Review article

Advance in pathogenesis of sarcoidosis: Triggers and progression

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ABSTRACT

Sarcoidosis, a multisystemic immune disease, significantly impacts patients' quality of life. The complexity and diversity of its pathogenesis, coupled with limited comprehensive research, had hampered both diagnosis and treatment, resulting in an unsatisfactory prognosis for many patients. In recent years, the research had made surprising progress in the triggers of sarcoidosis (genetic inheritance, infection and environmental factors) and the abnormal regulations on immunity during the formation of granuloma. This review consolidated the latest findings on sarcoidosis research, providing a systematic exploration of advanced studies on triggers, immune-related regulatory mechanisms, and clinical applications. By synthesizing previous discoveries, we aimed to offer valuable insights for future research directions and the development of clinical diagnosis and treatment strategies.

1. Introduction

Sarcoidosis, a systemic immune disease, is characterized by the development of granulomas in different organs or tissues. Globally, the incidence of sarcoidosis varied from 0.02 to 1.6 per thousand in adults and 0.006 to 0.01 per thousand in children [1,2]. Lung and lymph nodes were the most commonly affected organs, accounting for over 90% of sarcoidosis cases [3,4]. Hepatic sarcoidosis had an incidence of 20–30%, cutaneous sarcoidosis prevalence was 25%, while neurologic and cardiac sarcoidosis were less common, with an incidence ranging from 2 to 10% [5–7]. Typical manifestations of sarcoidosis encompassed lymph node enlargement, granulomas, cough, shortness of breath, and chest pain [8]. Certain symptoms might manifest at specific age groups; for instance, Blau syndrome predominantly affected children under four years old, exhibiting characteristic clinical features such as erythra, uveitis, and residual arthritis [9,10]. Alternatively, another phenotype known as Löfgren's syndrome, denoted as acute sarcoidosis, demonstrated geographical variability. Prevalent among young patients in Sweden, this syndrome was characterized by an acute onset of erythema nodosum, bilateral hilar lymphadenopathy, fever, and migratory polyarthritis [11].

Due to the lack of in-depth research and systematic theoretical system, the diversity and complexity of the pathogenesis had brought a great challenge to the clinical diagnosis and treatment of sarcoidosis in recent years [12]. On the one hand, the triggers of sarcoidosis were various, leading a distinct clinical manifestation, disease course and prognosis. 70–90% of patients had insidious onset and resolved spontaneously, while 10–30% of patients have received treatment but with a poor therapeutic effect, resulting in

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chronic inflammation and even local regional fibrosis [13,14]. Among the 10% of patients with the most severe symptoms, 12%–18% did not survive within five years [1]. On the other hand, the lack of systematic understanding of the pathogenesis of sarcoidosis led to the lack of reliable diagnostic markers and appropriate treatment strategies for sarcoidosis. Some patients were underdiagnosed, misdiagnosed as other diseases (e.g., tuberculosis) or unable to receive timely and appropriate treatment, resulting in irreversible damage to relevant organs and functions, death or other adverse prognosis, which greatly affects the patients' working ability to, quality of life, and health.

Hence, the exploration and refinement of pathogenic triggers and molecular mechanisms in sarcoidosis were crucial for improving diagnosis and optimizing therapeutic strategies to enhance patient prognosis. Current research and guideline consensus indicated that sarcoidosis was caused by the abnormal accumulation of immune cells (e.g., activated macrophages, dendritic cells, helper T-cells, etc.) and excessive immune reaction in organs or tissues triggered by susceptibility genotypes, self or foreign antigens. As research advances, it had been discovered that, in addition to the dominant role of immune cells, pro-inflammatory factors (such as tumor necrosis factor α (TNF-α), interleukin (IL)-17) created a conducive inflammatory response environment for granuloma formation. Furthermore, the abnormal activation of signaling pathways (such as mTORC1, Rac1) had been identified as a crucial regulatory measure. These pathways contributed to maintain an over-responsive state of immune cells and facilitate the transition of immune responses into the chronic phase [15]. A deeper understanding of these molecular mechanisms held the key to developing targeted interventions for sarcoidosis.

In this review, we systematically delved into the occurrence and progression of sarcoidosis, focusing on key aspects such as triggers (including susceptibility genotypes, self-antigens, and foreign antigens) and immune-related regulatory mechanisms (involving immune cells and associated signaling pathways in granuloma formation). By shedding light on these critical elements, we aspired to provide a foundation for deeper understanding the pathogenesis of sarcoidosis, so as to guide future research directions and contribute to the development of innovative clinical diagnosis and treatment strategies.

2. Sarcoidosis triggered by susceptibility genotypes and autoimmune abnormalities

Epidemiological studies on sarcoidosis conducted by numerous researchers revealed distinct racial or ethnic variations in the distribution of sarcoidosis patients, along with a noticeable tendency for familial aggregation [16]. Notably, Sarcoidosis was more prevalent and clinically severe in black than in white populations in the same region. Pacheco et al. demonstrated a genetic predisposition to sarcoidosis by reporting that multiple members of the same family were affected sarcoidosis and that monozygotes were more likely to be affected than dizygotes [17]. These findings strongly suggested the influence of genetic factors on both incidence and clinical manifestations of sarcoidosis. Indeed, a consensus had emerged among most researchers that genetic factors played a significant role in the pathogenesis of sarcoidosis. Years of genetic research had revealed that it was not a single gene but rather multiple genes that collectively influenced the course of the disease and these genetic factors interacted with each other, contributing to the complexity of sarcoidosis.

In addition to genetic susceptibility, autoimmunity abnormalities also played a crucial role in the pathogenesis of sarcoidosis. As early as 1970, Karlish AJ et al. identified a potential correlation between sarcoidosis and autoimmune diseases such as thyroiditis and Addison's disease [18]. Subsequent research had further confirmed organ-specific or non-organ-specific associations between sarcoidosis and autoimmune diseases [19,20]. K I Papadopoulos et al. discovered clinical or serologic evidence of endocrine autoimmunity in nearly 20% (15/89 cases) of patients with sarcoidosis [21]. D Alessandro M et al. conducted a comparison between sarcoidosis and three other autoimmune diseases, namely idiopathic inflammatory myopathies (IIM), five cases of granulomatosis with polyangiitis (GPA), and ten cases of microscopic polyangiitis (MPA). They analyzed T and B lymphocyte subpopulations and identified similar patterns of cellular immune dysregulation [22].This observation implied a shared pathogenic pattern of autoimmune dysregulation in sarcoidosis [23].

This section aimed to summarize the auto-pathogenic triggers of sarcoidosis, focusing on genes and autoimmune abnormalities.

2.1. Human major histocompatibility complex

The human major histocompatibility complex (MHC), also known as human leukocyte surface antigen (HLA) in genetic variation mapping studies, stood out as a crucial autoantigen in sarcoidosis. Positioned on the short arm of chromosome 6, the MHC encompasses the HLA-F gene to the HLA-DPB1 gene region. According to the type of products encoded by the gene, HLA were categorized into HLA class I (HLA-A, HLA-B, HLA-C, etc.), HLA class II (HLA-DP, HLA-DM, HLA-DO, HLA-DQ, HLA-DR, etc.), and HLA class III (including certain complement and cytokines, as well as heat shock proteins) [24–26].

Recent studies revealed that HLA allele polymorphisms exhibited strong association with the susceptibility and prognosis of sarcoidosis [24–26].

2.1.1. The relationship between HLA class I gene and sarcoidosis

The link between HLA and sarcoidosis was first reported in 1973 [20]. Their findings revealed that HLA-A7 positivity was twice as common in sarcoidosis patients as in healthy individuals (52% vs. 27%). Subsequent investigations by various researchers identified other self-antigens, such as HLA-B8, as highly correlated with the development of sarcoidosis. In the Icelandic region, the prevalence of HLA-B8 and HLA-B14 antigen positivity was significantly higher in 36 patients with nodular arthritis than in the healthy population. For instance, 24% vs. 11% (p < 0.01) for HLA-B8, and 6.5% vs. 2.4% (p < 0.05) for HLA-B14 [27]. In a study of a South African population, HLA phenotyping of 51 sarcoidosis patients suggested that positivity for HLA-B15, C4, C7, C12, C15, C16, and C17 was a

risk factor for sarcoidosis, whereas HLA-A9, A28, B12, and B17 were negatively associated with the development of sarcoidosis [28].

2.1.2. The relationship between HLA class II gene and sarcoidosis

As research advanced and testing techniques developed, researchers had shown increased interest in the A and B genotyping of the HLA-DR region, serologic specificity, combinations of alleles, and their variations across different populations. Löfgren's syndrome (LS) is characterized by a genetic association with HLA-DRB1*03 [23]. In a genotyping study comparing 122 Scandinavian sarcoidosis patients with 250 healthy Swedish individuals, the proportion of HLA-DRB1*17 positivity was significantly higher in patients with sarcoidosis [29]. Another study on Scandinavian sarcoidosis found that a combination of alleles of HLA-DRB1*15, HLA-A3, and HLA-B7, rather than individual alleles, was a risk factor for sarcoidosis. Furthermore, there were differences in gene expression between patients at different stages, with 78% of patients in remission being HLA-DRB1*03 positive, while 52% of patients with persistent sarcoidosis were HLA-DRB1*15 positive [30]. Similarly, the HLA-DRB1*05 antigen was detectable in 52% of patients with pulmonary fibrosis caused by chronic sarcoidosis, which was significantly higher than that in patients with pulmonary fibrosis caused by chronic extrinsic allergic alveolitis and 162 healthy volunteers (52% vs. 14% vs. 14%) [31]. A study of Turkish sarcoidosis patients indicated that HLA-DRB1*15 was an independent risk factor for sarcoidosis, while HLA-DRB1*11 was a protective factor [32]. A review summarizing articles on HLA genotypes and susceptibility to sarcoidosis published between 1960 and 2019 highlighted the promotional role of HLA-DRB1*03/07/15 in the development of sarcoidosis and the protective role of HLA-DRB1*04 [33].

In addition to HLA-DR, HLA-DQ, and HLA-DP genotyping and their expression also played essential roles in the pathogenesis of sarcoidosis. Genotyping 93 Croatian sarcoidosis patients showed that the HLA-DQB1*0201 genotype of acute sarcoidosis patients was significantly higher than that of chronic sarcoidosis patients and healthy individuals [34]. In a large population-based study, the HLA-DQB1*0501 genotype was identified as a protective factor. HLA-DQB1*0301 haplotype presented a protective role in Dutch sarcoidosis patients, while it was categorized as a risk factor in British and Japanese populations [35]. Regarding the HLA-DP gene, fewer relevant studies existed, but it had been suggested that HLA-DPB1 had a similar role in sarcoidosis as HLA-DRB1 and HLA-DQB1, particularly in populations of African descent [36].

While HLAs can be categorized into three groups based on their coding products, each type of HLA contributed to the development of sarcoidosis in diverse ways. Consequently, further research was essential to investigate and consolidate the roles of various HLA genes in the progression of sarcoidosis.

2.2. Angiotensin-converting enzyme (sACE)

Serum angiotensin-converting enzyme (sACE) was widely recognized as a valuable indicator for assisting in the diagnosis and evaluation of sarcoidosis. In a study in 1975, Lieberman et al. reported that 88% of a subgroup of sarcoidosis patients had elevated sACE levels, while those who were treated with steroids and in remission exhibited normal sACE levels [37]. These findings prompted researchers to explore the sACE gene as a potential causative factor for sarcoidosis development. However, different studies in recent years had shown that one of the single nucleotide polymorphisms (SNPs) of the sACE gene, specifically the I/D genotype based on presence or absence of a 287-base pair insertion in the 16th intron, was not found to be significantly associated with sarcoidosis [38]. Conversely, in a new class of SNPs of sACE (rs9905945), researchers discovered an association with a more favorable prognosis [39].

2.3. Nucleotide oligomerization structural domain 2 (NOD2) gene

As research progressed, an increasing number of phenotypes and mutations in the NOD2 gene had been reported in association with a special type of sarcoidosis called early onset sarcoidosis (EOS) [40]. EOS, also known as Blau syndrome, was an autosomal dominant sarcoid-like disease that manifested in childhood, with a higher prevalence in children under 4 years of age characterized by granulomatous polyarthritis and uveitis. Among the reported mutations of NOD2, the most frequently and typically type was p.R334W [41, 42]. Besides, other mutations such as p.W490S, D512V, C483W, and p.Lys 442 Phe had also been reported subsequently [42–44]. Mao et al. discovered that NOD2 played a regulatory role in the NF-κB pathway, and its mutation hindered the interaction with RIPK2, impeding NF-κB activation by influencing the NOD2 ligand (MDP). Additionally, NOD2 mutation failed to contribute to the regulation of the innate immune response, resulting in an intensified TLR-mediated pro-inflammatory cytokine response, ultimately contributing to the development of Blau syndrome [45]. More in-depth studies were needed to complement and improve the direct relationship between the NOD2 mutation and Blau syndrome.

2.4. Macrophage-derived chemokines (MDC), chemokine-related and other genes

Macrophage-derived chemokines (MDC) had been found to promote the pulmonary nodule formation, and its secretion was affected by a polymorphism in promoter region −942(C/T) (MDC-942(C/T)) [46]. Zhou et al. analyzed the level of MDC in bronchoalveolar lavage fluid (BALF) and serum of 11 patients with sarcoidosis and detected MDC-942(C/T) SNP. When comparing with healthy group, they found that the serum concentration of MDC in patients was higher and the MDC-942(C/T) SNP was a risk factor for sarcoidosis in the population under 40 years old. Moreover, MDC levels in the serum of patients with each genotype of MDC-942(C/T) SNP showed a decreasing trend in the order of CC, CT, and TT, indicating the significant role of MDC-942(C/T) in the pathogenesis of sarcoidosis [46].

Besides, up-regulated expression of chemokine-related genes XCL1, CCL2, and RANTES in the BALF of sarcoidosis patients, especially those with advanced sarcoidosis, emphasized the involvement of chemokine genes in the disease's pathogenesis [47]. In a

genetic susceptibility study of ocular sarcoidosis patients, an association was found between the IL-23R gene region and sarcoidosis [48].

While the aforementioned studies had pinpointed various genes linked to sarcoidosis, the majority had merely delineated differences in gene expression between sarcoidosis patients and healthy population. They had not, however, provided a mechanistic perspective on the direct involvement or influence of these genes in the progression of sarcoidosis. Future investigations were imperative to substantiate the mechanisms through which genetic susceptibility and autoimmune abnormalities contribute to sarcoidosis.

3. Sarcoidosis triggered by foreign antigens

Beyond genetic susceptibility and autoantigenic factors, sarcoidosis can also be triggered by exogenous factors such as microbial infections, exposure to inorganic substances in the peripheral environment, and the effects of certain drugs.

3.1. Bacterial microbial infections

Bacterial microbial infections not only elicited specific immune responses to distinct bacterial antigens but also contributed to the development of an exaggerated autoimmune reaction. Recent cross-sectional studies on pathological samples of sarcoidosis have indicated a strong association between *Mycobacterium tuberculosis* (*M. tuberculosis*) and Cutibacterium acnes infections, yet their direct involvement in the development of sarcoidosis still remained controversial [49]. In most sarcoidosis samples examined, only DNA or protein components of the associated pathogens were detected, and no evidence of living bacteria could be directly or indirectly captured through isolation culture or immunostaining. Moreover, the study conducted by Drake et al. demonstrated that anti-tuberculotic treatment in sarcoidosis patients with detected tubercle bacilli components in pathological samples of nodules did not effectively improve their lung function [50]. Despite several researchers successfully isolated Propionibacterium acnes from samples of patients with sarcoidosis and constructed sarcoidosis mouse models using in vitro cultured Cutibacterium acnes and *M. tuberculosis* and their derivatives, however, the modalities of modeling and the conditions of nodule formation still differed significantly from the occurrence scenes of sarcoidosis in clinical patients [51–55]. Therefore, further investigation was still needed to confirm the direct contribution of microbial infections and their related mechanisms in the development of sarcoidosis.

3.2. Metal, carbon, silicon inorganic antigen factors in the peripheral environment

In recent years, metals and inorganic substances such as carbon and silicon in the external environment were reported can act as antigens to induce sarcoidosis. Several studies investigating the etiology of sarcoidosis had highlighted that individuals in occupations with prolonged exposure to dust, smoke, metal, and carbon nanoparticles (such as workers and firefighters) were at a significantly higher risk of developing sarcoidosis compared to those in other occupations [56–59]. An examination of blood samples from sarcoidosis patients revealed that metals such as aluminum, beryllium, silicon, zinc, and silicon were more likely to function as allergens in the blood of a significant proportion (27%) of sarcoidosis patients, leading to a pronounced immune response when compared to normal individuals [60]. Furthermore, studies involving multiwall carbon nanoparticles (MWCNTs) and cadmium nanoparticles (QD705) demonstrated their ability to induce chronic granulomatous lung inflammation in mice [61–64]. The mainly mechanisms involved were that metals, carbon, and silicon are more likely to combine with susceptibility genes (such as HLA-DP2) to induce immune response or increase cytokines such as transforming growth factor-β (TGF-β) and IL-13 in vivo, thereby affecting the differentiation and proliferation of T cells in specific organs and the aggregation of specific T cells, resulting in the occurrence of nodules [65,66].

3.3. Drug factors

In recent years, several reports suggested that patients treated with drugs such as interferon-α (IFN-α), immune checkpoint inhibitors, and BRAF inhibitors may develop sarcoidosis as a result of drug effects [67–72]. Investigators observed that the histopathologic features of nodular granulomas in these treated patients were consistent with sarcoidosis granulomas which provided clinical evidence for drug antigens. Furthermore, the consensus had emerged that the expression of CTLA4 on the surface of CD4+ T cells in sarcoidosis patients was downregulated to enhance recognition of self-antigens [73]. Simultaneously, the number of CD4+ T cells was regulated by the PD-1 signaling pathway. Blocking the PD-1 signaling pathway promoted the proliferation of CD4+ T cells, thereby facilitating the inflammatory response [74]. Consequently, treatment with *anti*-CTLA4 or *anti*-PD1 antibodies might create a sarcoidosis-like inflammatory environment characterized by active proliferation of CD4+ T cells and heightened recognition of self-antigens [75–78]. However, such sarcoidosis granulomatous lesions occurred in only a small percentage of patients receiving immunosuppressive, chemotherapy, and antiviral therapy and were not common [79]. Hence, some researchers preferred to classify such drug-induced granulomatous lesions as sarcoidosis-like drug reactions rather than sarcoidosis. After reviewing these studies, we suggested that, to solve the controversy of whether drugs can be used as a trigger of sarcoidosis, on the one hand, more clinical studies with large sample sizes should be conducted to verify the prevalence of drug-induced granulomatous lesions. On the other hand, more in-depth mechanistic studies were needed to obtain direct evidence of the mechanism of drugs involved in the pathogenesis of sarcoidosis.

4. Mechanisms associated with granuloma formation in sarcoidosis

Sarcoidosis is characterized by the formation of granulomas, accompanied by varying degrees of immune cell infiltration and inflammatory reactions. It was a complex process that many factor including inflammation-related cytokines, small molecule poly-peptides, immune cells and their immune microenvironment were involved during the acute and chronic phase of granulomatous formation. One of the crucial processes in granuloma formation was the aberrant immune response orchestrated by macrophages, Th cells, and B cells, along with their associated regulatory signaling pathways [80]. The following section summarized the roles of immune cells involved in granuloma formation, as reported in recent years, along with their related signaling pathways.

4.1. Macrophage and dendritic cell

Macrophages, integral to the innate immune system, played a pivotal role in various aspects of granuloma formation in sarcoidosis. While earlier studies primarily focused on immune cells dominating adaptive immunity, recent research had highlighted the crucial synergistic and facilitating role of the intrinsic immune system, particularly macrophages, in granuloma formation. Macrophages not only acted as feed-forward steps to trigger and continuously enhance the subsequent adaptive immune processes, but also fully participated in the key components of antigen presentation, pro-inflammatory response and granuloma formation.

Following bacterial, inorganic or self-antigenic stimulation, macrophages increased their activity, upregulated the expression of MHC on their membranes and enhanced their recognition of antigens, thereby initiating a downstream adaptive immune response [81]. Simultaneously, the secretion of large amounts of serum amyloid A (SAA) and heat shock proteins (HSPs) by macrophages induced an acute inflammatory response, fostering an environment conducive to the maintenance of inflammation and the involvement of immune cells in granuloma formation.

At the same time, Toll-like receptors (TLRs) and Nod-like receptors (NLRs) were upregulated on the macrophage surface or in the cytoplasm, serving not only in antigen recognition and activation of antigen-presenting cells but also as key upstream factors mediating the autophagy signaling pathway [15,82]. Chen et al. found that the expression of TLR2 and TLR4 on the surface of macrophages was significantly elevated in sarcoidosis patients, and the combined stimulation of TLR2 and NOD2 receptors resulted in the secretion of inflammatory factors (e.g., TNF-α and IL-1β) from PBMCs of patients. Meanwhile, TLR2 can bind to SAA, activating the NF-KB pathway and creating an inflammatory environment conducive to granuloma formation [83]. Boissier, P. et al. and Koo, T.H. et al. also found that NOD2, TLR4 and TLR9 expressed by macrophages and dendritic cells (DCs) can recognize and bind to EPHA2 and KALRN, activating the RAC1 autophagy signaling pathway [84,85].

Additionally, the study by Miyamoto et al. revealed that IL-4 and IL-13 cytokines in patients with sarcoidosis can promote the fusion of macrophages through STAT6 signaling pathway to further enhance their phagocytic function [86].

Furthermore, macrophages (e.g., alveolar macrophages), which were critical for antigen presentation, secreted large amounts of IL-12, IL-18, IL-6 and TGF-β upon activation, which promoted polarization of naïve T-cells aggregated in the affected organs towards Th1, Th17 and Th17.1 types and inhibited the function of Treg cells, directing the aberrant immune response at this point towards the outcome of chronic granuloma formation [4,87].

Similar to alveolar macrophage function, dendritic cells (DCs) were also involved in the aberrant immune process of granuloma formation. Several research had reported that DCs showed a strong correlation with sarcoidosis in epidemiological investigations and their role as antigen-presenting cells to activate and determine subsequent adaptive immunity in sarcoidosis patients has been vali-dated experimentally. Liu et al. and Zaba et al.'s studies on tissue specimens from sarcoidosis patients showed that mature DCs were predominantly clustered in lymph nodes from sarcoidosis patients and stimulated T-cell clonal proliferation more strongly than alveolar macrophages, while immature DCs were predominant and less active in target organs or tissues (e.g., lung, skin, peripheral blood) [88–90]. Ten et al. found that myeloid dendritic cell (mDC) levels were up regulated in BALF from sarcoidosis patients. After co-culturing mDC isolated from BALF with naïve CD4$^+$ T cells, the ability of CD4$^+$ T cells to secrete TNF-α was significantly higher than that of the mDC group isolated from non-sarcoidosis patients, which further validated the role of DCs in antigen presentation for subsequent adaptive immune responses during granuloma formation [91]. Meanwhile, Broos et al. found that chemokines such as CCL20 produced by alveolar macrophages induced aggregation of monocyte-derived DCs, which fused to form multinucleated giant cells that participated in granuloma formation in response to IL-17A [92]. In addition, DCs also expressed TLR and NLR similar to those derived from macrophages to activate inflammatory responses and related downstream signaling pathways in vivo.

4.2. Effector T cell

In normal human immunity, naïve CD4$^+$ T cells can undergo differentiation into Th1, Th2, Th17, and Treg cell subtypes under the influence of cytokines. Current research suggested that the main cause of sarcoidosis granuloma formation was the expansion and functional overactivity of Th1 and Th17 subtypes of CD4$^+$ helper T cells, the essence of which was Th1/Th2 cell immune disorder and Treg/Th17 type imbalance and dysfunction [93–97].

4.2.1. Th1/Th2 in development of sarcoidosis

Th1 cells primarily differentiate from IL-2, TNF-α, and interferon-y (IFN-γ) (by autocrine or other immune cells) stimulation. They were responsible for cytotoxicity, mediating cellular immunity, and playing an important role in anti-infective as well as intracellular pathogens clearance, and the induction of autoimmune diseases. The naive CD4$^+$ T cells were stimulated to differentiate into Th2 cells by IL-4, IL-6, and IL-10, which not only encouraged the production of immunoglobulins like IgG1, IgE, and IgA to mediate humoral

immunity but also regulated the anti-allergic and parasite clearance. Since IFN-γ secreted by Th1 inhibited naïve CD4+T differentiation to Th2, and IL-4 secreted by Th2 inhibited Th1 differentiation, there was a dynamic balance of Th1/Th2 in the normal immune system.

In recent years, it had been found that the elevation of chemokines such as CCL10 in granulomatous affected organs of patients with sarcoidosis led to the influx and accumulation of Th1 CD4$^+$ T cells with corresponding ligands. Meanwhile, due to the inflammatory response and the activity of upstream macrophages, IFN-γ, TNF-α, and IL-2 were elevated, which then led to the activation of the Th1 immune response involved in n the acute phase of granuloma formation [81,98,99].

As we mentioned before, the abnormal immune response activated by Th1 was considered key to granuloma formation in the acute phase, the immune pattern and related mechanisms in the chronic phase of sarcoidosis remain unclear. Recently, some studies found that the formation of chronic sarcoidosis might be the process of switching from CD4$^+$ T cells to Th2 cell-dominated immune response in the affected organ [100]. Th2 related cytokines usually regulated the proliferation of fibroblasts and their interactions with macrophages, and then participated in the process of post-inflammatory fibrosis in tissues, and the fibrosis of granuloma structures was the key to the chronic phase of sarcoidosis [101,102].

However, previous studies had shown that the amplification and function of Th2 was often inactive in an environment where Th1 was active of function. How CD4$^+$ T cells change the balance of Th1/Th2 differentiation during the progression from acute to chronic phase of granuloma formation and related mechanism were still unknown, which may need more research to explore in the future.

4.2.2. Th17/Treg imbalanced in sarcoidosis

Th17 cells were mainly differentiated after the stimulation of cytokines such as transforming growth factor β (TGF-β), IL-1β, and IL-6, and secreted IL-17 (mainly IL-17A and IL-17F), IL-23, and IL-22 to induce inflammation [103]. Recent research on sarcoidosis granuloma formation, in addition to the traditional Th1-dominated perspective, emphasizes the pivotal role of Th17. Studies by Crouser et al. demonstrated that the elevated ratio of Th17/Treg cells in peripheral blood and BALF in patients with active pulmonary sarcoidosis was associated with recurrent pulmonary sarcoidosis after corticosteroid discontinuation [104]. Ostadkar et al. reported that Th17 was significantly more active in peripheral blood of patients with Löfgren syndrome (LS) than in healthy individuals [105]. Investigations by Okamoto Yoshida et al. also confirmed the necessity of Th17 cells for mature granuloma formation in a mouse sarcoidosis model [106]. All these studies revealed that Th17 amplification and functional activity were important markers of sarcoidosis.

Further exploration uncovered that IL-17A, expressed by Th17, induced inflammatory cells to release pro-inflammatory chemokines and cytokines, affecting monocyte differentiation and promoting granuloma formation and stability. Studies by Ten Berge et al. showed significantly higher levels of IL-17A in the blood and lung lavage fluid of active sarcoidosis patients compared to healthy controls. They also found the production of IL-17A was closely associated with elevated expression of the chemokine CXCL9-11 which further promoted Th1 cell recruitment and facilitating granuloma formation [91]. Broos et al. 's research revealed that IL-17A can promote monocyte fusion to form multinucleated giant cells to participate in granuloma formation [92]. Additionally, IL-23 secreted by Th17 might also participate in the formation of sarcoidosis. The IL-23/Th17 signaling pathway was found to play an important role in the genetic etiology of sarcoidosis in an immuno-microarray screening of sarcoidosis samples by Fischer et al. [107]. Crouser et al. and Nurieva et al. also highlighted IL-23 as a key cytokine in Th17 induction. The IL-23 gene was significantly expressed in cutaneous sarcoidosis and IL-23 was able to influence Th17 cell function independently of the IL-17 pathway [108,109]. Furthermore, STAT3 and TGF-β signal pathway had also been shown to be closely associated with Th17 cell proliferation, differentiation and functional activation [108,110].

Apart from the pro-inflammatory role of Th17, Treg cell abnormalities emerged as another key factor in sarcoidosis granuloma development [111]. Treg, a class of CD25+Foxp3+CD4$^+$ T cells, regulated the immune response and maintain immune homeostasis by producing immunosuppressive factors like TGF-β and IL-10. Miyara et al. found that, although Treg cells were present in lesioned tissue of sarcoidosis patients, their inflammatory suppressive function and cellular activity were diminished [112]. Liu et al. also found that the ratio of circulating Treg/Th17 cells was negatively correlated with disease activity and decreased in patients with recurrent pulmonary sarcoidosis, returning to the normal range after treatment [113]. Idali et al. observed increased proliferative capacity of Treg cells in renal and lymph node granulomas of sarcoidosis patients, contrasting with their decreased function in peripheral blood and pulmonary perfusion [114]. Despite the number and distribution of Treg cells in the active phase of sarcoidosis remained controversial, it was evident that the anti-inflammatory function of Treg cells were impaired in sarcoidosis development compared to the pro-inflammatory function of Th17. From Broos et al.'s perspective, on the one hand, the dysfunctional or hypoactive state of Treg cells might be due to the suppression of the number and function of CTLA-4 molecules expressed by them [73]. On the other hand, upregulation of CD95 expression in sarcoidosis patients in vivo promoted apoptosis of Treg cells, in turn, the body did not have enough Treg reserves to suppress the inflammatory response [115]. Additionally, Several studies also identified aberrant activation of the PI3K/Akt signaling pathway, mediated by elevated PD-1 expression in sarcoidosis patients, inhibiting Treg cell function and affecting the Th17/Treg cell immune response balance [116–118].

4.2.3. Special Th17 in sarcoidosis

In recent years, a new subtype of T helper cell known as Th17.1 cells has been discovered, exhibiting a robust association with granuloma formation in patients suffering from sarcoidosis [100]. Th17.1 cells differentiated from Th17 cells, stimulated by IL-12, IFN-γ, and IL-23, displayed a mixed of characteristics from Th1 and Th17 cells. Approximately 60% of Th17.1 cells secreted IFN-γ, 5% secreted IL-17A, and 1% secreted both [87,97,119]. Although the subpopulation of Th17.1 was controversial and the specific mechanism of its involvement in sarcoidosis was unclear, the correlation between Th17.1 abundance and the type of cytokine secreted

by Th17.1 and the severity and regression of sarcoidosis patients had been confirmed by a number of studies [120–122]. An environment rich in Th17.1 cells, which mainly secreted IFN-γ, was associated with chronicity and poor prognosis of the disease, while a predominant Th17.1 cell population, which mainly secreted IL-17A, was beneficial to the suppression of inflammation and better prognosis [120,123,124].

4.3. B cells in sarcoidosis

The evidence that humoral immunity dominated by B cells was involved in granuloma formation had been revealed in recent years. Lee et al. and Kudryavtsev et al. found that B cells were accumulated in granulomas through immunohistochemical detection of lesion tissues from patients with pulmonary sarcoidosis [125,126]. Besides, several studies had shown that sarcoidosis was closely related to the high-level expression of Ig-secreting B cells and their antibodies [127–130]. Kudryavtsev et al. performed an immune cells subsets analysis in peripheral blood of 37 patients with pulmonary sarcoidosis by using flow cytometry. The results not only confirmed the fluctuations level of peripheral B cell subsets, but also led a new finding that Th cells were involved in regulating differentiation of B cell, which was manifested as the increase of B cells involved in antibody production and decrease of memory B cells [125]. Moreover, reports of several clinical trials suggested that anti-B-cell drugs (anti-CD20 antibody, Rituximab®) can greatly improve the progenies of patients with sarcoidosis which further emphasized the role of B cells in the progression of sarcoidosis [131,132].

However, investigations into the participation of B cells in the pathogenesis of sarcoidosis had been confined to cross-sectional analyses of results from various test methods, and research on the exploration and verification of related mechanisms were still lacking. In-depth mechanistic studies were crucial to further describe and verify the significant role of B cells in the progression of sarcoidosis in the future.

5. Aberrant activation of signaling pathways

5.1. mTORC1 signaling pathway

Whole exome sequencing (WES) analysis by Calendar et al. and Besnard.et al., for patients with familial sarcoidosis suggested that genetic susceptibility of sarcoidosis might be associated with mutations in the gene lines encoding the mammalian target of rapamycin complex 1 (mTORC1) and the Rac1 signaling pathway [121,122]. Currently, these two pathways stood out as the most extensively and systematically studied during the process of sarcoidosis granuloma formation.

The mTORC1 signaling pathway, activated by signaling molecules like IFN-γ, IL-17A, and other molecules secreted by upstream Th1 and Th17 cells through the JAK/STAT pathway, dominated and connected multiple links in the formation of sarcoidosis granuloma [15]. Firstly, mTORC1 induced macrophage aggregation, a fundamental step in the development of all granulomatous diseases. Moir LM et al. and Linke et al. demonstrated that deletion of tuberous sclerosis complex 2 (Tsc2) chronically activated the mTORC1 signaling pathway to enhance differentiation, proliferation, and migration of macrophages [133,134]. Secondly, the expression of cyclin-dependent kinase 4(CDK4) can be induced by mTORC1 signaling pathway to enhance the glycolysis metabolic pathway of macrophages to induce the proliferation of macrophages. Rapamycin-mediated inhibition of the mTORC1 pathway, as observed by Linke et al. resulted in the inhibition of granuloma formation and macrophage glycolytic activity [133]. Furthermore, evidence from human in vitro sarcoidosis models and mouse models indicated that chronic activation of the mTORC1 pathway induced M2-type polarization of macrophages, promoting the formation of granulomatous structures [135,136].

Additionally, the mTORC1 pathway also influenced autophagy-related mechanisms. Autophagy is known to be an important immune means by which the body clears aberrant immune cells or aberrant deleterious components to protect the body from exogenous hazards, including infection, and from endogenous inflammatory damage such as aggregates and damaged organelles. The PI3K/AKT/mTOR pathway inhibited autophagy signaling precisely by inhibiting the formation of Unc-51-like autophagy activating kinase1 (ULK1) and autophagosome [137]. Although exome sequencing results by Alain Calendar et al. in familial sarcoidosis demonstrated a correlation between activation of the mTORC1 pathway in sarcoidosis patients and defective autophagy regulatory mechanisms due to mutations in genes involved in autophagy and intracellular vesicle trafficking (e.g., ATG9B and SEC31B) [138]. The specific mechanism of how the mTORC1 pathway affected the autophagy mechanism and promoted the formation of sarcoidosis granuloma remained to be further explored and verified by future studies.

5.2. Rac1 signaling pathway

Rac1 was activated by NOD2, TLR4 and TLR9 which were expressed by upstream macrophages and DCs and were able to recognize and bind EPHA2 and KALRN. Similar to mTORC1, the Rac1 signaling pathway was involved in the regulation of several aspects of granuloma formation. Firstly, this pathway can affect the transcription of IL-17A. Ahmed T Kurdi et al. found that Rac1 was involved in the formation of a GTPase complex that regulated IL17A transcription by binding the IL17A promoter through a complex with the nuclear receptor RORγt, a key factor in proinflammatory th17 cell differentiation, while knockdown of the Rac gene greatly affected the pro-inflammatory function of Th17 and IL-17A secretion [139]. Secondly, Rac1 was also a negative regulator of autophagy. Carroll et al. found that Rac1 was able to competitively bind CXCR4 on the membrane of antigen-presenting cells or lymphocytes with the autophagy regulator microtubule-associated protein light chain 3 (L3) to prevent the formation of autophagosomes and thereby suppressed the autophagic immune response of the body [140].

Interestingly, it had been shown that Rac1 bound directly to mTOR in response to growth factor stimulation and regulated its
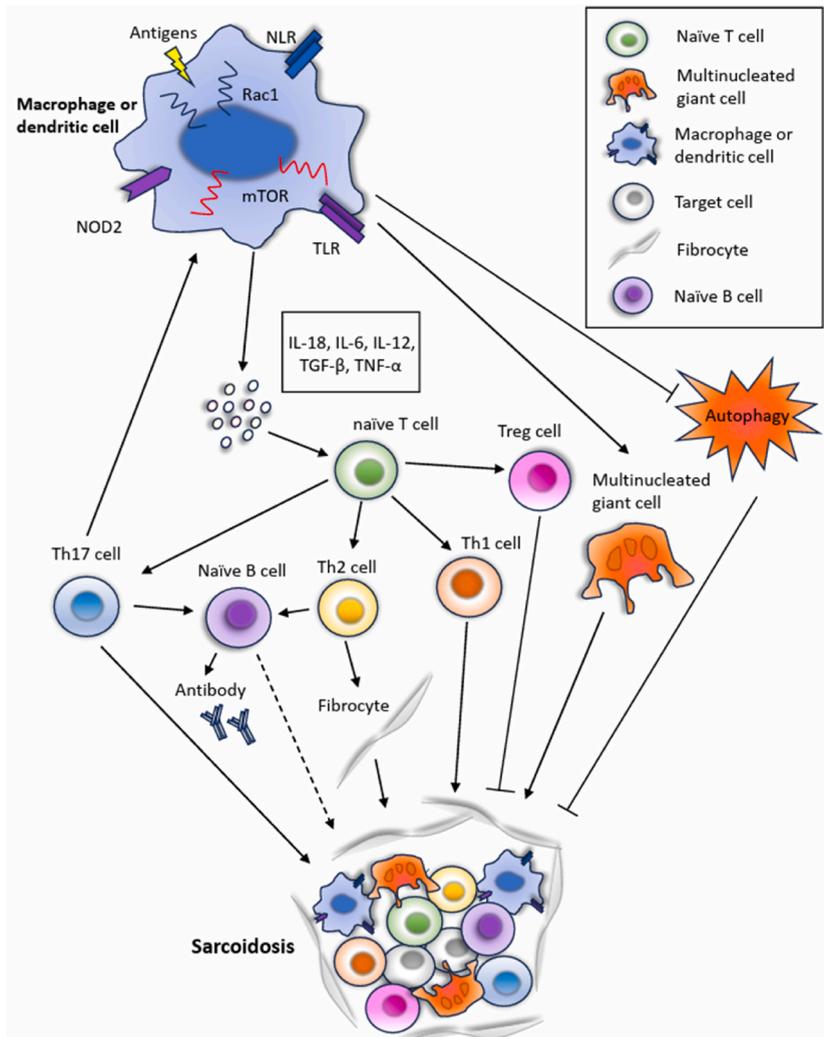
Fig. 1. Schematic representation of immune cells and associated pathways involved in pathogenesis of sarcoidosis. Sarcoidosis is characterized by the formation of granulomas, accompanied by varying degrees of immune cell infiltration and inflammatory reactions. The structure of the granulomas included the middle foci (including foreign antigens, abnormal cells or residual debris after cell death), multinucleated giant cells, macrophages, dendritic cells, B cells, various T cells and the outermost granulomatous skeleton composed of fibrocytes. The progression of sarcoidosis included an acute inflammatory phase and a chronic granulomatous formation phase. Due to genetic susceptibility, self-or foreign antigen stimulation, receptors (such as NLR, NOD2, TLR, etc.) on the membrane of macrophages/DC cells were continuously activated, the expression levels of signaling pathways such as mTOR1 and Rac1 were up regulated, leading to abnormal strengthening of macrophage life activities and functions. On the one hand, the metabolic mode of macrophages was changed, resulting the enhanced of proliferation, migration ability and they became more active and aggressive to participate pathogenesis of sarcoidosis in the whole body. On the other hand, the secretion and antigen presentation functions of macrophages were also continuously enhanced. Large numbers of inflammatory factors (IL-12, IL-18, IL-6, TGF-β, etc.) secreted by macrophages not only created an inflammatory cell environment suitable for the progression of sarcoidosis, but also recruited inflammatory cells and T cells around the lesion. At the same time, these inflammatory factors can also promote macrophages fusion to form multinucleated giant cells to enhance their phagocytic function. Notably, macrophages began to polarize to type II macrophages under the stimulation of these factors, making the progression of sarcoidosis transition to the chronic phase. Furthermore, the increase of inflammatory factors and the enhancement of macrophage antigen presentation function activated cellular immune response which induced the polarization of Th1 and Th17 from naïve T cells. On the contrary, the function and number of Treg cells were inhibited. Th2 cells were reported to participate in the formation of fibrous skeleton in chronic granulomatous formation in recent years. Subsequently, factors secreted by T cells such as IL-17 can activate naïve B cells to become secretory and a large number of antibodies such as γ-globulin, anti-nuclear antibodies and autoantibodies to double-stranded DNA) were secreted to create a more complex inflammatory environment. Although B cells were detected in the granuloma of patients with sarcoidosis, the mechanism dominated by B cells in granulomatous formation needed to be confirmed by further studies (as marked by the dashed line). In particular, as one of the important defense mechanisms to eliminate abnormal immune cells, autophagy was also inhibited by the abnormal activation of macrophage signaling pathways such as mTOR1 and Rac1, which further promoted the activity of abnormal immune cells. TLR: Toll-like receptor; NOD2: nucleotide oligomerization structural domain 2; NLR: Nod-like receptor; IL: Interleukin; Th: helper T-cells; TNF-α: tumor necrosis factor α; TGF-β: transforming growth factor-β; mTOR1: mammalian target of rapamycin complex 1.

activity by mediating the localization of mTORC1 and mTORC2 at specific membranes [141]. These results suggested that mTORC1 and Rac1 not only regulated immune and inflammatory mechanisms independently, but also played a synergistic role in the formation of granuloma.

6. Diagnosis markers and treatment for sarcoidosis

While exploring the pathogenesis of sarcoidosis, researchers were trying to find new reliable diagnostic markers or targeted drugs for sarcoidosis based on the existing results. In the search for reliable diagnostic markers, Several studies investigated the reliable of antibodies (such as the level of γ-globulin, anti-nuclear antibodies and autoantibodies to double-stranded DNA) and they found the high level of these antibodies only appeared in a small group of patients. In addition, some laboratory markers (such as TNF-α, SAA, number of Th17, sIL-2R i.e.) [142] and clinical markers (composite physiologic index (CPI), diffuse lung carbon monoxide (DLCO), etc.) [14,143–145] revealed strong correlations with the progression of sarcoidosis, suggesting their potential as diagnostic markers.

As for the therapeutic drugs, biologics targeting TNF-α to inhibit inflammatory factors (e.g., infliximab (IFX) and adalimumab) had shown good efficacy in the treatment of some sarcoidosis patients, and had become a major choice in the treatment of sarcoidosis [146]. mTORC1 inhibitors (such as radamycin) used in the treatment of sarcoidosis patients can effectively resolve the granuloma in the affected organ or tissue [147]. Furthermore, As an important downstream of the mTOR signaling pathway, JAK/STAT inhibitors (such as tofacitinib and ruxolitinib) were also be reported successfully treat patients with sarcoidosis by several clinical case [83, 148–150].

7. Conclusion and future perspectives

Current studies had shown that sarcoidosis was a complex immune disease caused by a combination of genetic susceptibility, adaptive immune abnormalities caused by various antigens and environmental factors. The development of sarcoidosis ended with the formation of granulomas in the affected organs or tissues, in which macrophages, dendritic cells, B cells and various T cells participated (mainly the balance ratio of Th1/Th2 and Th17/Treg), as well as the regulation of the network formed by signaling pathways such as mTORC1 and Rac1 that regulated cytokine secretion, inflammatory response, immune cell metabolism, proliferation and differentiation (the main immune cells and signaling pathway participated in occurrence and development of sarcoidosis was shown in Fig. 1).

As for diagnosis and treatment, on the one hand, although a large number of potential diagnostic markers have been screened by various advanced detection methods, there is still no reliable candidate that covers all patients with sarcoidosis. On the other hand, inhibitors targeting signaling pathways or cytokines involved in the pathogenesis of sarcoidosis have shown good application prospects. With the in-depth research on the mechanisms related to sarcoidosis, more patients will benefit from the clinical transformation products of sarcoidosis research in the future.

Upon reviewing the literature, we also recognized that there were some limitations to the current research on sarcoidosis which may be the directions for future research. Firstly, despite the discovery of numerous genes associated with sarcoidosis, there was still a lack of studies that can identify the major genes and their related mechanisms or target cells that dominated the pathogenesis of sarcoidosis. Secondly, due to lack of verification of related mechanism, the involvement of humoral immunity dominated by B cells in granuloma formation was still controversial, several studies also found there was no correlation between humoral immunity and sarcoidosis [126,151]. In addition, whether there was an interaction regulatory mechanism between B cells and T cells still needs to be further explored in the future. Finally, but most importantly, due to the complexity pathogenesis of sarcoidosis which still remained unknown and controversial part on the interactive mechanisms between immune cells and related signaling pathways, a single diagnostic marker or drug therapeutic strategy may be effective in a subset but not all patients. Only by further exploring the related mechanisms of sarcoidosis can the diagnostic marker be more reliable and patients with sarcoidosis benefit more from treatment.

Data availability statement

Since the study was a review, data associated with the study has not been deposited into a publicly available repository.
No data was used for the research described in the article.

Ethics approval and consent to participate

Not applicable.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

CRediT authorship contribution statement

Cong Chen: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Nanzhi Luo:** Writing – review & editing, Writing – original draft, Conceptualization. **Fuqiang Dai:** Writing – original draft, Investigation. **Wenjing Zhou:** Investigation. **Xiaoqing Wu:** Investigation. **Jian Zhang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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