The Immune Paradox of Sarcoidosis: A Review of Literature

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Authors’ contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

This review briefly summarises the literature concerning our current understanding of the aetiology and immunopathogenesis of sarcoidosis, and the identification of novel markers of this disease. Although the immune paradox is a key part of sarcoid immunology, the mechanisms underlying this remarkable phenomenon are not well understood. Biomarkers may further the current understanding of the granulomatous inflammation seen in sarcoidosis. Exhaled breath condensate (EBC) is a novel, minimally invasive tool to sample the fluid lining the respiratory tract. EBC can be used to identify sarcoid specific biomarkers, which may shed light on the sarcoid immune paradox.

Keywords: Sarcoidosis; immune paradox; sarcoid pathogenesis; sarcoid biomarkers; exhaled breath condensate.
1. INTRODUCTION

Sarcoidosis is a rare multi-system inflammatory disorder that is characterised by the formation of non-specific, non-caseating granulomas. While first described in the 19th century, there is much about the disease that is yet unknown, including its aetiology and pathogenesis [1,2]. Notably, the disease entails what is known as the “immune paradox”, with the coexistence of intense localised granulomatous inflammation and peripheral anergy (poor response to common antigens in vitro and in vivo) [3].

Sarcoidosis has been reported worldwide in males and females, but distinctive differences in manifestation have been identified in particular ethnic and racial groups [1,4]. Sarcoidosis has variable organ involvement. While it typically involves the pulmonary (>90%) and lymphatic systems, it can also affect the skin, and cardiovascular and neurological systems. Clinically apparent disease is generally limited to a few organs however, and is typically fixed within the early presentation of the disease [5]. Sarcoidosis is most often asymptomatic (>60%), but can manifest with non-specific constitutional or organ-specific presentations [6]. Currently, while no “gold standard” diagnostic tests or pathognomonic criteria exist for sarcoidosis, compatible clinical and radiological findings guide clinicians towards the diagnosis. Characteristically, the histological appearance of non-caseating epitheliod cell granulomas obtained via invasive tissue biopsy warrants the exclusion of other known causes of such inflammation such as tuberculosis [5,7].

The clinical course which sarcoidosis follows is difficult to predict. Most patients require no treatment; those who do, improve with moderate doses of corticosteroid therapy [8]. While two-thirds of patients experience remission post diagnosis, for up to 30%, the condition is chronic and progressive. In most of these patients, unremitting disease leads to the destruction of lung structure and irreversible loss of lung function [5]. While mortality in sarcoidosis is <5%, given the unpredictable course of the disease, a major area of interest in research is to prospectively identify patients with unfavorable outcomes. Currently there is much interest in determining a minimally invasive and sensitive method of diagnosing and staging sarcoidosis [5,9,10].

This report reviews current literature on sarcoid aetiology and immunopathogenesis, and describes current methods for the detection of immunological mediators in patients with sarcoidosis.

2. DISCUSSION

2.1 Aetiology

The aetiology of sarcoidosis remains unclear and no single causative agent has been identified. Due to the heterogeneous nature of the disease, it is postulated that sarcoidosis may not represent a single disease entity, but a reaction pattern common to multiple independent causative agents and dependent on host factors [11,12]. Controversy exists however, as evidence from clinical studies also supports the presumption that sarcoidosis involves a directed immune response to a small number of specific antigens [13]. Ultimately candidate aetiological agents must be able to induce the T-helper (Th)-1 driven formation of the non-caseating sarcoid granuloma, and yet allow for the varying clinical manifestations and outcomes of the disease. Additional research has been directed towards genetic profiles and environmental exposures associated with the sarcoid immune response, as it has long been suspected that exposure to extrinsic antigens in a genetically susceptible individual triggers the amplified sarcoid inflammatory reaction [10-12].

A genetic predisposition to developing sarcoidosis has been suspected due to two main observations; firstly, that the disease clusters in families [14]. The multicenter epidemiological study ‘A Case Control Etiologic Study of Sarcoidosis (ACCESS)’ demonstrated a significant elevated risk of sarcoidosis among first- and second-degree relatives of sarcoidosis cases compared with relatives of matched control subjects. Increased concordance in monozygotic twins compared to other siblings was also found [15]. Secondly, the frequency of sarcoidosis varies widely between ethnicities and populations from different geographic regions around the world, with higher prevalence rates in Scandinavian, Japanese and African American populations [2,15,16].

The notion of a genetic predisposition to sarcoidosis has been supported by the success of various genetic association and family studies in identifying genes implicated with sarcoid risk. While no unifying genetic signature has been discovered, a number of genes have been linked to particular sarcoid subtypes in specific populations [17]. This delineates the complex,
polygenic nature of genetic susceptibility in sarcoidosis, and the need for population stratification and careful clinical phenotyping of patients in future research [18].

While investigation of genes has focused primarily on association with the Human Leukocyte Antigen (HLA) genes, genome-wide studies have also implicated a range of non-HLA genes. Many of these have been implicated in affecting sarcoid risk, phenotype, or outcome [14,19], and they are summarised in Table 1.

There are suggestions that some genotypes that predispose to sarcoidosis may also be linked to detrimental autoimmune responses. Antigenic peptides recognised as auto-antigens in various conditions, including vimentin, ATP synthase, and lysyl tRNA synthetase, were identified in the bronchoalveolar lavage (BAL) fluid of sarcoid patients with the HLA-DRB1*0301 genotype [37]. These peptides also elicited strong autoimmune T-cell responses in the peripheral blood and BAL fluid of HLA-DRB1*0301 patients. The pathological significance of these antigenic peptides in the aetiology of sarcoidosis however, remains unclear [38].

Ultimately, it appears that sarcoidosis is associated with a complex genetic risk profile of many variant genes. Future research is needed to clarify the genetics of sarcoidosis and identify specific signatures with clinical relevance [17]. As DNA polymorphisms have so far been unable to explain the phenotypic variability seen within sarcoidosis, of recent interest are small sections of non-coding RNA called microRNA [39], which will be discussed later.

Epidemiological studies have provided a basis for the suggestion that environmental exposure may act as a risk factor for developing sarcoidosis [40]. This notion has been supported by the similar histological pattern of inflammation found in sarcoidosis and other granulomatous lung diseases including tuberculosis and chronic beryllium disease, which both have established environmental aetiological agents [41]. Table 2 summarises the evidence available regarding the role of specific environmental agents in contributing to sarcoidosis.

2.2 Pathogenesis

The immunopathogenesis underlying sarcoidosis is not entirely understood. It has been postulated that extrinsic factors such as those outlined in Table 2 could represent potential antigens responsible for triggering the sarcoid immune response. Antigen presenting cells (APCs), which are mostly macrophages or dendritic cells (DCs), phagocytose this presumptive antigen and display the antigen peptide (AP) on the surface HLA Class II molecule [67]. When the AP is displayed by an APC to a compatible T-cell receptor (TCR) of a naïve CD4+ T-cell, the T-cell is activated. Effective T-cell activation is also dependent on the binding of co-stimulatory molecules (CD28) on the cell surface to specific ligands on the APC (CD80) [68,69].

Upon TCR activation, naïve T-cells are then induced to develop a Th1 phenotype and secrete an array of Th1 cytokines. The sarcoid immune response has thus long been described as a Th1 response, with Th2 involvement implicated in the eventual outcome of granulomatous inflammation [70]. Recently however, other relevant mechanisms including Th17 and Natural Killer T-cells have been identified, although a full overview of these is beyond the scope of this review [71-73].

Predominantly, the production of Th1 cytokines Interleukin-2 (IL-2) and Interferon-γ (IFN-γ) is amplified. IL-2 is a local growth, survival and differentiation factor for T-cells and thus its autocrine production results in clonal proliferation of CD4+ T-cells [67,74]. IFN-γ, has shown to be highly expressed in the BAL fluid of patients with sarcoidosis, promotes granulomatous inflammation and inhibits fibrosis and also been implicated in the activation of alveolar macrophages [75]. Given the critical role of IFN-γ in the formation of the sarcoid granuloma, considerable interest exists in its action, and mechanisms involved in its production [76] (Figure 1). TCR activation results in amplified IFN-γ transcription and enhanced Tbx21 gene expression. Enhanced Tbx21 expression then leads to an increase in the production of T-bet, a protein increasing IFN-γ transcription [77]. A significant function of IFN-γ is ultimately to inhibit the activity of the immunosuppressive molecule peroxisome proliferator-activated receptor-γ (PPAR-γ) within APCs. Under typical conditions, PPAR-γ promotes the production of immunosuppressive IL-10. Thus its inhibition by IFN-γ means the immunosuppressive effects of IL-10 are minimised, promoting inflammation and tissue damage [78].
Table 1. List of genes implicated in sarcoidosis

| Genes                  | Evidence for link to sarcoidosis                                                                 |
|------------------------|-------------------------------------------------------------------------------------------------|
| HLA-DQB1               | Predisposition demonstrated in Japanese, Swedish, British, Dutch, German and African American populations [19-23] |
| HLA-DRB1*01 & HLA-DRB1*04 | Protective & under-represented in patients [24].                                               |
| HLA-DRB1*14 & HLA-DRB1*15 | Increased risk & disease chronicity [20,25]                                                    |
| HLA-DRB1*03            | In Swedish patients, linked to Löfgren’s syndrome & disease remission [26], and spontaneous resolution [20] |
| Non-HLA genes          |                                                                                                 |
| Toll-like receptors    | Some alleles associated, but inconclusive links [27-30].                                      |
| RAGE transmembrane receptor | Gene mutations linked to sarcoid. Close proximity to HLA region means association may instead be due to linkage with HLA genes [31]. |
| BTLN2                  | Gene mutations linked to sarcoidosis in German & Caucasian, but not African American patients. [25, 32, 33] |
| TNF                    | Mutation associated increased risk [34].                                                        |
| Annexin A11            | Mutation associated with sarcoidosis; unconfirmed [35].                                         |
| Chromosome region 5p & 5q | Regions with disease susceptibility in African American patients [36]                           |

Table 2. List of non-infectious and infectious causative agents implicated in sarcoidosis

| Nature                     | Causative agent                  | Evidence for link to sarcoidosis                                                                 | Evidence against link to sarcoidosis                                                                 |
|---------------------------|----------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Non infectious            | Environmental & occupational exposure | Agricultural employment, pesticides, insecticides, organic solvents, and mould/mildew exposure [40,42]. | [-] Non dominant environmental factor [17].                                                          |
|                           |                                  | Rural lifestyle (wood stove & fireplace usage) [43].                                              | [-] No positive or negative association to previously hypothesised exposure materials (wood dust, metals) [11,17,40]. |
|                           |                                  | Nanoparticulates (common minerals & metals) linked to immune dysregulation [44].                 | [-] Microbial exposure may be contributing trigger rather than coexisting environmental exposure [45]. |
|                           |                                  | Granulomatous inflammation post bone marrow transplant [46], heart and lung transplants [47-49]. |                                                                                                       |
|                           | Transplantation                   |                                                                                                  |                                                                                                       |
| Infectious                | Mycobacteria                      | PCR evidence of mycobacterial nucleic acid [50,51]                                               | Mycobacterial organisms not found in routine acid-fast stain and culture of sarcoid specimens [59]. |
|                           |                                   | Mycobacterial antigens elicit increased responses in sarcoid CD4+ and CD8+ T cells compared to controls [52-58]. | Mycobacterial DNA not in all patients with sarcoidosis [60,61].                                      |
|                           | Propionibacterium spp.            | Higher propionibacterial DNA in sarcoid BAL fluid [62]                                           | No evidence of active/reactivated latent tuberculosis in patients with sarcoidosis receiving corticosteroid treatment [17]. |
|                           | Viruses, fungi & other infectious agents | Increased incidence in communities with higher fungal exposure. Anti-fungal medications shown to improve disease outcome [64]. | Healthy lung & mediastinal tissue culture yields this commensal organism [63].                        |
|                           |                                   | Serum antibodies to human herpes virus-8, herpes simplex virus, and Epstein-Barr virus elevated in patients with sarcoidosis [65] | Viruses do not cause epithelioid-type granulomas & no known mechanism for granuloma formation via molecular mimicry after viral exposure [17]. |
|                           |                                   |                                                                                                  | Elevated serum antibodies may be due to non-specific polyclonal hypergammaglobulinemia common in sarcoidosis [66]. |

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APCs secrete a number of cytokines that promote the Th1 immune response. Notably, IL-12 and IL-18 act synergistically to upregulate IFN-γ expression [79]. IL-15 has been shown to perform a similar function to IL-2 in that in acts as a proliferative factor for T-cells, even binding to IL-2R to trigger growth [74]. TNFα acts to upregulate IL-15 activity and induce the expression of IL-2R, encouraging CD4+ T cell proliferation and survival. Ultimately, the milieu of inflammatory cytokines result in granuloma formation [78].

Granulomas are the histologic hallmark of sarcoidosis and develop largely from the aggregation of cells around inflammatory foci in an attempt to localise the inciting antigen. This is a chemotactic process that occurs via the induction of cell adhesion molecules and their ligands, and increased expression of Th1 cytokines and their receptors [76]. The outcome of the granuloma is either resolution or fibrosis. Disease remission is postulated to occur due to antigen clearance and/or increased IL-10 leading to suppression of Th1 cell and APC activity. Alternatively, disease chronicity results in a predominance of Th2 cytokines, resulting in lung remodelling by fibrosis [83,84].

Structurally, the core of the granuloma consists of macrophages, epithelioid cells, and multinucleated giant cells interspersed with CD4+ T-cells. These cells are encircled by CD8+ T-cells, regulatory T-cells, fibroblasts and B-cells which become predominant as the granulomatous inflammation regresses to give way to fibrosis [76,85]. An abundance of serum amyloid A (SAA) proteins have also been found in sarcoid granulomas where they are capable of eliciting Th1 immune responses through the Toll-like Receptor 2 (TLR2) expressed on APCs [86].

Despite this localized inflammation, sarcoidosis also entails anergy in sites unaffected by inflammatory hyperactivity. Notably, cutaneous anergy to certain antigens and lymphopenia in the peripheral blood have been noted in patients with sarcoidosis. This coexistence of localised granulomatous inflammation with peripheral anergy is known as the “immune paradox” of sarcoidosis [3]. A number of theories have been postulated to explain this remarkable phenomenon, including the paradoxical activity of T-regulatory cells, impaired dendritic cell function and defective T-cell co-stimulation [83,87]. Some differences in the inflammatory activity between the peripheral blood and disease sites are outlined in Table 3.

However this difference between the immunological responses at disease sites compared to the rest of the body is not always pronounced. Multiple studies indicate that several inflammatory markers including angiotensin-converting enzyme, chitotriosidase, soluble IL-2 receptor, IL-12, IL-18, neopterin, monocyte chemoattractant protein-1 and TNF receptors, are significantly altered peripherally, and at sites of localized granulomatous inflammation [84,88-95].

Ultimately, the mechanisms underlying the pathogenesis of sarcoidosis and particularly the immune paradox are complex, and further research is required to understand this [82].
2.3 Detection of Biomarkers

Methods by which the immunopathogenesis of sarcoidosis has been studied have evolved over time, from the use of blood and serum, to BAL fluid, which provides insight into the inflammatory processes occurring at the lungs [96]. As sarcoidosis affects the lungs in the majority of patients [17], this is a particularly useful means to study inflammatory cells and mediators at the sites of disease activity in patients with sarcoidosis. While BAL fluid is reported to have high positive predictive values for the diagnosis of sarcoidosis (in the absence of other causes) by detecting lymphocytosis with elevated CD4+/CD8+ T-cells in a ratio of more than 3.5 [97,98], the interpretation remains controversial [99,100].

Recently, elevated levels of exhaled eicosanoids 8-Isoprostane (8-IP) and cysteinyl leukotrienes have been detected in the BAL fluid of patients with sarcoidosis. The lack of correlation between these eicosanoids and the percentage of lymphocytes in BAL fluid however, suggests they are poor markers of disease activity [101,102]. Despite this, 8-IP levels have been shown to reflect disease persistence, indicating it may be useful as a prognostic marker [103].

Notably, BAL fluid has provided insight into the inflammatory profile of the disease. Ex-vivo studies have demonstrated a greater activation of unstimulated CD4+ and CD8+ T-cells in BAL fluid compared to peripheral blood lymphocytes [104]. This compartmentalisation of the sarcoid immune response has also been confirmed with increased expression of Th1 chemokine and cytokine receptors (CXCR3, CCR5, IL-12R, IL-18R) in CD4+ T cells in sarcoid BAL fluid compared to peripheral blood [105], which is stimulated by IFN-γ activity [106].

Under unstimulated conditions, the difference in percentages of IFN-γ secreting CD4+ lymphocytes in BAL fluid and peripheral blood of patients with sarcoidosis is insignificant [107,108]. After stimulation with ionomycin and phorbol12-myristate acetate however, there was a notable increase in levels of IFN-γ secreted by CD4+ T-cells was detected in the BAL fluid of patients with sarcoidosis [109]. Upon stimulation, elevation of the number of CD4+ IFN-γ + cells was detected in the BAL fluid of patients with sarcoidosis compared with healthy controls [110,111].

Although a number of other inflammatory mediators have been detected in the BAL fluid of patients with sarcoidosis, BAL and other methods (e.g. transbronchial biopsy) are considered too invasive for repeated use [112,113]. Induced sputum has been considered as an alternative method for sampling airway secretions in patients. Although the CD4+:CD8+ T cell ratio and TNFα levels in induced sputum correlated strongly with that in BAL fluid, no correlation has been found in differential cell count [114]. Ultimatey, the usefulness of this technique is called into question as induced sputum primarily samples the more proximal airways, potentially providing an incomplete picture of airway inflammation in sarcoidosis. [115,116]. More importantly, while less invasive than BAL, there is concern that induced sputum collection is still too invasive a means by which to sample airway secretions [117].

Thus there remains a need to identify a minimally invasive sampling method by which to comprehensively assess sarcoid inflammation [80,112,113]. Considerable attention has therefore been paid to exhaled breath condensate (EBC), a simple and minimally invasive method of sampling airway-lining fluids. EBC has been shown to be useful for analysing

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Table 3. Peripheral anergy and localized granulomatous inflammation

| Feature | Peripheral blood | Localized inflammatory activity |
|---------|------------------|---------------------------------|
| Lymphocytes | Reduced levels of circulating T-cells. | Increased levels of activated T-cells |
|          | Normal/slightly reduced CD4+:CD8+ cell ratio | Elevated CD4+:CD8+ cell ratio |
| Anti-proliferative T-regulatory cells: | Supress cell-mediated systemic immune response | Unable to control localized inflammation |
|          | Anti-proliferative effect on naive T-cells | Weakly inhibit TNFα production |

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| Anti-proliferative effect on naive T-cells | Weakly inhibit TNFα production |
exhaled breath markers and is less invasive compared to BAL fluid [118,119].

An EBC collecting device is illustrated in Figure 2. During exhalation, water droplets and volatile molecules (e.g. nitric oxide, carbon monoxide) diffuse as gases. Non-volatile molecules (e.g. leukotrienes, prostanoids) from the airway lining fluid join this gaseous mixture, which then condenses with the aid of a refrigerator device [120]. There are, however technical limitations to EBC analysis. While BAL fluid notably provides relevant biological material, problems of dilution apply to both BAL and EBC [118,121]. The lack of a dilution denominator means that quantitative assessment of inflammatory mediators is limited, and the absence of standardised analytical procedures limits comparison between laboratories [119].

The device consists of glass condensing chamber, which is cooled by ice. EBC collects between the two glass walls and falls to the bottom of the outer glass container in a liquid form [117].

Although total protein is at much higher levels in BAL fluid compared to EBC, a number of mediators have been detected in the EBC of patients with sarcoidosis [113,118]. In particular, levels of TNFα, Insulin- like growth factor-1 (IGF-1), and plasminogen activator inhibitor-1 (PAI-1) have been identified in EBC as closely correlating with BAL fluid samples. One study found that IL-6 levels however, were significantly lower in EBC compared to BAL fluid though this is potentially attributable to likelihood that IL-6 formed high molecular weight complexes compared to other cytokines. On the whole, these findings indicate the ability of EBC to mirror cytokine production in the lung as effectively as BAL fluid [122]. Another study detected TGF-ß1, PAI-1, TNFα, IL-8 and vascular endothelial growth factor in sarcoid EBC, though it had a small sample size and lacked a control group [123].

Elevated levels of exhaled eicosanoids (8-IP) and cysteinyl leukotrienes detected in BAL fluid have also been detected in EBC. These eicosanoids are unlikely to be useful mediators for sarcoid disease activity, as levels did not correlate with lymphocyte percentage in BAL fluid [101,102,124]. While other inflammatory mediators discovered in BAL fluid and serum of patients with sarcoidosis (such as eosinophils, neutrophils, serum angiotensin converting enzyme, soluble IL-2R and neopterin) have been suggested as potential EBC biomarkers [84,125-128], few have demonstrated sufficient sensitivity and specificity [129]. Aside from a few recent studies, most inflammatory mediators are yet to be assessed in the EBC of patients with sarcoidosis [113].

Figure 2. Schematic diagram representing an EBC device
2.4 Novel Immunological Markers

MicroRNA (miRNAs) are small non-coding segments of RNA that act post-transcriptionally to inhibit mRNA production. They exist within exosomes, which are small secretory vesicles allowing transfer of miRNA between cells [133]. Through the dysregulation of fundamental biological processes, abnormal tissue miR-29 expression has been associated with the pathogenesis of various cancers and fibrotic and obstructive lung disease [134-136], and in the fibrotic progression of sarcoidosis [39]. MicroRNA PCR array analysis has identified the down-regulation of a number of miRNAs in the BAL fluid of patients with sarcoidosis, although further research is required to determine the significance of the identified miRNA sequences [137].

MicroRNA 29 (miR-29) has been found to modulate IFN-γ production by directly targeting IFN-γ mRNA [138,139]. Specifically, miR-29a and miR-29b have been demonstrated to be down-regulated in IFN-γ-secreting T cells. The miR-29 deficiency is believed to initiate a positive feedback loop which enhances IFN-γ production. Mice with suppression of miR-29 activity demonstrated enhanced Th1 responses and greater resistance to infection with Mycobacterium tuberculosis [139,140]. A recent study in our laboratory identified impaired expression of miR-29a in EBC of patients with sarcoidosis compared to healthy controls (Loke et al. [141] unpublished), suggesting that miR-29 family members may potentially be implicated in sarcoid pathogenesis.

PPAR-γ has been implicated in a number of chronic inflammatory conditions [142]. In BAL fluid of patients with sarcoidosis, alveolar macrophages were found have lower levels of PPAR-γ, although only a small sample size was studied [143]. In another study, PPAR-γ gene expression was found to be decreased and IFN-γ significantly elevated in BAL fluid of patients with severe, treatment-requiring sarcoidosis. In patients with mild disease, levels of PPAR-γ were comparable to that of controls but still accompanied by increased IFN-γ, suggesting that PPAR-γ rather than IFN-γ levels best correlates with disease severity [144].

There is a paucity of studies that measure PPAR-γ levels and expression in the EBC or PBMCs of patients with sarcoidosis. The literature also lacks studies of miR-29b expression in EBC or PBMCs of patients with sarcoidosis compared to healthy controls.

3. CONCLUSION

Sarcoidosis is a multi-system inflammatory disorder characterized by non-specific, non-caseating granulomas. Currently the aetiology and pathogenesis of the disease are unclear, complicating the diagnosis and staging of patients with sarcoidosis [17]. As the majority of patients with sarcoidosis have pulmonary involvement, EBC and results from PBMC activation can offer novel insights into the “immune paradox” associated with sarcoidosis. A range of inflammatory mediators have been identified in sarcoid EBC, but further research is needed to identify sarcoid specific biomarkers involved in the pathogenesis [113].

CONSENT
Not applicable.

ETHICAL APPROVAL
Not applicable.

COMPETING INTERESTS
Authors have declared that no competing interests exist.
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