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# Immunopathology of Sarcoidosis

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## ABSTRACT

The immunopathology of sarcoidosis remains elusive despite years of research into this multiorgan disease.However, recent studies have provided new insights into the genetics and immune components involved in the clinical manifestation of the disease.

Granulomatous inflammation is due to the host immune response to a persistent poorly degradable unknown antigen.Mycobacterium tuberculosis (MTB) is the major disease driver in many patients.

The immune mechanisms that cause this disease start with the antigenic stimulus, followed by T-cell, macrophage and dendritic cell activation via a classic MHC II–mediated pathway.

In addition, the profile of immune mediators reported in sarcoidosis indicates that the inflammasome pathway plays a critical role in disease pathogenesis. Increased understanding of the signal transductions pathways involved in the induction of inflammatory processes in sarcoidosis could give rise to new therapeutic approaches in future.

**Keywords:** Inflammatory cells; Sarcoidosis; Tuberculosis

## INTRODUCTION

Ever since the first clinical description of sarcoidosis, the immunopathology of this multiorgan disease has remained elusive.[1]

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However, recent studies have provided new insight into the genetic risks for sarcoidosis and how the genetic makeup of a patient (genotype) determines the clinical manifestation of the disease.[1-3] Genome wide association studies (GWAS) have confirmed previous association for Class I and Class II Human Leukocyte Antigen (HLA) genes including HLA-B7, HLA-B8, DRB1*03, DRB1*11, DRB1*12, DRB1*14 and DRB1*15 as risk factors in sarcoidosis.In contrast, HLA-DRB1*01 and DRB1*04 are protective against



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disease.[3]GWAS studies have also identified 2 non-HLA associations.The first is a risk factor and involves the butyrophilin-like 2 (BTNL2) gene, which is a negative costimulatory molecule, whose lack of function could result in amplified T-cell activation. The second allele is protective and is associated with the annexin A11 (ANXA11) gene which has been implicated in the pathogenesis of several autoimmune disorders through effects on autoantibody production.Its possible role in sarcoidosis, however, is unclear although an effect on T-cell apoptosis may be important.[3] Although the individual effects of these genes is small and accounts for a limited proportion of risk, the combined presence of many of these alleles may have a significant effect on critical pathways involved in disease pathogenesis.

Granulomatous inflammation in sarcoidosis is believed to be caused by the host response to a persistent poorly degradable antigen.[2] This antigenic stimulus can arise from non-infectious or infectious sources.Various non-infective agents have been suspected primarily because of their epidemiologic association,[4] however, these have not stood the test of time.[5]

Similarly, anumber of infective organisms have also been implicated as the cause of sarcoidosis.[6]Of these, Mycobacterium tuberculosis (MTB) has been suggested as a major disease driver in many patients.[7-9] Theevidence for a causative role of MTB in sarcoidosis is multidimensional and it is estimated that a positive test for mycobacterial nucleic acids in sarcoidosis samples averages 30% overall, although the individual studies reported a wide variation in detection rates (0–50%).[10]Sarcoidosis is a systemic disease characterized by non-caseating granulomas in many organs, especially the lung, skin and eyes. The immune mechanisms that cause this disease are not completely understood[11-15]but the process probably starts with the antigenic stimulus, followed by T-cell and macrophage activation via a classic MHC II–mediated pathway.[2,11,16-21]In this short review we highlight the relationship between sarcoidosis and tuberculosis (TB) with a focus on the cells and mediators implicated in the pathogenesis of sarcoidosis and the implications of this link for clinical practice.

**Cell Mediated Response**

Sarcoid granulomas are comprised of epithelioid cells, mononuclear cells and CD4+ T cells with a few CD8+ T cells around the periphery. The proportion of T cells is increased in bronchoalveolar lavage (BAL) fluid from patients with sarcoidosis, where they typically comprise 20-60% of the total cell count. CD4+ T cells dominate, with a CD4+:CD8+ T-cell ratio typically >3-5:1 compared with a ratio of 2:1 in healthy subjects.[22]These CD4+T cells express surface receptors consistent with an effector memory phenotype.[23] Overall, analysis of BAL cells has greatly expanded our understanding of the inflammatory responses that occur in the lung.[2]The basic information obtained from such an evaluation guides the clinician towards conducting the appropriate tests and to making the correct diagnosis.

The sarcoid granuloma is thought to form as a consequence of a crippled immunological response against an unidentified antigen resulting in the progressive accumulation and activation of Th1 clones (Figure 1).[24]Thus, local presentation of the unknown antigen by macrophages to T lymphocytes results in the preferential accumulation of Th1–like CD4+ T-cells.[25,26]These T cells act in a two ways: in antigen recognition and in the amplification of the local cellular immune response.[25]The presence of both α/β T-cell receptors which recognize antigens in a major histocompatibility complex (MHC class II restricted (exogenous antigen presentation) manner[27,28]and of the B7:CD28/CTLA-4 costimulatory pathway[29]are essential for T cell activation in sarcoidosis. Activated macrophages and T-lymphocytes within the granuloma release a number of key inflammatory cytokines[30, 31] including interferon (IFN)-γ.[32]However, in contrast to the ‘‘hyperimmune’’ milieu within the affected granulomatous tissue, a state of immune hyporesponsiveness has been indicated in the peripheral circulation of patients with sarcoidosis[22]and in subacute thyroiditis.[33] The antigen-presenting macrophages and dendritic cells (DCs) within the granuloma are distinguished by the increased presence of Anti-Follicular Dendritic Cells 1 RFD1 and RFD7 cell surface markers (RFD1+/D7+ Antigen presenting cells APC cells) in active sarcoidosis.[34] DCs are now known to play a critical role in the pathogenesis of sarcoidosis. In their normal steady-state, APCs constitutively express peroxisome proliferator–activated receptor (PPAR)γ, a transcription factor that induces macrophage Interleukin (IL)-10 production and inhibits myeloid DC development and function.However, in sarcoidosis, antigen-driven

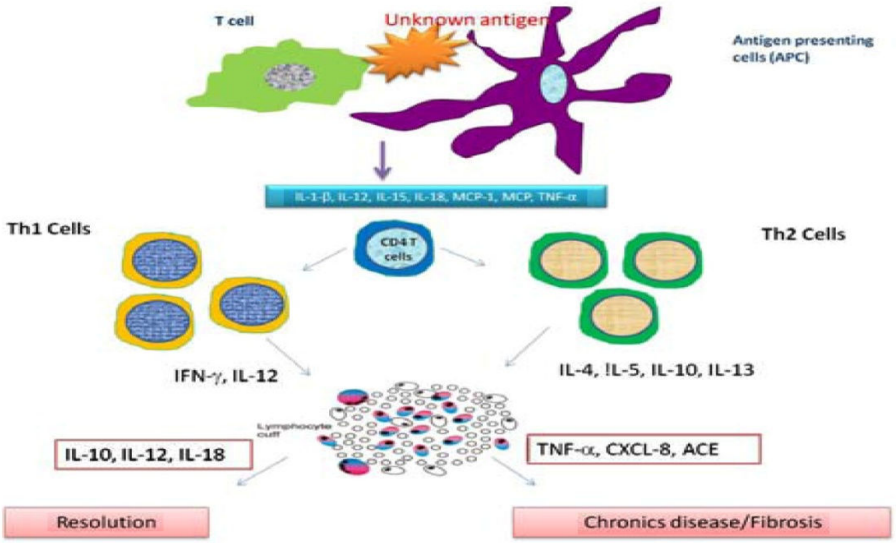


**Figure 1. The cartoon indicating simple pathogenesis of Sarcoidosis. Exposure of body to unknown sarcoid antigen leads to activation of the T cells and APCs which leads to releasing of cytokines. CD4 activation can skew the immune system to Th1 and Th2 response which in turn induces the granuloma formation. Formation of granuloma in later phases can end up to resolution or chronic status of diseases with fibrosis condition.**

inflammation causes DC activation and increased maturation and migration of DCs to the draining lymph nodes driving T cell expansion. In addition, these activated DCs also release the Th1-polarizing inflammatory mediators Tumor Necrosis Factor (TNF)-α, IL-12, and IL-18.[35]

Other T-cell subsets have also been reported in sarcoidosis.The accumulation of CD8+ T-cells in the sarcoid lung probably reflects a homing of memory cells due to the ongoing immunologic response against the unknown antigen causing the disease. Although CD8 alveolitis can be considered a relatively rare event in sarcoidosis, the possibility that an increase of CD8+ cells in the BAL fluid might be sustained by an underlying sarcoid inflammatory process should never be dismissed on clinical grounds in patients with interstitial lung disease.[36] Furthermore, the number of CD4+ T cells bearing a phenotype consistent with Th17 polarization is elevated in lung tissue and bronchoalveolar cells from patients with sarcoidosis, suggesting that Th17 responses contribute to granulomatous inflammation.[37] Finally, there is a deficiency in the number of naturally occurring T regulatory (TREG) cells in sarcoidosis[38] although whether this deficiency has a critical role in the pathogenesis of disease remains uncertain.

## Mediator Response

The expression of the signature Th1 cytokine,IFN-γ and of related cystokines including IL-12, IL-18 and IL-27 is upregulated in tissues affected by sarcoidosis.[23,24,39,40]In addition, the enhanced expression of a plethora of other cytokines including IL-1β, IL-10, IL-12, IL-15, IL-18 and TNF-α, TGF-β has been reported in sarcoidosis.[41-44]The production of these inflammatory mediators are critical for mediating the immune response in sarcoidosis.IFN-γ activates macrophages, thereby enhancing phagocytosis and oxidant production, and synergizes with cytokines (such as TNF-α) to cause microbial killing.[45]Furthermore, IL-2 and IL-15 which are upregulated in patients with sarcoidosis,have a proliferative and antiapoptotic effect on T cells[46]Chemokines and chemokine receptors typically associated with a Th1 response are also upregulated in sarcoidosis. By contrast, IL-4 and IL-5, cytokines released by Th2 cells, and many chemokines and chemokine receptors associated with Th2 responses are

downregulated at the sites of inflammation in patients with sarcoidosis.[47,48]The elevated expression of the cytokine IL-13, produced by Th2 cells, might be a possible exception to the rule in a subgroup of patients.[49]

**Sarcoidosis and TB: What are the Links?**

The relationship between sarcoidosis and TB remains an enigma. Even the earliest description by Caesar Boeck of a case of 'multiple benign sarcoid of the skin' was thought to be allied in some way to TB.[50]The potential of MTB to cause sarcoidosis has been extensively studied albeit with conflicting results[51]For example, Dumouchel-Champagne et al. described the occurrence of disseminated non-TBinfections with Mycobacterium genavense during sarcoidosis.[52]These studies indicate overall that non-TB mycobacterium (NTM) opportunistic infections are not restricted to HIV-infected patients.The possibility of a role for NTM should be taken into consideration for each patient undergoing significant clinical worsening of their chronic systemic disease while currently treated with long-term immunosuppressive therapies.

**Role of the Inflammasome and Toll-Like Receptors (TLRs) in the Pathogenesis of Sarcoidosis**

TLRs are innate immunity receptors responsible for the molecular recognition of pathogens.TLRs can initiate the inflammatory and anti-microbial innate immune responses, thereby dictating the ensuing adaptive immune response.As indicated earlier, sarcoidosis is not caused by a single pathogen, but rather results from an abnormal immune response to an unknown pathogen.In general, activation of pathogen activated molecular patterns (PAMPS) results in the activation of a number of complex signal transduction pathways including that of the inflammasome.Taking into consideration the types of bacteria involved in the pathogenesis of sarcoidosis, it is more likely that TLRs recognising microbial components of Gram-positive bacteria such as TLR2 and not TLR-4, which recognises Gram-negative bacteria, might be good candidates for genetic association in sarcoidosis. However, an association between the TLR-4 polymorphisms Asp299Gly and Thr399Ile and the chronic course of sarcoidosis has been reported rather than any polymorphisms in TLR2.[53] Cell surface components of *P. acnes* or *M. tuberculosis* are recognised by TLR-2 which therefore still remains a prime candidate for functional studies interrogating the role of intracellular pathogens in the pathogenesis of sarcoidosis and for the modulation of the local innate immune response.[54-56] TLR-2 signalling also seems to be important for the correct function of TREG cells, another population of T cells which might be functionally impaired in sarcoidosis[57,58]and whose expression is reduced in sarcoid as described above.[59,60]These data highlight the possible critical role for Gram-negative bacteria acting through TLR2 in the pathogenesis of sarcoidosis.Indeed, TLR2 may not act alone in this process since the interaction of TLR2 and TLR7 has been shown to occur in pulmonary sarcoidosis.[24]

Activation of the NLRP3 inflammasome down-stream of TLR activation results in the expression of the inflammasome-regulated mediators IL-1β, IL-18 and IL-33 following caspase 1 cleavage of mediator pro-forms.[61]Recent evidence suggests a role for the inflammasome in driving the pathological response to the unknown pathogen in sarcoidosis.Serum and BAL fluid IL-18 levels are increased in sarcoid patients[62] were significantly higher than in healthy controls and subjects with Idiopathic pulmonary fibrosis IPF. In addition, serum IL-18 levels correlated with BAL fluid CD4/CD8 ratios.This confirmed a previous meta-analysis of IL-18 expression in sarcoidosis[63] and data from Mroz and colleagues[64] and Antoniou and co-workers[65] who reported increased BAL fluid IL-12 and IL-18 levels compared to those in healthy control subjects.There were no significant differences in sputum IL-18 levels between sarcoid patients and healthy controls reported in these studies. However, the percentage of sputum macrophages expressing IL-1, IL-6 and TNF-α and the levels of these cytokines in induced sputum have been shown to be higher in patients with sarcoidosis compared to control groups.[66]Finally, increased IL-18 expression in epithelial lining fluid from sarcoid patients was associated with a higher frequency of the -607C allele and -607(C/C) genotype in the sarcoidosis population compared with control subjects.[67]IL-18 has been implicated in driving effective antimicrobial and antiviral immunity and in the pathogenesis of sarcoidosis[68] and in animal models of disease, IL-18 synergises with IL-12 to induce IFN-γ production.[69,70]

The infectious cause of sarcoidosis implicates a role for pattern-recognition receptors, such as TLRs and nucleotide-binding domain, leucin-rich repeat

containing family proteins (NLRs), in disease pathogenesis.Indeed, baseline levels of TLR2 and TLR4 expression in blood monocytes are significantly higher in patients with sarcoidosis than in healthy controls. In addition, stimulation of both TLR2 and Nucleotide-binding oligomerization domain-containing protein 2 NOD2 on blood monocytes resulted in a 4-fold higher secretion of TNFα and a synergistic 13-fold higher secretion of IL-1β in sarcoid patients compared to healthy controls.[71]In addition, NOD2 mutations have also been implicated in early-onset sarcoidosis.[72-74]

In conclusion, the inflammasome pathway could be considered as a potential therapeutic target in sarcoidosis as it increases the serum levels of selective inflammatory cytokines known to be elevated in sarcoidosis. Increased understanding of the signal transductions pathways involved in the induction of inflammatory processes in sarcoidosis could give rise to new therapeutic approaches in future.

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