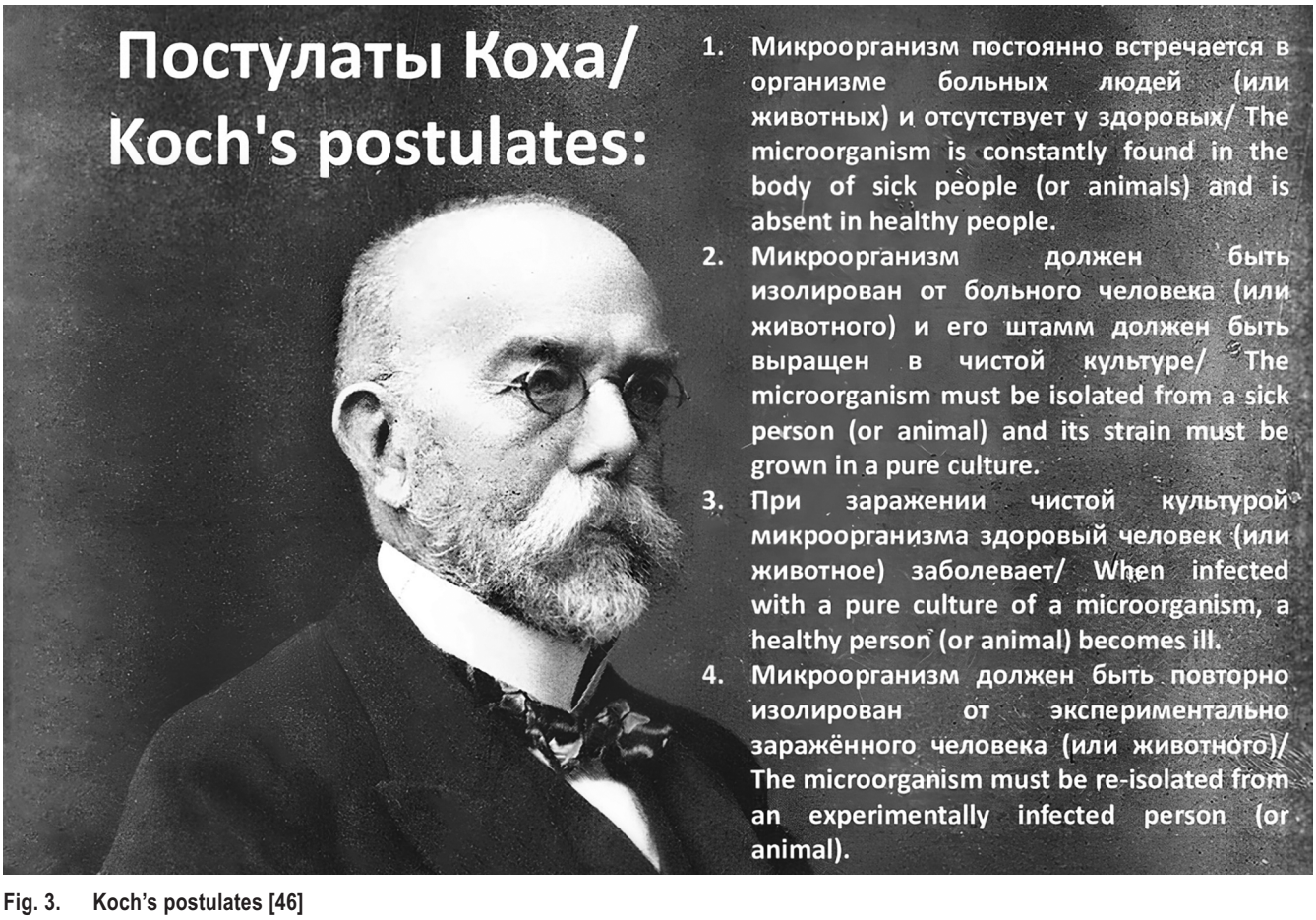

Fig. 3. Koch's postulates [46]

Рис. 3. Постулаты Коха [46]

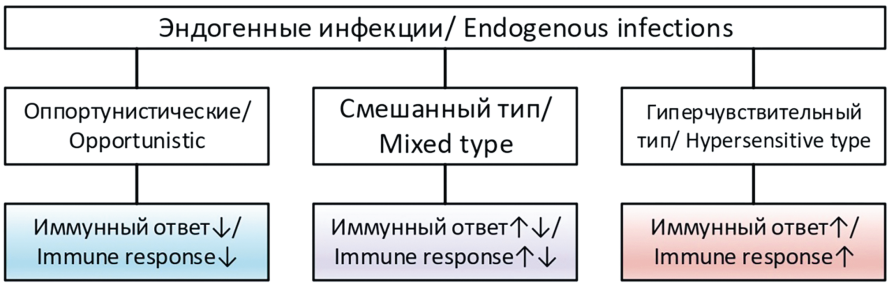

Fig. 4. Types of endogenous infections according to Casadevall and Pirofski [16]

Рис. 4. Виды эндогенных инфекций по A. Casadevall и L.-A. Pirofski [16]

1) opportunistic — develop with decreased immunity (*Pneumocystis jiroveci* in AIDS);
2) mixed type — *Candida* and *Aspergillus* (can cause both opportunistic infections and hypersensitivity pneumonitis (previously exogenous allergic alveolitis);
3) hypersensitivity type — sarcoidosis associated with *C. acnes* (Fig. 4) [34].

Moreover, recently, scientists demonstrated that *C. acnes* also can be detected in granulomatous tissue of patients with hypersensitivity pneumonitis and eosinophilic granulomatosis with polyangiitis (EGPA) [35]. In such patients, the number of lymphocytes in the BAL consistently exceeds that of other subjects. That is, in these diseases, *C. acnes,* if not the direct cause, at least acts as a mitogen, stimulating the mitosis of immune cells [13, 35].

Pathogenesis of sarcoidosis in relation to *C. acnes*

Commensal *C. acnes* lives extracellularly on human skin and hair follicles and also asymptomatically persists inside lung cells and intrathoracic lymph nodes [9, 28]. *C. acnes* can induce the innate immune response mediated by monocytes, neutrophils and macrophages [13, 36]. Antigen-presenting cells present *C. acnes* AG to naive T lymphocytes, activating the acquired immune response. Naive T lymphocytes differentiate into type 1 T helpers (Th1) [37], Th17 [38], natural killer T cells (NKT cells), and to a lesser extent into Th2 [13]. Th1 secrete cytokines such as interferon-alpha (IFNα), interferon-gamma (IFNγ), interleukin 1B (IL-1B), IL-12, which in turn stimulate the cellular component of immunity (macrophages) and suppress the activity of Th2, which are responsible for humoral immunity [13, 37]. A marked shift in the balance from a Th2 to Th1/Th17-mediated immune response is observed [9, 38]. This is a distinctive feature of *C. acnes* [14].

Spontaneous remissions of sarcoidosis presumably occur due to a spontaneous shift in the balance towards the humoral immune response [2, 13].

NKT cells stimulate natural killers [39]. Th17 secrete IL-17, which induces and maintains autoimmune inflammation, and IFNγ [38].

Thus, sensitization of the macroorganism to *C. acnes* antigens is formed according to the delayed-type hypersensitivity (DTH) type [9, 13].

At the same time, the latent intracellular infection occurs in macrophages of the lungs and intrathoracic lymph nodes [40]. Under the influence of any external factors, such as physical and mental stress and some medications (parenteral interferons, TNF-α antagonists, antiretroviral drugs), reactivation of the infection occurs. Active intracellular proliferation of *C. acnes* begins [2, 9, 40].

Then, pathogenesis progresses in two possible ways. If there is the DTH (described above), caused by the intrinsic properties of *C. acnes*, as well as the genetic predisposition of the macroorganism, a granuloma begins to form [41]. Under the influence of Th1, macrophages are attracted to the site of inflammation, which then transform into epithelioid cells and giant multinucleated cells [42]. Thus, sarcoid granuloma contains T lymphocytes, macrophages, epithelioid cells, giant multinucleated cells and fibroblasts and does not contain foci of necrosis [5].

The hereditary factors that most likely contribute to the development of sarcoidosis include:

- some Human Leukocyte Antigens (HLA) system haplotypes, such as HLA-B8/DR3 and HLA-DRB1*14;
- polymorphism of TNFα genes;
- polymorphism of the angiotensin-converting enzyme (ACE) gene;
- polymorphism of the vitamin D receptor (VDR) gene [8].

The other possible way is the overload of the macroorganism's cell with bacteria, initiation of the autophagy [43] (suppressed by the hyperactivated mTOR signaling pathway) [44], exit of *C. acnes* from the cell and its dissemination through the bloodstream. The bacteria reach other organs, including skin, heart, liver, kidneys, central nervous system (CNS) and so on, where they are phagocytosed again. The cycle repeats with the development of new granulomas outside the lungs [9, 14].

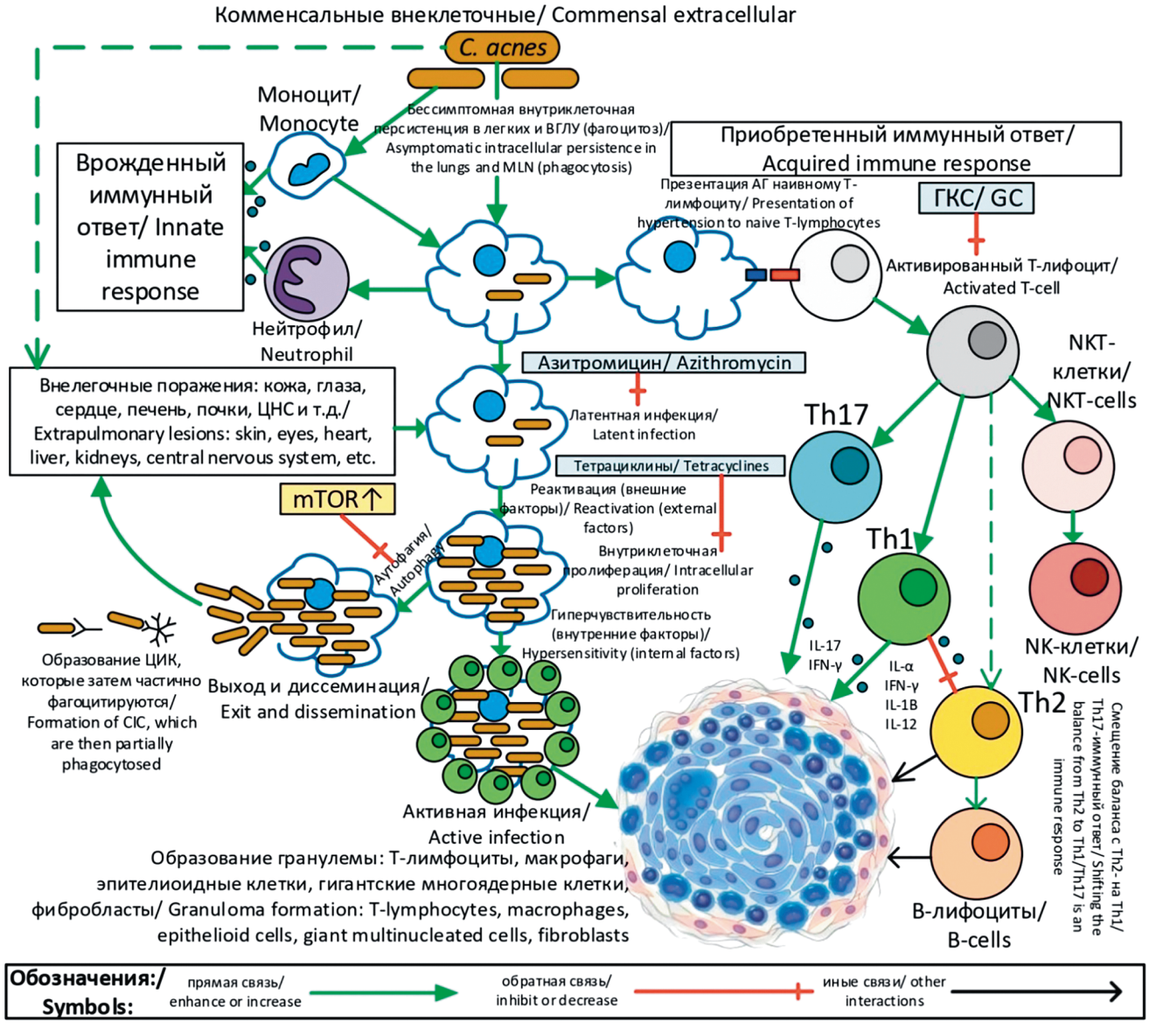

Fig. 5. **Pathogenesis of sarcoidosis in connection with *C. acnes*. MLN — mediastinal lymph nodes; GC — Glucocorticoids; CIC — circulating immune complexes; mTOR — mammalian target of rapamycin; Th — T-helpers; NKT-cells — Natural Killer T-cells; NK-cells — natural killers cells; IL — interleukin; IFN — interferon (the scheme was compiled by the authors)**

Рис. 5. **Патогенез саркоидоза в связи с *C. acnes*. ВГЛУ — внутригрудные лимфатические узлы; ГКС — глюкокортикостероиды; ЦНС — центральная нервная система; ЦИК — циркулирующие иммунные комплексы; mTOR — мишень рапамицина млекопитающих; Th — Т-хелперы; NKT-клетки — Т-клетки натуральных киллеров; NK-клетки — натуральные киллеры; IL — интерлейкин; IFN — интерферон (схема составлена авторами)**

During the period of dissemination, the formation of circulating immune complexes is also possible, which are then also phagocytosed or, presumably, can cause polyarthralgia and erythema nodosum in Löfgren's syndrome [45]. High antigenemia in patients with active sarcoidosis has been confirmed in the laboratory [46–49].

Sometimes extrapulmonary lesions can develop when *C. acnes* penetrates into the corresponding organs by routes other than systemic spread [9, 14].

Thus, **three main conditions** must be met for the formation of sarcoid granulomas:

1) latent intracellular infection (*C. acnes* as an antigen);
2) reactivation of infection under the influence of environmental factors;
3) DTH (Th1 hypersensitivity to intracellular proliferation of *C. acnes*) [9, 13, 14].

The pathogenesis of sarcoidosis in connection with *C. acnes* is clearly presented in the form of a generalizing scheme in Figure 5.

ETIOTROPIC THERAPY OF SARCOIDOSIS

The most widespread drugs for the treatment of sarcoidosis are glucocorticosteroids (GCS), however, therapy with them is not etiological. GCS suppress the immune response, which threatens the dissemination of viable *C. acnes* [14, 50].

Due to this fact, it has been suggested that antibiotics should be used in the treatment of sarcoidosis. Tetracyclines have been shown to effectively suppress intracellular proliferation of *C. acnes* [51], while macrolides are more effective against latent infection [52]. Good results were demonstrated in treatment of cutaneous and other forms of sarcoidosis with this combination of drugs [52, 53]. However, many experts believe that this effect is associated with the anti-inflammatory action of some antibiotics [54].

Calcium metabolism disorders in sarcoidosis are well-known. The pathogenesis of this condition is as follows: macrophages, under the influence of constant antigen stimulation, express the *CYP27B1* gene encoding calcidiol-1-monooxygenase, which converts $25(OH)D_3$ (calcidiol) into the active form of vitamin D — $1,25(OH)_2D_3$ (calcitriol). Calcitriol acts on the nuclear receptors of vitamin D (VDR), stimulating the release of the antimicrobial peptide cathelicidin. Excess calcitriol causes hypercalcemia and hypercalciuria [55]. However, bacterial ligands can block VDR over time, and a vicious circle develops.

In this regard, a treatment protocol for sarcoidosis was proposed, which, in addition to antibiotics, includes the angiotensin II receptor antagonist olmesartan at a specifically adjusted dosage. It was found that olmesartan, besides its primary action, also activates VDR by displacing bacterial ligands. Additionally, it inhibits TNF-α release, protecting the body from excessive inflammation. The efficacy of this protocol remains a subject of debate.

CONCLUSION

Thus, the concept of sarcoidosis as a disease in which *C. acnes* plays a major pathogenic role aligns with the modern understanding of autoimmune diseases as conditions triggered by latent bacterial, rather than viral, infections. However, this approach remains insufficiently proven, involves numerous controversial aspects, and requires further research. Nevertheless, significant progress has already been made in treating sarcoidosis, which was previously considered incurable.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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