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Review

# A sarcoidosis clinician's perspective of MHC functional elements outside the antigen binding site

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ABSTRACT

Sarcoidosis is a multisystem granulomatous disease of unknown cause. Evidence supports an integral role for interactions at the MHC binding site in the development of sarcoidosis. However, despite this evidence, there are clinical data that suggest that additional mechanisms are involved in the immunopathogenesis of this disease. This manuscript provides a brief clinical description of sarcoidosis, and a clinician's perspective of the immunopathogenesis of sarcoidosis in terms of the MHC binding site, MHC functional elements beyond the binding site, and other possible alternative mechanisms. Input from clinicians will be essential in establishing the immunologic cause of sarcoidosis as a detailed phenotypic characterization of disease will be required.

## 1. Introduction

Although often obscured in a fog, a long bridge extends from the medical scientific researcher in his laboratory to the clinician at the patient's bedside. The scientist's world is one of objectivity, quantification and reproducibility. The clinician's world is inexact, and, although based in science, is overlaid with complex psychosocial and financial issues. Nonetheless, it is imperative to the clinician that the bridge remains open, for numerous scientific breakthroughs that have travelled down that thoroughfare have resulted in medical cures and the alleviation of patient suffering.

As a clinician with an interest in sarcoidosis, I am constantly peering at what is cruising down that bridge from the worlds of basic and translational science, because the immunopathogenesis of sarcoidosis is currently unknown. Clearly, an understanding of the mechanisms that lead to the development of sarcoidosis is likely to have a major impact on the patients whom I care for. In this manuscript, I will briefly outline the clinical manifestations of sarcoidosis, describe the prevailing thoughts concerning the immunobiology of sarcoidosis, explain inconsistencies with these theories, and discuss the importance of alternate postulations, including the potential for sarcoidosis to be impacted by MHC functional elements outside the antigen binding site.

## 2. A basic clinical description of sarcoidosis

Sarcoidosis is a multisystem granulomatous disease of unknown cause. Any organ may be involved with sarcoidosis. The lung is the most frequent organ involved, and other common organs include the skin, eye, peripheral lymph nodes, and liver [1,2]. The clinical manifestations of sarcoidosis may vary from an asymptomatic state to a life-threatening condition [3]. Sarcoidosis may cause harm by granulomatous infiltration of vital tissues or by the release of toxic mediators from the granulomatous inflammation into the systemic circulation (so-called parasarcoidosis syndromes [4]).

The prevalence of sarcoidosis has been estimated at 60/100,000 in the United States [5] and 160/100,000 in Sweden [6]. In the United States, prevalence rates are much higher in Blacks (141/100,000) than Whites (18/100,000) [5].

Histologically, the lesions of sarcoidosis appear as granulomas, which are compact organized collections of mononuclear phagocytes (macrophages or epitheliod cells) and may contain additional inflammatory leukocytes [7]. These granulomas are frequently surrounded peripherally by lymphocytes [7]. Although the granulomas of sarcoidosis tend to be well demarcated from surrounding tissues ("tight granulomas") and usually necrosis is not a common feature, these are not universal findings and the diagnosis of sarcoidosis cannot be securely made by virtue of the pathological findings alone [7].

The diagnosis of sarcoidosis may be established in one of two ways. First, there are clinical presentations that are so specific for sarcoidosis that the diagnosis can be made without the need for a confirmatory biopsy. These presentations include certain chest radiographic features (e.g., bilateral hilar lymphadenopathy on a chest radiograph without symptoms of fever, night sweats or weight loss), and certain physical findings (e.g., Herfordt's syndrome: uveitis, parotitis, and fever) [8]. If such a specific presentation is not present, the diagnosis of sarcoidosis requires biopsy-confirmation of granulomatous inflammation and

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exclusion of alternative causes that might cause such inflammation (e.g., tuberculosis, chronic beryllium disease) [8].

Sarcoidosis has a markedly variable clinical course. The disease may never cause symptoms and does not necessarily require treatment. On the other end of the clinical spectrum, sarcoidosis may cause progressive disease leading to organ failure and death [9]. Most of these deaths result from sarcoidosis-induced end stage fibrosis [9–11] or from cardiac sarcoidosis causing sudden death or heart failure [10,12]. Presently, there is no biomarker available to reliably predict if sarcoidosis will follow a benign or malignant course [13]. Establishing such a biomarker is a major unmet need, because the current drug of choice for sarcoidosis is corticosteroids which have significant toxic side effects. Without a biomarker that can reliably distinguish inconsequential from progressive and fibrotic disease, many sarcoidosis patients who are treated unnecessarily develop corticosteroid side-effects, whereas some patients who are not treated develop end-stage disease that could have been prevented with treatment.

## 3. Prevailing theory concerning the immunopathogenesis of sarcoidosis

The prevailing theory concerning the immunopathogenesis of sarcoidosis involves a mechanism that is thought to be common across most granulomatous lung diseases; that is, antigens enter the host, are phagocytosed by antigen presenting cells such as macrophages and dendritic cells, and are subsequently presented via human leukocyte antigen (HLA) Class II molecules to a restricted set of T-cell receptors on naive T lymphocytes that are primarily of the $CD4^+$ class [14]. These events induce an immune response that results in polarization of the T lymphocytes to a Th1 phenotype, followed by cellular recruitment, proliferation, and differentiation leading to formation of the sarcoid granuloma. An interplay of antigen, HLA class II molecules, and T-cell receptors is thought to be essential for sarcoidosis to develop [15]. This interplay is thought to occur at the HLA molecule binding site.

There is a large body of evidence to support this proposed mechanism for sarcoidosis immunopathogenesis. Various HLA gene alleles are associated with development of sarcoidosis [16,17], protection from developing sarcoidosis [16,17], and specific phenotypes of the disease [16,17]. Further analysis suggests that such HLA gene polymorphisms result in conformational changes in the antigen binding pockets of HLA molecules [18]. Additional evidence supporting this proposed mechanism for sarcoidosis relates to chronic beryllium disease (CBD), a granulomatous condition that is radiologically and histologically indistinguishable from sarcoidosis. The immunopathogenesis of CBD is more secure than sarcoidosis and is associated with a glutamic acid substitution at position 69 of the HLA-DBP1 chain and position 71 of the HLA-DRB1 chain [19,20]. Beryllium-specific oligoclonal CD4+ T lymphocytes recognize beryllium in an MHC class II restricted manner (usually via E69 or E71) and this recognition leads to CD4+ lymphocyte proliferation [21]. These dividing CD4+ T cells then migrate from the peripheral blood into the lungs in response to retained beryllium and recruit other T cells and monocytes to the lung [21], and produce Th1 cytokines, including tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2) and γ-interferon (IFN-γ) [21,22], eventually resulting in granuloma formation and progression to CBD. This mechanism is strikingly similar to that proposed for sarcoidosis.

## 4. Problems with the prevailing theory concerning the immunopathogenesis of sarcoidosis

Despite the aforementioned evidence supporting the prevailing theory of the immunopathogenesis of sarcoidosis, there are significant inconsistencies with this schema. First, the associations between various HLA alleles and sarcoidosis phenotypes are not universal, but rather race or ethnicity-specific [16,17]. Second, although patients with specific phenotypic features of sarcoidosis have statistically higher percentages of certain alleles than sarcoidosis patients without those specific phenotypic features or the general population, a significant percentage of individuals in these latter two groups carry the allele of risk [17,23]. In addition, in most cases, these allele-specific phenotypes explain a small minority of cases [17,18,23]. Another criticism of the prevailing theory is that it is problematic to explain the systemic features of the disease. The granulomas of sarcoidosis are often found in multiple and disparate organs. It is unclear how causative sarcoidosis antigens could disseminate throughout the body. It is possible to explain this by molecular mimicry, where the initial antigenic response triggers a response against host antigens that are similar to the initial antigen. However, although there is some evidence supporting molecular mimicry occurring with sarcoidosis [24–27], its importance currently remains conjectural.

## 5. Explanations for the problems with the prevailing theory concerning the immunopathogenesis of sarcoidosis

Most of the problems with the prevailing theory of the immunopathogenesis of sarcoidosis involve the inexactness of the available data. There is an obvious signal that the binding pocket of the HLA class II molecule, antigen(s), and the T-cell receptor are involved in the development of sarcoidosis. However, these factors do not reliably distinguish who is at risk of sarcoidosis or the phenotypic expression of the disease.

One explanation for this inexactness may relate to the variations in disease phenotype. Sarcoidosis may not be one disease but rather several, each with its own antigenic cause. Therefore, a sarcoidosis cohort may contain individuals with differing combinations of causative antigen exposures and HLA Class II molecules that bind each of them (Fig. 1). If this is the case, it would be expected that predictions of sarcoidosis risk or disease phenotype would be inaccurate based on information concerning the HLA molecule antigen binding site. Incorporating disease phenotype into an analysis of antigen binding sites may increase the accuracy of these predictions, assuming that differences in sarcoidosis phenotypes relate to different causative antigens. This problem is compounded by the fact that even if different sarcoidosis phenotypes relate the different causative antigens, it is not known which specific phenotypic differences account for the differences in antigen binding. The phenotypic differences may relate to variability in specific organ involvement of sarcoidosis, the duration or severity of disease, or response to treatment. Because the appropriate stratification

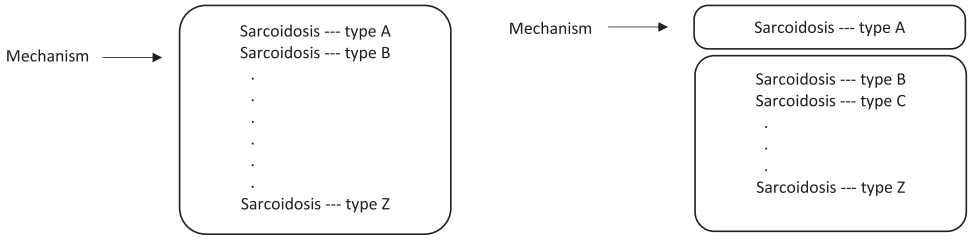


**Fig. 1.** Sarcoidosis may not be one disease but a myriad of different diseases. Each of these diseases develop by virtue of a specific mechanism. If sarcoidosis is truly one disease, there may be a unifying mechanism that explains all forms of sarcoidosis (left-hand figure). However, if sarcoidosis is a conglomeration of several different diseases, there may be distinct mechanisms responsible for each individual form of sarcoidosis (right-hand figure).

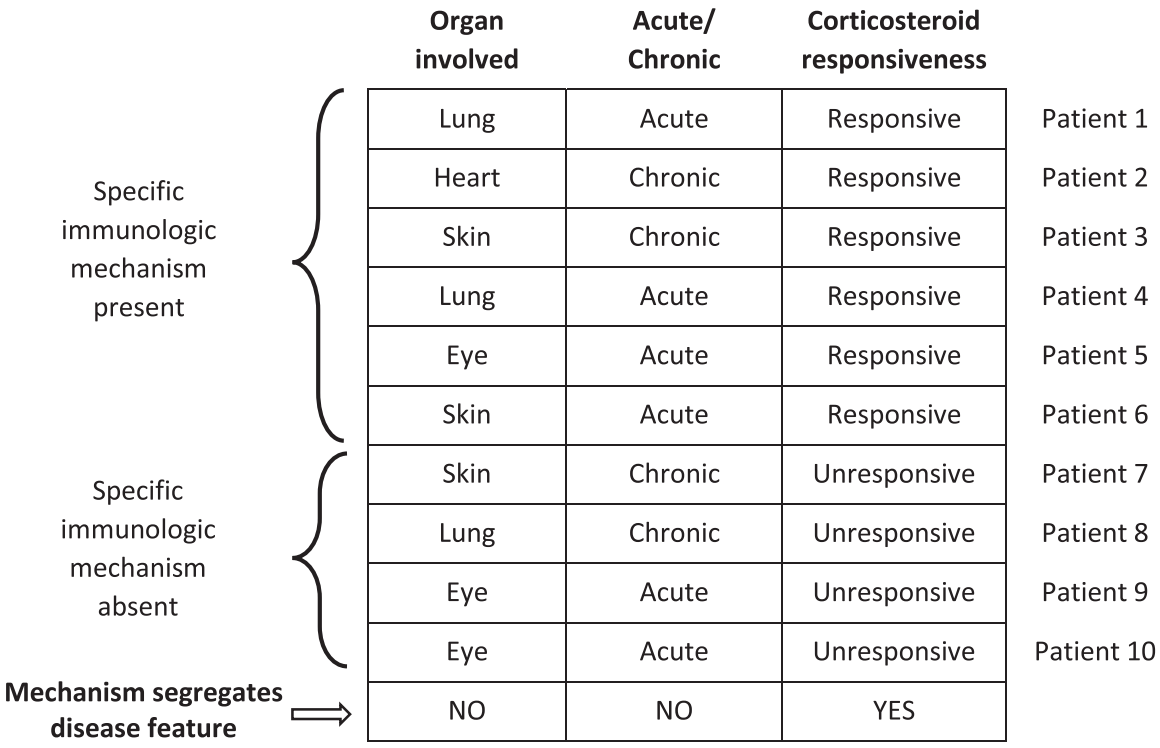


**Fig. 2.** Relationship of immunologic mechanism to sarcoidosis phenotype. An immunologic mechanism may be associated with a particular phenotypic characteristic of sarcoidosis but not others. In the example displayed in the figure, the mechanism distinguishes corticosteroid-responsive from corticosteroid-unresponsive cases. If the cases were only described in terms of sarcoidosis organ involvement or the duration of disease, it would be falsely assumed that the mechanism was not clinically relevant in sarcoidosis. This example justifies the importance of defining clinical phenotypes in detail to fully understand the impact of a purported mechanism of disease.

of disease phenotypes is unknown, it is prudent to partition the phenotypes in multiple ways (Fig. 2). However, this requires a large cohort of sarcoidosis patients and controls to find significant differences, and this may defeat the purpose of such analyses as sarcoidosis is a rare disease, and it may not be possible to collect an adequate number of sarcoidosis cases.

Another explanation for the inexactness of the available data supporting of the prevailing theory of sarcoidosis immunopathogenesis is that the development of sarcoidosis probably depends on antigen exposure. An individual may be at risk of developing sarcoidosis but may never develop the disease because he/she never was exposed to the causative antigen. Therefore, using genetic information, it may be problematic if not impossible to distinguish those at risk for sarcoidosis from those who develop sarcoidosis, and the former group will be classified as "not having sarcoidosis." This problem could be potentially solved through gene expression analyses or determination of the causative sarcoidosis antigens.

Finally, the inexactness of the prevailing theory of the immunopathogenesis of sarcoidosis may be because the theory is incomplete or incorrect. Alternative theories are briefly described in the following section.

## 6. Alternate theories concerning the etiology and immunopathogenesis of sarcoidosis

In addition to mechanisms involving the MHC antigen binding site, numerous other theories of the immunopathogenesis of sarcoidosis have been proposed. The details of these alternative theories are beyond the scope of this manuscript, but they will be discussed briefly in this section. These proposed mechanisms are not necessarily mutually exclusive, and components of several of them may play a significant role in causing sarcoidosis.

Several non-HLA genes have been associated with sarcoidosis and may contribute to its immunopathogenesis. A leading gene candidate is butyrophilin-like 2 (BTNL2), an immune regulatory gene that is thought to be involved in immune surveillance, serving as a negative T-cell regulator by decreasing T-cell proliferation and cytokine release. Naturally occurring mutations in the BTNL2 gene explained more than 20 percent of the attributable risk of sarcoidosis in a genome-wide analysis of German families [28,29]. A similar analysis in the United States found an association of the BTNL2 gene with sarcoidosis in white but not black patients [30]. It is plausible that mutations in the BTNL2 gene that lead to a loss in function could result in T-cell proliferation and cytokine release that predisposes an individual to develop sarcoidosis.

NOD-like receptors may be involved in the development of sarcoidosis. Allelic polymorphisms of NOD1 have been found to be statistically more common in sarcoidosis patients than controls [31]. In addition, the NOD2 gene has been found to be responsible for the development of Blau's syndrome [32,33], an idiopathic granulomatous disorder that is histologically similar to sarcoidosis except that it tends to occur in young children and almost exclusively involves the joints, skin, and eyes [34].

The granulomas of sarcoidosis are characterized by extensive deposition of serum amyloid A protein (SAA), and SAA deposition appears to be relatively specific for sarcoidosis in that it is rarely found in granulomas of alternative etiologies [35,36]. SAA elicits immune responses and triggers cytokine release through an interaction with toll-like receptor 2. Involvement of SAA in the granulomatous process might impair clearance of antigen allowing for persistent granulomatous inflammation [14].

Regulatory T-lymphocytes (T-reg) may play an important role in the development of sarcoidosis. T-reg cells normally suppress cell-mediated immune responses. Although T-reg cells are expanded in the peripheral

blood, bronchoalveolar lavage fluid, and granulomas of sarcoidosis patients, they are functionally defective or "exhausted" [14,37]. This may lead to chronic and continuous granulomatous inflammation.

Infectious agents have also been implicated as potential causes of sarcoidosis. Genes from propionibacterium acnes, the common acnes bacterium, have been identified by PCR in the granulomas of sarcoidosis patients whereas they have not been detected in controls [38]. Although mycobacterium tuberculosis does not appear to cause sarcoidosis, other mycobacteria may cause a portion of sarcoidosis cases. Mycobacterial catalase-peroxidase (mKatG) is a mycobacterial protein that has been detected in sarcoid granulomas [39]. mKatG elicits a T-cell response in peripheral blood lymphocytes of sarcoidosis patients [40,41] as well as the T-cells recovered from bronchoalveolar lavage fluid from these patients [40,42]. T-lymphocytes from patients with other lung diseases besides sarcoidosis tend not to be as strongly activated in the presence of mKatG [42].

Active sarcoidosis has been associated with expansion of IL-17-producing cells including CD4+ T-helper (Th) 17 cells [43,44]. Th17 cells are prevalent in epithelial surfaces including the lungs, skin, and gut, where they participate in host immune responses against bacterial, fungal, and mycobacterial pathogens predominantly by orchestrating the recruitment of inflammatory cells [45]. Bronchoalveolar lavage of active sarcoidosis patients has recovered a subset of Th17 cells that co-express interferon (INF) gamma [46]. These IFN-γ–producing Th17 cells (termed Th17.1 or Th17/Th1 cells) are thought to be the major producer of IFN-γ in the sarcoidosis lung [47]. These findings may have profound clinical implications, because Th17 and Th17.1 cells are relatively resistant to the anti-inflammatory effects of glucocorticoids that are currently the drug of choice for the treatment of sarcoidosis [48].

The programmed cell death protein 1 (PD-1) pathway is upregulated in active sarcoidosis, with increased PD-1 expression demonstrated on CD4+ T cells and lymphoid areas surrounding granulomas [49]. Downregulation of PD-1 expression on CD4+ T cells was associated with spontaneous resolution of sarcoidosis [49]. These data suggest that the PD-1 pathway may be integral to the development of sarcoidosis. Given these data, it is surprising anti-PD-1 immune checkpoint inhibitor antibody therapy has been associated with the development of sarcoidosis like syndromes [50–52]. This phenomenon may be explained by the fact that anti-PD-1 immune checkpoint inhibitors can increase the number and function of Th17 cells [53].

The immunopathogenesis of sarcoidosis may depend not only on the characteristics of the MHC antigen binding site but also on MHC functional elements outside the antigen binding site. This is a particularly appealing theory, since there are a multitude of data supporting the importance of MHC binding site in the development of sarcoidosis; however, as explained above, these data are incomplete and inadequately explain all the facets of the disease. Perhaps the "inexactness" of the associations between sarcoidosis disease phenotypes and the characteristics of the MHC binding site relate to MHC functional elements outside the antigen binding site that influence associations with membrane lipid sub-domains that may impact both signaling and antigen presentation [54]. In other words, binding of antigen to the MHC binding site requires specific characteristics in the binding site itself as well as at other portions of the MHC molecule.

In addition, SNPs outside of the MHC region may have numerous functional roles beyond simply placing antigens in the proper position for interacting with T-lymphocytes. Although the functional significance of such SNPs remains virtually unknown, it is estimated that 90 percent of causal immune disease variants reside within non-coding regions of the MHC [55,56]. Such SNPs may affect intracellular signaling molecules, immune enhancers and/or gene regulation [56], possibly from histone acetylation [56], or cell-tail ubiquitination or micro-RNA alteration. In the previous decade, analyses of the non-antigen binding site portions of HLA molecule in terms of the relationship to diseases was ad hoc, incomplete, and cumbersome [57]. It is only relatively recently that specific nucleotide/amino acid sequences for these elements have been identified [57]. Perhaps grouping alleles based on polymorphisms in them might reveal previously unknown associations. If such SNPs were found to be integral in the immunopathogenesis of sarcoidosis, it could potentially have a major impact on the diagnosis, prevention, and treatment of the disease. It may be the case that some SNPs in the antigen binding site and other SNPs outside the MHC antigen site are involved in different phenotypic expressions of the disease.

Finally, the presumption that the immune response in sarcoidosis is antigen-specific in all cases may be incorrect. It is possible that sarcoidosis is a non-specific hyperimmune response to a large class of environmental antigens. This hypothesis would be consistent with the observed genetic variation in MHC class II antigen binding characteristics that are associated with sarcoidosis. If may be that environmental factors may be responsible for the development of sarcoidosis, modify the severity of sarcoidosis, or influence the disease phenotype. A two-hit hypothesis may explain sarcoidosis, where sarcoidosis requires a genetic predisposition and then a nonspecific environmental stress or exposure might lead to the development of disease. Evidence supporting this hypothesis includes the fact that the is a correlation between obesity and sarcoidosis [58], and nonspecific inhaled exposures such as World Trade Center dust [59] and wood burning [60] have been associated with sarcoidosis.

## 7. Summary

The immunopathogenesis of sarcoidosis is currently unknown. There is strong evidence to suggest that sarcoidosis results from antigen detection, processing, and then presentation via HLA Class II molecules to T-cell receptors $CD4^+$ T cells that are polarized to a Th1 phenotype and subsequently lead to cellular recruitment, proliferation, and differentiation to form the sarcoid granuloma. Clearly, the binding site of the MHC molecule is involved. Despite the evidence supporting the importance of the MHC binding site region, it is incomplete and does not explain all the clinical features of the disease. Additional immunologic phenomena have been detected in active sarcoidosis that may be integral in explaining the inconsistencies with the prevailing theory of sarcoidosis immunopathogenesis. The characteristics of the MHC molecule outside of the binding site may be also be highly relevant in resolving these inconsistencies, as the binding of antigen within the MHC binding site is highly dependent on the structure of the molecule's non-binding regions.

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