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Review Article

Overview of Multi-Omics Approaches for Pulmonary Sarcoidosis

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Abstract

Purpose: Here, we review recent findings in the transcriptome, proteome, metabolomics, and microbiome of pulmonary sarcoidosis and highlight differentially expressed genes, specific pathways, mechanisms, microorganisms, metabolites, and targeted therapeutics in the field.

Recent Findings: The transcriptome and proteome of pulmonary sarcoidosis have been widely studied in recent years. Many differentially expressed genes and signaling pathways have been identified. Several proteins have been identified as potential molecular markers of pulmonary sarcoidosis. The microorganisms and metabolites of patients with sarcoidosis also have certain specificity. We compared pulmonary sarcoidosis with other diseases, such as idiopathic pulmonary fibrosis, tuberculosis, and chronic beryllium disease, and found some differential diagnoses. Based on the identified pathways and mechanisms, targeted therapeutic strategies have been proposed.

Summary: Many differentially expressed genes have been identified, including CBX8, CCL5, CXCL9, CXCL11, GBP1, GBP5, LINC01278, MMP12, PSMB9, STAT1, and TLE3, as well as the related enriched pathways, such as the IFN-γ, IL-1, IL-17, MHC, T-cell receptor, TNF, Th1, and Th2 signaling pathways. Proteins such as ABCG1, Apo A–I, CXCR5, MMP12, PD-1, PPARγ, and vitamin D-binding protein, together with the Fc galactosylation status of IgG4, are potential molecular markers for pulmonary sarcoidosis. Many specific microorganisms and metabolites in patients with sarcoidosis have also been found. Targeted drugs such as infliximab, nintedanib and rituximab have been proposed according to the discovered pathways and mechanisms.

Keywords: *Pulmonary Sarcoidosis; Transcriptome; Proteome; Metabolomics; Microbiome; Multi-Omics*

Abbreviations

LS: Löfgren's Syndrome; BAL: Bronchoalveolar Lavage; BALF: Bronchoalveolar Lavage Fluid; DEGs: Differentially Expressed Genes; RNA-seq: RNA-Sequencing; PBMCs: Peripheral Blood Mononuclear Cells; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genome; Th: Thelper T-Cell; Tfh: T Follicular Helper; TGFB1: Transforming Growth Factor-β1; MTOR: Mechanistic Target of Rapamycin; MWCNT: Multiwall Carbon Nanotube; Tregs: Regulatory T Cells; DAPs: Differentially Abundant Proteins; MUC5AC: Mucin-5AC; ERICH3:

Glutamate-Rich Protein 3; ACSL1: Long-Chain-Fatty-Acid-CoA Ligase 1; K1C18: Keratin and Type I Cytoskeletal 18; MUC5B: Mucin-5B; SERA: D-3-Phosphoglycerate Dehydrogenase; PDLI1: PDZ and LIM Domain Protein 1; VINC: Vinculin; MBD2: Methyl-CpG-Binding Protein 2; Apo: Apolipoprotein; PPARγ: Proliferator-Activated Receptor Gamma; ABCG1: ATP-Binding Cassette Lipid Transporter; MMP: Metalloproteinase; CCL18: CC-Chemokine Ligand 18; PUFA: Polyunsaturated Fatty Acids; IPF: Idiopathic Pulmonary Fibrosis; *CAT1*: Calcium Transport Protein 1; *SMURF1*: SMAD Specific E3 Ubiquitin Protein Ligase 1; TB: Tuberculosis; CBD: Chronic Beryllium Disease; CTSS: Cathepsin S; CCLs: C-C Motif Chemokine Ligands; IgG4-RD: Immunoglobulin G4-Related Disease; IFN: Interferon; TNF: Tumor Necrosis Factor; PPARγ: Proliferator-Activated Receptor γ; PPARγ-KO: PPARγ-Knockout; IL: Interleukin

Introduction

Sarcoidosis is an immune-mediated, multisystemic inflammatory disease. It is characterized by the presence of noncaseating granulomatous inflammation that is clustered with a large number of activated Th1 CD4+ T cells and macrophages. Sarcoidosis can affect multiple systems including lung, skin, spleen, lymph nodes, eye, bone tissue, salivary and lacrimal glands, striated muscle, central nervous system, endocrine glands, and liver [1]. Lungs and intrathoracic lymph nodes are the most commonly injured organs. Pulmonary damage is found in 90% of sarcoidosis cases. Sarcoidosis can be classified as Löfgren's syndrome (LS) or non-LS. There is no gold standard for diagnosing sarcoidosis, but three key points are required: compatible clinical manifestations, discovery of noncaseating granulomatous inflammation in one or more specimens, and exclusion of other causes of granulomatous tissue [2].

In this review, we summarize the progress of multi-omics studies in pulmonary sarcoidosis over the last few years (Figure 1). We also discuss targeted therapies based on these studies and some perspectives on treatments. In some articles it was not made clear whether sarcoidosis firstly occurred in the lung, but because the most common site of sarcoidosis is the lung, we included these studies in the review.

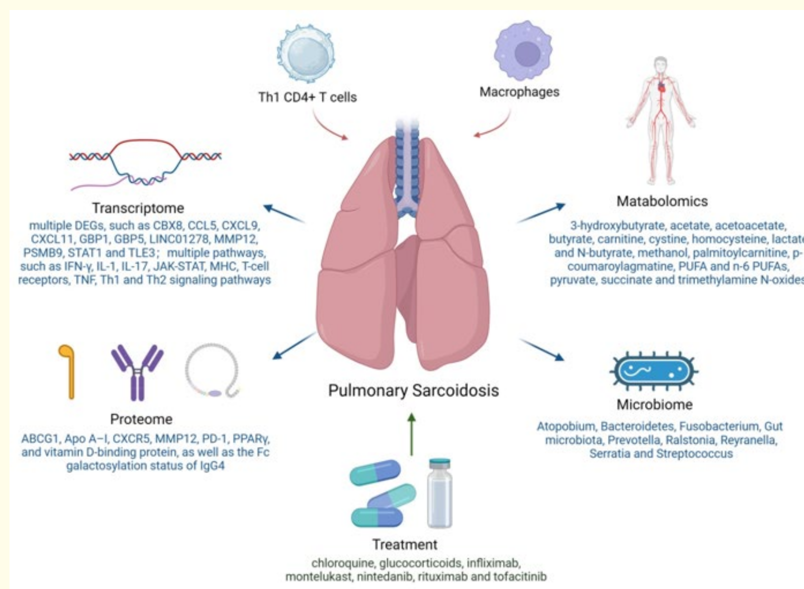

Figure 1: *Variants in multi-omics data of pulmonary sarcoidosis.*

Transcriptome

In recent years, proteome analyses have identified differentially abundant proteins (DAPs) in peripheral blood, BALF, and lung tissue. Comparison of protein abundance in patients with pulmonary sarcoidosis and healthy controls can identify molecular markers suitable for clinical use to diagnose sarcoidosis or determine the progressive state of the disease.

A comparison of protein abundance in BAL cells and BALF from patients with sarcoidosis and healthy controls identified 272 DAPs [21]. Among them, the top ten differentially abundant cellular proteins were mucin-5AC (MUC5AC), glutamate-rich protein 3 (ERICH3), long-chain-fatty-acid-CoA ligase 1 (ACSL1), keratin and type I cytoskeletal 18 (K1C18), mucin-5B (MUC5B), D-3-phosphoglycerate dehydrogenase (SERA), PDZ and LIM domain protein 1 (PDLI1), vinculin (VINC), methyl-CpG-binding protein 2 (MBD2), and cluster of endoplasmin. These DAPs are involved in a large number of pathways, including integrin-linked kinase and IL-8 signaling, phagosome maturation, clathrin-mediated endocytic signaling, redox balance, aryl hydrocarbon signaling, communication between innate and adaptive immune response, integrin, PTEN and phospholipase c signaling, serotonin and tryptophan metabolism, autophagy, B cell receptor signaling, CD28 signaling, and PFKFB4 signaling pathways.

In sarcoidosis, the content of HIF-α, functioning as an oxygen-sensitive transcription factor, is upregulated, which confirmed that HIF-α can specifically regulate IL-1β and IL-17 [16].

A comparison of BALF from patients with sarcoidosis and normal controls detected 690 DAPs. Notably, the abundance of inflammation-associated proteins and complement-activating factors increased, whereas the abundance of complement regulator CD55 decreased. Vitamin D-binding protein was highly abundant in BALF exosomes, and is a potential marker of sarcoidosis [22].

Bauer., *et al*. found that a new kind of Tfh-like cells highly expressed B helper molecules CD40L and IL-21 in BAL cells. In blood, the content of PD-1high/CXCR5-/CD40Lhigh/ICOShigh Tfh-like cells was high, whereas the content of classical CXCR5+ Tfh cells was low [11]. CXCR5 and PD-1 can help distinguish between the two different functional types of Tfh cells. Firstly, cells with CXCR5- and single-positive PD-1 were associated with the residence of tissue-resident Tfh-like cells in circulation. Secondly, the function and transcription of cells with double-positive CXCR5 and PD-1 were similar to classical Tfh cells from secondary lymphoid organs. Activated T cells of patients with sarcoidosis had more CD40L and ICOS in the blood than activated T cells of healthy controls. Some chemokine receptors, such as CCR2, CCR5, CCR8, and CX3CR1, were highly increased.

The BALF protein levels from eight stage I patients with sarcoidosis and five stage IV patients with sarcoidosis showed that apolipoprotein (Apo) A-I (Apo A-1) fragment, fibrinogen γ chain, calcyphosin, complement C3, and surfactant protein A levels were considerably higher in stage I than they were in stage IV. Validation of these findings in a larger study group, confirmed that the density of Apo A-1 was higher in stage I than it was in stage IV [23]. Apo A-I can block IL-12p70 and IFN-γ production by inhibiting the stimulation of dendritic cells from T cells and natural killer cells. It is also possible that damage to the alveolar–capillary barrier caused by the initial inflammation allows plasma proteins to leak, resulting in increased Apo A-I in BALF [24].

Recently, proliferator-activated receptor gamma (PPARγ), ATP-binding cassette lipid transporter (ABCG1), and MMP12 have been confirmed to have an effect on sarcoidosis [25]. PPARγ and ABCG1 levels were significantly reduced in sarcoidosis, which may affect their function in delaying the formation of pulmonary sarcoidosis and the production of inflammatory mediators. However, MMP12 was the most outstanding mediator in transcriptomic analyses, and is essential for the development of granulomas. The abundance of MMP12 and ADAMDEC1 was higher in the lung tissue and BALF of patients with sarcoidosis compared with their abundance in normal controls. Furthermore, MMP12 and ADAMDEC1 levels were related to the severity of sarcoidosis [14].

Three potential markers of pulmonary fibrosis have been identified, namely plasma matrix metalloproteinase 7 (MMP7), CC-chemokine ligand 18 (CCL18), and periostin. The protein concentration of these markers in serum and BALF was compared, and it was found that MMP7 may reflect the status of pulmonary sarcoidosis [26].

Smoking has potential effects on the composition of proteins related to oxidative stress and influences protease/antiprotease imbalance (such as alpha 1 antitrypsin, alpha-1-antichymotrypsin, Apo A-1, peroxiredoxin 1, and glutathione S transferase P) in BALF, which increases the risk of developing lung diseases including sarcoidosis [27].

Patients with non-LS showed a considerable trend towards higher TNF levels compared with patients with LS and healthy controls. Moreover, the incidence of unstimulated IL-6-expressing mononuclear phagocytes was higher in patients with LS than it was in patients with non-LS and healthy controls. TNF-producing monocytes or monocyte-derived cells without additional stimulation in BAL cells may have an important function to distinguish patients with non-LS from patients with LS. Additionally, TNF-expressing unstimulated CD14+ and CD16+ monocytes or monocyte-derived cells can indicate the progression of the disease, but the expression of TNF and IL-6 in plasma and BALF or IL-6-producing mononuclear phagocytes from BAL cells cannot [15].

Fc galactosylation was compared in serum and BALF of sarcoidosis phenotypes (LS, n = 11; non-LS, n = 12), with controls (n = 12) [28]. The Fc galactosylation status of IgG4, a potential blood test marker for chronic lung inflammation, was found to be the most significant in the sarcoidosis group. Compared with LS, non-LS had more diverse Fc glycan profiles, such as FA2G2, than the controls. Altered Fc galactosylation in IgG4, which is relatively easy to obtain from blood, may also aid in diagnosis and prognosis and in assessing lung disease status.

In conclusion, proteins such as ABCG1, Apo A-I, CXCR5, MMP12, PD-1, PPARγ, and vitamin D-binding protein, as well as the Fc galactosylation status of IgG4 are potential molecular markers for pulmonary sarcoidosis.

Microbiome

Sarcoidosis microbiotas in the respiratory and digestive tracts are of interest in this context. Some studies have suggested that airway microbes associated with sarcoidosis include *Serratia, Prevotella*, *Streptococcus, Reyranella, Ralstonia, Bacteroidetes, Atopobium*, and *Fusobacterium*, whereas other studies did not detect these airway microbes [34-38]. Abnormal microbiota and low levels of antimicrobial peptides in the lower airways of patients with sarcoidosis indicate that interactions take place between the microbiota and the innate immune system [39]. Gut microbiota, including class Methanobacteria, order Methanobacteriales, and family Methanobacteriaceae were significantly associated with sarcoidosis [40]. Alterations in the gut microbiota can lead to elevated trimethylamine N-oxide levels, resulting in a high inflammatory state and disrupted energy metabolism in patients with sarcoidosis [29]. A decrease in gut microbiome diversity can increase female-dominated interstitial lung disease such as estrogen-driven pulmonary fibrosis in sarcoidosis [41].

Authors	Sample source	Experimental group	Control group	Having significant difference or not	Metabolites having significant difference
Banoei., *et al*. [33]	Plasma	Veterans with sarcoidosis	Civilians with sarcoidosis	Yes	Arginine, glutamine, creatinine, glycine, taurine, methionine
Banoei., *et al*. [33]	Plasma	Veterans with sarcoidosis	Veterans with COPD	No	/

Geamanu., *et al*. [29]	Serum	Patients with sarcoidosis	Healthy controls	Yes	3-hydroxybutyrate, acetoacetate, carnitine, cystine, homocysteine, pyruvate, trimethylamine N-oxide (increased); succinate (decreased)
Mirsaeidi., *et al*. [32]	Plasma	African Americans with confirmed sarcoidosis with pulmonary fibrosis	African Americans without confirmed sarcoidosis with pulmonary fibrosis	Yes	p-coumaroylagmatine, palmitoylcar-nitine, collagen pathway metabolites especially those in the arginine-proline pathway
Duchemann., *et al*. [31]	Saliva	Patients with sarcoidosis	Controls	Yes	Methanol, butyrate (decreased); lac-tate, acetate, N-butyrate (increased)

Table 1: *Key differential metabolites in sarcoidosis.*

Multi-omics

Despite the successful application of multiple single platform "omic" technologies to characterize the molecular landscape of sarcoidosis, these technologies reflect mainly one aspect of the biological system. Multi-omics approaches allow the systematic understanding of information flow across different omics layers, including genomics, transcriptomics, proteomics, metabolomics, and microbiomics. Recently, Konigsberg et al. reported that the widespread molecular changes associated with disease involve mainly the immune response, leverage of the DNA methylome, transcriptome, and miRNA-sequencing in sarcoidosis BAL cells [42]. Hočevar et al. conducted a comprehensive integrative literature analysis of global data on sarcoidosis, including genomic, transcriptomic, proteomic and phenomic studies [43]. Significant advances in integration methods of multi-omics datasets by machine learning promise a holistic view of disease pathogenesis and yield biomarkers for disease diagnosis and prognosis. Multi-omics data can be integrated with clinical information to develop predictive models that identify risk before the condition is clinically apparent, thus facilitating early interventions. Integrating multi-omics and clinical data related to sarcoidosis will pave the way for precision medicine.

Comparison with other diseases

Idiopathic pulmonary fibrosis (IPF)

Similarities and differences in the transcriptome and proteome of sarcoidosis and IPF have been investigated by analyzing transcriptome and/or proteome data [44-50]. Differentially regulated genes between fibroblastic foci in end-stage IPF and sarcoidosis were similar; 69 of 136 genes that had altered expression profiles were similarly expressed in the transcriptome and proteome, and only two genes were expressed opposite. The two genes were calcium transport protein 1 (CAT1) and SMAD specific E3 ubiquitin protein ligase 1 (SMURF1). The protein levels of FAP, VCAM1, CD86, and COL5 were identical in IPF and sarcoidosis, whereas the COL6 level was higher in IPF lung tissue [44]. In addition, the protein levels of SCF and CDCP1 in serum and CCL19 in both BALF and serum were considerable different between sarcoidosis and IPF [45]. The galectin-1 and CCL8 levels in BALF were higher in patients with IPF compared with their levels in patients with sarcoidosis, suggesting that these two proteins are potential markers for IPF [46,50]. The mRNA expression levels of genes associated with ribosome biogenesis and upregulation of lymphocytes were higher in sarcoidosis than they were in IPF [47]. The expression levels of ABC-derived genes were elevated in BAL cells of patients with IPF compared with their expression levels in BAL cells of healthy volunteers, whereas no differences in expression levels of these genes was detected in the BAL cells of patients with nodal disease [48].

Tuberculosis

Sarcoidosis and tuberculosis (TB) both have granulomatous lesions, and several articles focused on the similarity and differences between their transcriptome and proteome have been published [51-54]. These two diseases have relatively similar transcriptional programs, and the DEGs shared by the two diseases are mainly extracellular, and are associated with the immune response or extracellular matrix. Unlike in sarcoidosis, the main biological processes in TB involve cytokine signaling, the inflammatory response, angiogenesis, and extracellular matrix organization. The most notable enrichment processes were cytokine-mediated signaling pathways, which include many genes that have been implicated in the pathogenesis of TB, most notably the upregulation of MMP1 expression. Only the lytic vacuole membrane and lysosomal pathways were downregulated in TB compared with sarcoidosis [52]. Immunohistochemical analysis showed an equal excess of interstitial extracellular matrix collagen type I and type III collagen in representative lungs of TB and sarcoidosis compared with the lungs of controls. Thus, intrapulmonary collagen matrix remodeling may be a common pathogenic feature of both tuberculosis and sarcoidosis [53]. ADAMTS1, NPR1, and CXCL2 were dysregulated in sarcoidosis, but not in tuberculosis. These findings suggest that gene expression in sarcoidosis is highly tissue- and disease-specific, and that these three genes are potential novel markers for the presence of sarcoidosis in lungs and lymph nodes [52]. The arachidonic acid metabolism pathway is enriched in the transcriptional profile of tuberculosis, with PLA2G6, PLA2G7, AKR1C1, AKR1C3, LTA4H, and PTGER4 being overexpressed. This finding suggests that these six genes may be markers that can distinguish sarcoidosis from tuberculosis [53]. It is possible that CBX5, BCL11B, and GPR18 may be biomarkers of sarcoidosis [54].

Chronic beryllium disease (CBD)

By comparing macrophages of progressive sarcoidosis, remitting sarcoidosis, and CBD with healthy controls, 82 overlapping genes were identified. Network analysis of the 82 overlapping genes identified three key hub genes: AP-1 complex (FOS/FOSB/ FOSL2/JUNB/ JUND), KLF4, and UBC [55]. Genes related to heat shock proteins such as ubiquitin and the HSP70 family, including HSPA1A, HSPA1B, and HSPA8, were shared and all were upregulated. A pathway analysis found several significant shared pathways, including the immune response HSP60 and HSP70/TLR signaling pathways and immune response antigen presentation by MHC class II with upregulated RHOB, upregulated RHOA, and downregulated MARCH1. By comparing disease groups with beryllium sensitized non-diseased subjects, 53 overlapping genes were identified, including AP-1 complexes. The pathway analysis also identified immune response antigen presentation by MHC class II as a significant shared pathway. These pathways ultimately modulate CD4+ T cells and facilitate immunogenic responses. The expression of CD55 and TNF-α was higher in CBD than it was in sarcoidosis; however, the expression of CXCL9 was higher in CBD than it was in sarcoidosis [56]. Therefore, these three markers together with the blood beryllium lymphocyte proliferation test may help in distinguishing CBD from sarcoidosis. Earlier, 287 DEGs were found to overlap in CBD and sarcoidosis, including genes involved in cytokine–cytokine receptor interactions, and Toll-like receptor, chemokine, and JAK–STAT signaling pathways were the most common shared pathways [57].

Other diseases

Tanaka., *et al*. found that compared with healthy controls, interstitial pneumonia, pneumoconiosis, and pulmonary mycobacteriosis, the concentration of cathepsin S (CTSS) was significantly increased in patients with sarcoidosis [58].

Recent progress of some key regulators

Among the large numbers of DEGs and DAPs that have been identified, the functions or mechanistic roles of many of them have been well studied in sarcoidosis. The dysregulation and function of some key regulators associated with sarcoidosis are summarized in table 2.

Authors	Genes	Related pathways	Proteins	Sample source
Ascoli., *et al.* [5]	CBX8, TLE3	/	/	PBMCs
Jiang., *et al.* [9]	GBP5, LINC01278, PSMB9, IL-17 (only in peripheral blood)	Autophagy, IFN-γ, IL-1, IL-18 signaling pathways, viral infection response	/	Blood, lung-associated tissues
Yoshioka., *et al.* [6]	genes involved in TNF and IL-17 signaling pathways and phagosomes, ribosome-related genes	Cellular response to IL-1 and IFN-γ, IL-8 secretion, IL-17 signaling pathways, phagosomes, regulation of IL-6 production, regulation of mononuclear cell migration, response to lipopolysaccharide, ribosomes, TNF signaling pathways, Toll-like receptor signaling pathways	/	PBMCs
Bauer., *et al.* [11]	/	The Tfh cell signature (in pulmonary T cells compared with peripheral blood memory T cells)	CXCR5, PD-1	BALF, lung tissue, peripheral blood
Lepzien., *et al.* [12]	Genes associated with T cell activation and antigen presentation in dendritic cells	/	/	BALF, blood
Vukmirovic., *et al.* [13]	/	Th1 and Th17 pathways (associated with hilar lymphadenopathy), TGFB and MTOR signaling pathways (parenchymal involvement), IL-7 and IL-2 signaling pathways (associated with airway involvement)	/	BAL cells
Lepzien., *et al.* [15]	Genes associated with cell maturation (CD40, CD80, CD83), inflammatory response (TLR3, TLR7), cytokine signaling (TNF, IL1B, CSF1, TGFβ) and chemotaxis (CCR6, CCR7 as well as CCL2, 19 and 20)	IL-6, IL-17, TLR, TNF signaling pathways	TNF-expressing unstimulated CD14+ and CD16+ monocytes or monocyte-derived cells	BAL
Talreja., *et al.* [16]	HIF-1β, EPAS1, p300	HIF-1α signaling pathway	HIF-1α, IL-1β, IL-17	BALF, PBMCs
Locke., *et al.* [17]	/	IL-13-regulated gene pathways	/	PBMCs
Kachamakova-Trojanowska., *et al.* [19]	/	TLR-2 signaling pathway, the downstream of NF-κB apoptosis and proliferation signaling pathways	/	BAL
Mohan., *et al.* [18]	CTSK, MMP12	Adaptive immunity, IL-12/IL-17 signaling, oxidative phosphorylation, T-cell signaling pathways	/	alveolar macrophages of MWCNT-based murine model and human sarcoidosis
Benn., *et al.* [8]	/	T-cell receptor signaling pathways	/	Blood

Talreja., *et al*. [7]	Genes involved in phagocytosis and lysosomal pathway, genes involved in proteasome degradation and ribosomal pathways	ribosome, phagocytosis, lysosome, proteasome, oxidative phosphorylation and metabolic pathways	/	Peripheral blood monocytes
Isshiki., *et al*. [26]	/	/	MMP7, CCL18, periostin	BALF, blood
Bhargava., *et al*. [21]	/	aryl hydrocarbon signaling, autophagy, B cell receptor signaling, CD28 signaling and PFKFB4 signaling, clathrin-mediated endocytic signaling, communication between innate and adaptive immune response, integrin, integrin-linked kinase and IL-8 signaling, redox balance, phagosome maturation, PTEN and phospholipase c signaling, serotonin and tryptophan metabolism pathways	Cluster of endoplasmin, D-3-phosphoglycerate dehydrogenase, Glutamate-rich protein 3, Keratin and type I cytoskeletal 18, Long-chain-fatty-acid-CoA ligase 1, Methyl-CpG-binding protein, Mucin-5AC, Mucin-5B, PDZ and LIM domain protein 1, Vinculin	BAL, BALF
Heyder., *et al*. [26]	/	/	Altered Fc galactosylation in IgG4	BALF
Nukui., *et al*. [23]	/	/	Apo A-I	BALF
Martinez-Bravo., *et al*. [22]	/	/	Vitamin D-binding protein, Leukotriene A 4 Hydrolase	BALF
Kamp., *et al*. [44]	CAT1, SMURF1	Fibrosis-related pathways, certain inflammatory pathways	COL6	Fibroblastic foci tissue
Majewski., *et al*. [45]	/	/	CCL19 (in BALF and serum), SCF and CDCP1(only in serum)	Peripheral blood, BALF
Bennett., *et al*. [46]	/	/	Galectin-1	BAL
Paplińska-Goryca., *et al*. [47]	Genes associated with ribosome biogenesis	Lymphocyte regulation process	/	BALF
Prasse., *et al*. [48]	ABC-derived Genes	/	/	BAL
Lee., *et al*. [50]	/	/	CCL8	BAL

Reichmann., *et al*. [51]	MMP1	Angiogenesis and extracellular matrix organization, cytokine signalling and the inflammatory response, lytic vacuole membrane and lysosomal pathways	/	Lymph node biopsies
Casanova., *et al*. [52]	ADAMTS1, CXCL2, HBEGF, NOTCH4, NPR1, STAB1	/	/	Lung and mediastinal lymph node tissues
Chai., *et al*. [53]	AKR1C1, AKR1C3, LTA4H, PLA2G6, PLA2G7, PTGER4	Arachidonic acid metabolism pathway	Interstitial ECM collagen type I and type III collagen	Lung tissues
Liao., *et al*. [55]	Ubiquitin, HSP70 family (including HSPA1A, HSPA1B and HSPA8)	Immune response HSP60 and HSP70/TLR signaling pathway, immune response antigen presentation by MHC class II	AP-1 complexes, heat shock proteins (Ubiquitin and HSP70 family), HLA-DPA1, JUNB, KLF4, PLAUR	BALF
Lin., *et al*. [56]	CD55, CXCL9, IFN-γ, TNF-α	/	/	Blood
Li., *et al*. [57]	ICAM1, LILRB4, NFKBIE (PBMC); CCL8, CXCL9, CXCL11, FAM26F, GBP4, STAT1, TAP1 (lung tissue)	Cytokine–cytokine receptor interactions, chemokine, JAK–STAT, Toll-like receptor signalling pathways	/	PBMC, lung tissue
Tanaka., *et al*. [58]	/	/	CTSS	Serum

Table 2: *Key differentially expressed factors and their related signaling pathways in sarcoidosis.*

C-C motif chemokine ligands (CCLs)

Blood levels of CCL1 and CCL18 in patients with sarcoidosis were higher than those in healthy people. The CCL1 level was positively correlated with clinical parameters such as total cell counts, lymphocyte counts in BALF, and serum T helper 1 mediators [26,59]. The Th1 immune response was dominant in sarcoidosis, whereas immunoglobulin G4-related disease (IgG4-RD) was more associated with the Th2 immune response. The concentration of CCL1 in the BALF of patients with sarcoidosis was higher than that in patients with IgG4-RD. CCL1 levels in patients with sarcoidosis were significantly associated with BALF levels of Th1 cytokines, such as TNF-α and IL-2, but not with Th2 cytokines. This finding suggests that CCL1 in sarcoidosis is more closely related to the Th1 immune response than it is to the Th2 immune response [60]. Serum amyloid A promotes the development of inflammation by increasing the expression of CCL20 and IL-17A in BALF and serum. Blocking CCL20 expression can partially reverse the level of Th17-related cytokines, ameliorate Th1/Th2 and Treg/Th17 bias, and prevent overactivation of the TGF-β/Smad2/Smad3 signaling pathway, suggesting that anti-CCL20 may be effective in the treatment of sarcoidosis [61]. In sarcoidosis, the number of exosomes in BALF was high, which can induce the release of CCL2. Montelukast reduced exosome-induced CCL2 production in a subgroup of patients with sarcoidosis [62].

Interleukin IL-1

IL-1 has a strong role in promoting inflammation in the pathogenesis of sarcoidosis [6]. BALF exosomes in sarcoidosis were elevated, which dose-dependently increased IL-1β in classical monocytes and induced the release of IL-1β [62]. HIF-α, an oxygen-sensitive

transcription factor, specifically regulates IL-1β and IL-17 levels in sarcoidosis [16]. The release of IL-1β from BAL cells in patients with sarcoidosis increased, and drug intervention with anti-IL-1β antibodies reduced granuloma formation [63].

Interleukin IL-17

In animal models, IL-17 was found to be associated with the development of pulmonary fibrosis. The expression of IL-17 in the lung tissues of patients with IPF was higher than it was in the lung tissues of patients with sarcoidosis [64]. A case report of a 52-year-old woman with psoriatic arthritis who developed multisystem sarcoidosis while receiving secukinumab (anti-IL17A), suggested that blocking IL-17 may promote the development of sarcoidosis [65]. Conversely, *Propionibacterium acne*-induced mice were found to be useful in establishing sarcoidosis-like granuloma mouse models, and IL-17A promoted sarcoidosis-like granuloma in this model [66]. The HIF-α signaling pathway was found to be enriched in sarcoidosis, and IL-1β and IL-17 can be specifically regulated by HIF-α [16].

Interferon gamma (IFN-γ)

IFN-γ, which is derived from CD4+ T cells, is a central cytokine mediator of macrophage activation in sarcoidosis. In cutaneous sarcoidosis, tofacitinib was proved to inhibit IFN-γ to ameliorate symptoms [67]. Increasing evidence indicates that Th17.1 cells play a central role in sarcoidosis, which may lose the expression of RORγt mRNA and secrete IFN-γ alone through uncertain mechanisms [68]. Overproduction of IFN-γ led to constitutive activation of the JAK-STAT pathway, and the use of JAK inhibitors that block these signals has led to significant improvements in some patients with sarcoidosis [69]. *Mycobacterium* antigen-specific Th-17 cells were found in the surrounding and actively affected sites of patients with sarcoidosis. Despite the Th1 immunophenotype of sarcoidosis immunology, Th-17 cells decrease IFN-γ expression compared with its expression in healthy controls, which may contribute to the pathogenesis of sarcoidosis [70].

Tumor necrosis factor TNF-α

TNF promotes granuloma formation, and high levels of TNF are associated with the progression of sarcoidosis [15]. Anti-TNF-α drugs such as infliximab are effective in the treatment of refractory sarcoidosis, but relapse is common after discontinuation of infliximab [71,72]. Sarcoidosis induced by TNF-α inhibitors may lead to cavitation due to vascular infiltration of granulomas [73].

Matrix metallopeptidases (MMPs)

MMP9 is an essential factor in the production of TGF-β [74]. Proliferator–activated receptor γ (PPARγ) can change the phenotype of macrophages from M1 to M2 [25]. Elevated MMP9 levels were observed in PPARγ-knockout (PPARγ-KO) mice by MWCNT and early secreted antigenic target protein 6 [74]. The plasma concentration of MMP7 in patients with sarcoidosis was higher than that in healthy controls, and there was a negative correlation between MMP7 concentration and lung function [26]. At day 60 after MWCNT perfusion, MMP12-KO mice showed significantly reduced granuloma formation and increased PPARγ, MMP14, and alveolar macrophage levels compared with their levels in wild-type mice [75,76]. Between days 10 and 60 after perfusion, the phenotype of the macrophage population in MMP12-KO mice shifted from M2c to M2a, and IL-13 levels decreased [76]. These results indicate that MMP12 is crucial for sarcoidosis [63].

Treatment of Sarcoidosis

The immune system is abnormally activated in patients with sarcoidosis, and therefore the first drugs used to treat it were glucocorticoids [77,78]. Because of the high incidence of adverse effects of glucocorticoids, new targeted therapies have been proposed. Infliximab targets the TNF-α downstream signaling pathway [79]. Anti-TNF-α drugs are effective in the treatment of refractory sarcoidosis in both pulmonary and extrapulmonary sarcoidosis, with slightly higher efficacy in extrapulmonary sarcoidosis [71]. The persistence of granulomas in sarcoidosis can lead to the development of fibrotic lesions, and anti-fibrotic drugs such as nintedanib have been used to treat fibrotic sarcoidosis [44,80]. B cells are closely associated with sarcoidosis, and patients with sarcoidosis have been treated with

B cell-depleting antibodies such as rituximab.11 HIF-α specifically regulates IL-1β and IL-17. Chloroquine can change the abundance of LAMP2 and HIF-1α proteins to inhibit IL-1β and IL-17 [16]. Blocking CCL20 can partially reverse the expression of Th17-related cytokines, ameliorate Th1/Th2 and Treg/Th17 bias, and prevent overactivation of the TGF-β/Smad2/Smad3 signaling pathway, and therefore anti-CCL20 could potentially affect sarcoidosis [61]. Montelukast reduced exosome-induced CCL2 production in a subgroup of patients with sarcoidosis, implying that montelukast is potentially a targeted agents for sarcoidosis [62]. Anti-IL-1β antibodies reduced granuloma formation. Additionally, tofacitinib inhibited IFN-γ to ameliorate symptoms [67]. JAK inhibitors that block the IFN-γ-mediated JAK-STAT pathway have facilitated significant improvements in some patients with sarcoidosis [69].

Outlook

There has been an increase in the number of research studies focusing on sarcoidosis. However, because of the low prevalence of pulmonary sarcoidosis, the sample sizes for transcriptomic or proteomic studies are usually small. There is also no exact standard for the diagnosis of sarcoidosis. Pulmonary sarcoidosis can be influenced by environment, age, ethnicity, and genetics. As a result, it is difficult to completely remove heterogeneity from studies and ensure the generalizability of findings. Because of the many phenotypes of sarcoidosis and the LS and non-LS forms of pulmonary sarcoidosis, it is difficult to fully capture the raw data when conducting data analysis in aggregate form. Studies on metabolomics and the microbiome related to sarcoidosis disease are also limited. Moreover, the low incidence of sarcoidosis makes it difficult to obtain a high and reliable sample size in experimental studies. Increasing the experimental sample size is an urgent problem that needs to be solved. Higher powered, more reliable studies can be developed by working collaboratively and sharing/pooling data with other researchers in this field. For example, researchers can collaborate to conduct multi-center studies. In such studies, basic situational and clinical data of patients should be collected as comprehensively as possible, allowing detailed studies to be conducted after accurate staging of the patients' conditions based on the collected data. Another option is for researchers to collect publicly available data to analyze and draw more reliable conclusions. Additionally, with the discovery of similarities in signaling pathways and gene expression, researchers can now explore the pathogenesis of pulmonary sarcoidosis and targeted therapeutic approaches in a more direct way. Cells and animal models could be used to compensate for the low number of patients with sarcoidosis. This allows researchers to focus on multiple common molecules in sarcoidosis, including CCLs, IL-1, IL-17, IFN-γ, TNF-α, and MMPs. With the development of multi-omics technologies, sarcoidosis can be studied from many aspects using a variety of new techniques, such as single-cell studies and multi-omics analysis. Because of the numerous pathways and biomarkers associated with sarcoidosis, translating these studies into clinically specific diagnoses and treatments is particularly important at this stage. This requires researchers to work out the mechanisms involved and identify molecules that can interfere with the initiation or progression of those mechanisms. Sarcoidosis is not confined to the lungs, so other potentially affected organs, including skin, eyes, and heart, also need to be studied. Whether there is a correlation between each area of sarcoidosis is also worth exploring. Such studies will require coordination and cooperation among multiple departments. Sarcoidosis is an immune disease, and therefore alongside studying mechanisms, appropriate antagonists or inhibitors can be selected from among immune molecules in the mechanism. This will allow researchers to find new possible treatment schemes for patients with sarcoidosis, such as infliximab, nintedanib, and rituximab.

Conclusion

Many studies about the transcriptome and proteome of pulmonary sarcoidosis have been published in recent years. Many DEGs have been identified, including CBX8, CCL5, CXCL9, CXCL11, GBP1, GBP5, LINC01278, MMP12, PSMB9, STAT1, and TLE3, as well as consequently enriched pathways, such as the IFN-γ, IL-1, IL-17, MHC, T-cell receptor, TNF, Th1, and Th2 signaling pathways. Proteins such as ABCG1, Apo A-I, CXCR5, MMP12, PD-1, PPARγ, and vitamin D-binding protein as well as the Fc galactosylation status of IgG4 have been proposed as potential molecular markers of pulmonary sarcoidosis. Many specific microorganisms and metabolites have also been identified in patients with sarcoidosis. We integrated omics studies and compared pulmonary sarcoidosis with other related diseases, such as IPF, tuberculosis, and CBD, and found some differential diagnostic features. Targeted therapies such as infliximab, nintedanib, and rituximab have been proposed according to the discovered pathways and mechanisms.

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Authors Contribution

Yifan Fei and Zhe Lei both the authors contributed equally.

Conflict of Interest and Funding Support

There is no financial interest or conflict of interest exists.

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