

## REVIEW

# Etiology of Sarcoidosis: Does Infection Play a Role?

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Sarcoidosis is a granulomatous inflammatory disorder of unclear etiology, which is known to affect multiple organ systems including the lungs, heart, skin, central nervous system, and eyes, among others. For this reason, sarcoidosis represents a systemic medical disorder that is clinically relevant to multiple medical sub-specialties. Despite extensive research, the etiology of sarcoidosis has yet to be elucidated, although most evidence supports that the pathogenetic mechanism of sarcoidosis is an aberrant immune response, driven by an unidentified antigen (or antigens) in genetically susceptible individuals. Multiple candidate etiologic agents, including microbial organisms and environmental agents, have been investigated, but study results are inconclusive. In this review, we describe the known histologic and immunologic features of sarcoidosis and discuss the evidence supporting a role for infectious processes in the pathogenesis of sarcoidosis.

## INTRODUCTION

Sarcoidosis is a granulomatous multi-system disorder of unclear etiology that most commonly affects the lungs, heart, skin, and central nervous system. Sarcoidosis in general represents a diagnostic

challenge, as clinical manifestations of the disease are protean. Aside from this, the diagnosis of sarcoidosis is further hindered by the lack of any reliable and specific diagnostic test, as there are no laboratory or imaging findings that enable the definitive

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†Abbreviations: ACCESS, A Case Control Etiologic Study of Sarcoidosis; BAL, bronchoalveolar lavage; CD, cluster of differentiation; Th, T helper; IFN, interferon; TNF- $\alpha$ , tumor necrosis factor-alpha; IL, interleukin; NK, natural killer; TCR, T cell receptor; HLA, human leukocyte antigen; mKatG, *Mycobacterium tuberculosis* catalase-peroxidase protein; PCR, polymerase chain reaction; ELISPOT, enzyme-linked immunospot assay.

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diagnosis of sarcoidosis. In addition, the histologic findings associated with sarcoidosis are non-specific, emphasizing the need to interpret histology, when obtained, within clinical context. Isolated non-pulmonary sarcoidosis poses even further diagnostic challenges, with a general reluctance among physicians to obtain extra-pulmonary biopsies (other than of the skin) on account of the potential complications associated with these procedures. Once the diagnosis of sarcoidosis is made, management may range from observation to administration of long-term steroids (often at high doses) or other immunosuppressive therapies, depending on disease severity and organ involvement [1].

A genetic predisposition to sarcoidosis is evidenced epidemiologically by demonstration of familial aggregation, differences in disease susceptibility and severity between racial groups, and the significantly increased incidence in monozygotic twins of affected individuals compared to other siblings [2-4]. Candidate gene and genome-wide association studies have identified multiple genes involved in the immune response to be responsible for this increased susceptibility to sarcoidosis [5]. Specific gene alleles also have been shown to be associated with different disease phenotypes [6].

It is hypothesized that sarcoidosis arises in genetically susceptible hosts from interaction with a single or multiple environmental factors. Multiple potential etiologic agents for sarcoidosis have been proposed without any definitive demonstration of causality. An enduring hypothesis is that of an infectious etiology, with *Mycobacterium spp.* being the most commonly implicated organism. The role of various non-infectious, organic, and inorganic environmental agents has been studied in the pathogenesis of sarcoidosis. The ACCESS† (A Case Control Etiologic Study of Sarcoidosis) study, despite its inability to definitively identify or determine a sole cause of sarcoidosis, provided evidence that certain environmental and occupational exposures increase the risk for developing sarcoidosis, although this risk is thought to be modest at best [7,8]. An important difficulty in identifying an etiologic agent under-

lying sarcoidosis is its wide variety of clinical manifestations, which must be reconciled with the complex immunologic processes underpinning the disease.

## HISTOLOGIC FINDINGS IN SARCOIDOSIS

The histologic hallmark of sarcoidosis, irrespective of organ involvement, is non-caseating epithelioid granulomas. Granulomas typically consist of a compact central area of macrophages that differentiate into epithelioid cells and then fuse to form multinucleated giant cells surrounded by lymphocytes [1]. Schaumann's bodies, asteroid bodies, birefringent crystals, and Hamazaki-Wesenberg bodies may all be present but are non-specific. Lymphocytes scattered within granulomas tend to be CD4+ T helper cells, while those around the periphery are predominantly CD8+ T cells, as well as B cells. There is generally minimal necrosis within sarcoid granulomas, unlike those associated with *Mycobacterium tuberculosis* infection [9]. Currently, it is thought that granulomas in sarcoidosis form around and isolate poorly degraded antigen as a means of preventing antigen dissemination and further tissue damage. While this hypothesized antigen in sarcoidosis has not been identified, possibilities include environmental antigens and microbial remnants. Importantly, the detection of granulomas alone are not specific enough to diagnose sarcoidosis, and due to the lack of any definitive diagnostic test, the diagnosis of sarcoidosis is conventionally governed by the appropriate combination of clinical, histologic, and radiologic findings. The demonstration of granulomas histologically (when biopsies are performed) mainly serves to support the diagnosis of sarcoidosis, rather for its definitive confirmation, as well as to exclude other potential etiologies from the differential diagnosis.

## IMMUNOPATHOGENESIS OF SARCOIDOSIS

The majority of immunologic data available on sarcoidosis are derived from

pulmonary studies, since the disease most commonly affects the lungs, although it should be borne in mind that sarcoidosis does have the capacity to afflict extra-pulmonary organs, sometimes without evidence of concomitant pulmonary involvement. Patients with pulmonary sarcoidosis have increased cellularity of bronchoalveolar lavage (BAL) fluid, with a predominance of CD4+ T helper cells [10]. T helper cell activation is a requisite for granuloma formation and further clinical evidence that CD4+ T cells play a pivotal role in the pathophysiology of sarcoidosis is demonstrated by the tendency of HIV patients with sarcoidosis to have CD4 counts greater than 200 cells/ $\mu$ L. Also, patients with sarcoidosis who acquire HIV generally do not demonstrate progression of their underlying sarcoidosis [11]. There are several studies demonstrating that the T cell response in sarcoidosis-affected tissues is strongly polarized toward a T helper 1 (Th1) cytokine profile. Expression of IFN- $\gamma$ , IL-2, IL-12, TNF- $\alpha$ , and other cytokines consistent with a Th1 phenotype is upregulated at sites of inflammation in sarcoidosis [12].

IL-2 is a potent inducer of T cell proliferation and IFN- $\gamma$  production and thus plays a key role in the immune response of sarcoidosis. Furthermore, administration of IL-2 or IFN- $\alpha$  (cytokines that promote a Th1 response) has been shown to be associated with new-onset sarcoidosis, or exacerbation of pre-existing disease [13,14]. Increased IL-12 levels in BAL fluid as well as increased production by alveolar macrophages also have been reported in sarcoidosis [15,16]. IL-12 promotes Th0 differentiation into Th1 cells and promotes activated natural killer (NK) cell and T cell proliferation. It also enhances NK and T cell mediated cytotoxicity and is a potent stimulator of IFN- $\gamma$  production [17,18]. Thus, IL-12 plays a critical role in the immunologic response to intracellular organisms such as *Mycobacterium tuberculosis*, *Toxoplasmosis gondii*, and *Listeria monocytogenes* [19-22]. Those with genetic defects in the IL-12/IL12R (receptor) system have diminished granuloma formation and are prone to atypical mycobacterial infections [23].

Increased production of tumor necrosis factor alpha (TNF- $\alpha$ ), a non-specific but potent pro-inflammatory cytokine secreted by a variety of immune cells, has been documented in sarcoidosis [24,25]. In mouse models of mycobacterial infection, TNF- $\alpha$  and IFN- $\gamma$  appear to drive granuloma formation, and inhibition of either of these cytokines results in diminished capacity for granuloma formation [26,27]. Thus, TNF- $\alpha$  has been proposed as a target for therapy in sarcoidosis, and the use of TNF- $\alpha$  inhibitors has been investigated for the treatment of sarcoidosis, but results of clinical trials are conflicting [28]. Understanding the role of TNF- $\alpha$  in the pathophysiology of sarcoidosis and TNF- $\alpha$  inhibitors as potential therapeutic agents is further complicated by multiple cases of paradoxical development of granulomatous disease following therapy with TNF- $\alpha$  inhibitors that have been reported [29].

Another key feature of the immunologic response in sarcoidosis is illustrated by the finding that at sites of inflammation in sarcoidosis, T cells exhibit a restricted T cell receptor (TCR) repertoire, shown to be consistent with oligoclonal expansion, strongly suggesting an antigen-specific response [12,30-33]. The Kveim test, now seldom used clinically, can offer further immunologic insight. Intradermal injection of the Kveim reagent (consisting of spleen or lymph node extracts from sarcoidosis patients) induces localized granuloma formation in 50 percent to 80 percent of sarcoidosis patients early in the disease process [34]. Furthermore, the site of the Kveim reaction is also infiltrated by CD4+ T cells with restricted TCR heterogeneity [35]. BAL or peripheral blood monocyte preparations are also capable of inducing a similar reaction [36]. These findings strongly support that sarcoidosis is caused by an antigen-specific immune response, with mononuclear phagocytes possibly responsible for systemic dissemination of the responsible agent.

In contrast to the previously described immune response present locally at sites of inflammation, a paradoxical state of anergy in the periphery exists, as evidenced by de-

creased responses to delayed cutaneous hypersensitivity tests, as well as decreased lymphocyte counts in the peripheral blood of sarcoidosis patients, especially during periods of increased disease activity [37,38]. The mechanism of this peripheral anergy is unclear, although it appears that T regulatory cells may play an important role [39].

Given the immune profile previously described and evidence supporting a familial predisposition to sarcoidosis, the immunogenetic background of sarcoidosis patients has been heavily studied. Alleles of genes involved in antigen presentation, cell signaling, and other immune functions have been reported to influence susceptibility to the disease, as well as disease course and prognosis. Multiple human leukocyte antigen (HLA) gene alleles have most consistently been shown to be linked to sarcoidosis. Non-HLA genes associated with sarcoidosis also include cytokine (notably TNF gene polymorphisms), toll-like receptor, chemokine receptor genes, and others [5,6]. These observations suggest that aberrations at multiple levels of the immune response may lead to the disease and that immunogenetic variability may account for the heterogeneity of disease manifestations and course. Notably though, with the exception of TNF and HLA, candidate-gene association studies of immune-related genes showing positive associations in populations have not been widely replicated [40]. This may signify that the genetic background that confers susceptibility to sarcoidosis differs between different populations, thus accounting (most likely in combination with environmental factors) for geographic and racial variation in disease incidence and phenotype.

## POTENTIAL INFECTIOUS PATHOGENS

One enduring etiologic hypothesis for sarcoidosis is that of an infectious etiology. Multiple pathogens have been investigated and implicated in the etiology of sarcoidosis, mainly *Mycobacterium*, although other microbial agents also have been suggested

to play a role. Furthermore, findings of the ACCESS study support that conditions of possible exposure to microbial bioaerosols are associated with sarcoidosis [7]. The immunologic features typical of sarcoidosis also support this infectious etiologic hypothesis, but the evidence for specific pathogens varies significantly.

### *Mycobacterium*

*Mycobacterium* has been the longest hypothesized and most investigated potential etiology of sarcoidosis, due to the histologic similarity between tuberculosis and sarcoidosis. Cultures and acid-fast stains of sarcoid specimens classically do not demonstrate the presence of mycobacterial organisms. Some immunohistochemical studies have demonstrated possible cell wall deficient mycobacterial remnants [41]. The mycobacterial cell wall component tuberculostearic acid has been identified in some specimens [42]. However, these findings have not been widely confirmed. Nonetheless, the use of techniques such as polymerase chain reaction (PCR) and enzyme-linked immunospot assay (ELISPOT) have demonstrated increasing evidence supporting a role of *Mycobacterium* in sarcoidosis. Studies investigating the presence of mycobacterial DNA or RNA in sarcoidosis tissue have yielded positive results in a range from 0 to 80 percent of specimens. Meta-analyses of such studies suggests that in 26 percent of sarcoidosis tissues, there is evidence of mycobacterial nucleic acid, insinuating a connection between sarcoidosis and mycobacterial infection, a 9- to 19-fold increased odds compared to non-sarcoidosis controls [43]. More recent studies have identified *Mycobacterium tuberculosis* DNA for the protein mKatG (*Mycobacterium tuberculosis* catalase-peroxidase protein) in 38 percent of biopsy specimens and evidence for circulating IgG to mKatG in almost half of sarcoid patients investigated [44]. Furthermore, sarcoidosis patients have an increased frequency of peripheral blood and lung T-cell responses to mKatG and other mycobacterial antigens compared to healthy controls [45,46]. The lack of active mycobacterial infection in sarcoidosis patients, either pre- or

post-diagnosis, may suggest a sarcoid-like reaction rather than presence of an active or latent infection following exposure to the organism [47]. However, it must be borne in mind that the mere presence or detection of mycobacterial antigens within sarcoid specimens does not substantiate proof of any causal relationship. Also, it is difficult to reconcile *Mycobacterium* as the sole “cause” of sarcoidosis, given that mycobacterial nucleic acid or other mycobacterial antigens are not detected in many sarcoid specimens. On the other hand, with multiple studies utilizing different methods substantiating an association between mycobacterial exposure and sarcoidosis, a plausible hypothesis is that, in a subset of patients, mycobacterial organisms are an important contributing factor to the pathogenesis of the disease.

### *Propionibacterium*

*Propionibacterium acnes*, a commensal bacterium predominantly of the cutaneous flora, is another organism that has been implicated in sarcoidosis. Notably, it has been shown that it is capable of inducing a granulomatous reaction in some experimental models [48]. *P. acnes* has been cultured from up to 78 percent of sarcoidosis samples, a finding that has been confirmed by different groups [49,50]. Additional evidence for a pathogenic role is that an antibody response to a *P. acnes* protein has been demonstrated in 40 percent of sarcoidosis samples obtained through BAL, as compared to 5 percent in healthy controls [51]. However, this commensal organism also has been found in a large proportion of control tissues (up to 57 percent) [52]. This calls into question the role of *P. acnes* as a true pathogenic organism in sarcoidosis, but interactions may exist between *P. acnes* and other factors to promote inflammation in sarcoidosis.

### *Viruses and other infectious pathogens*

Viral infection has been proposed as a possible initiating factor in sarcoidosis with several different viruses being implicated based on serologic evidence, notably the herpes viruses [53]. An important limitation of this hypothesis is that viruses are not

known to cause the epithelioid granulomas typical of sarcoidosis [47]. While antibodies to a variety of these viruses have been demonstrated in sarcoidosis patients, there is also a significant proportion of the general population with previous exposure to these organisms. Also, non-specific polyclonal hypergammaglobulinemia is a feature of sarcoidosis and may account for increased antibody titers to these viruses [54]. While antibody-antigen complexes could hypothetically serve as a trigger for granuloma formation, this has never been demonstrated with respect to viruses. Molecular mimicry following virus exposure also lacks a known mechanism for granuloma formation, making this a less likely pathogenesis.

Other pathologic organisms, especially cell wall deficient forms of mycobacteria, have been implicated, predominantly through case report observations, but none have been widely confirmed. Recently, the ACCESS study identified these organisms in healthy controls as frequently as in sarcoidosis patients, calling into question any potential link with sarcoidosis [55].

### *Active vs. latent infection*

If the etiology of sarcoidosis is truly related to an infectious agent, a key question is whether this is an active or latent infection or, alternatively, whether sarcoidosis represents an aberrant reaction to remnants of a previously, but only partially, cleared organism. An important clue regarding these questions is the successful use of (often chronic) corticosteroids and other immunosuppressive therapies in the management of sarcoidosis. Despite proposed evidence for the role of an underlying latent infection in sarcoidosis, patients generally do not demonstrate any increased risk of mycobacterial disease or other opportunistic infections while receiving such therapies [47,56]. Additionally, for the most part, antimicrobials have not been shown to be helpful in the management of sarcoidosis, with the exception of tetracyclines and antimalarials, which have a limited role in the treatment of cutaneous sarcoidosis. However, these particular antimicrobials also have anti-inflam-

matory properties unrelated to their antimicrobial mechanisms of action and generally do not mitigate the need for concomitant corticosteroid therapy for the treatment of the systemic aspects of sarcoidosis [57,58].

Although these findings make an active infection seem unlikely in sarcoidosis, there is evidence that sarcoidosis may be transmissible. Bone marrow transplants from patients with sarcoidosis have resulted in granulomatous inflammation in recipients [59,60]. Donor macrophages also have been shown to be the origin of granulomatous inflammation in the allograft of a heart transplant recipient who subsequently developed recurrent cardiac sarcoidosis [61]. While these examples do not directly indicate active infection, they do suggest that the inciting agent in sarcoidosis may be an antigen contained within mononuclear phagocytes. One plausible explanation of these phenomena is that the immune system effectively overcomes an inciting infection, but is unable to completely clear the organism, leaving behind organism remnants (which may be intracellular) to serve as antigens and potentially act as niduses for granuloma formation.

## NON-INFECTIOUS ETIOLOGIES

There are several proposed non-infectious causes for sarcoidosis, notably exposures to various environmental agents. Multiple environmental and occupational exposures have been reported to confer increased risk of sarcoidosis, including organic dusts, solvents, mold/mildew, pesticides, wood stoves, and others [1,7,8,62]. Also of interest is the fact that in the first year following the World Trade Center disaster, New York City firefighters developed sarcoidosis at significantly higher than normal rates [63]. Some of these exposures however, are associated with increased environmental microbe exposure and thus are not specific for non-infectious agents. The ACCESS study identified modestly positive and negative relationships between multiple exposures and sarcoidosis, but a puzzling finding was that occupational metal dust/metal fume ex-

posures were associated with decreased risk of sarcoidosis in the study group, especially in light of the fact that exposures to metals such as beryllium are known to cause pulmonary granulomas that are histologically identical to those observed in sarcoidosis [7,8,64,65].

Known exposure-related granulomatous disorders (e.g., berylliosis) are considered separate from sarcoidosis, but the role of yet unidentified organic or inorganic dusts as potential etiologic agents in sarcoidosis remains possible. One hypothesis is that sarcoidosis may be caused by a dysregulated immune response to nanoparticles (<1µm) derived from common metals and minerals in the environment [66]. It is proposed that due to their size, their presence cannot be reliably demonstrated in sarcoid lesions with available methods. The shortcomings of dusts as a sole cause of sarcoidosis are primarily related to the extra-pulmonary manifestations of sarcoidosis, since extra-pulmonary organ involvement is not a prominent feature of berylliosis or other known dust exposures.

## CONCLUSIONS

Despite advances in our understanding of the pathophysiology of sarcoidosis, definitive etiologic agents or specific pathophysiologic mechanisms underpinning this disorder remain elusive. Furthermore, there have been no definitive, reproducible trials allowing clarification of such issues. It is clear, though, that sarcoidosis develops in individuals with an immunogenetic predisposition to the disease, many occupational and environmental exposures confer an increased risk for developing sarcoidosis, and the underlying inflammatory process is an antigen-driven, strongly polarized Th1 immune response. A large body of evidence supports the role of a mycobacterial organism and possibly of *P. acnes*, but few other organisms have been as heavily studied. This supports that infections do participate in the pathogenesis of sarcoidosis, but the exact role infections play in the underlying mechanism of disease remains to be elucidated. Aside from establishing a direct

causal relationship with any specific pathogen, one possibility is that there are multiple triggers required for the development of sarcoidosis, such as a preceding viral infection that primes an overactive immune response, which then responds to a secondary microbial organism or environmental agent, with a subsequent granulomatous reaction.

The inability to identify a single "cause" of sarcoidosis, as well as the wide variability of disease course and manifestations, suggests that sarcoidosis may represent a heterogeneous spectrum of disorders, caused by a complex interplay of a variety of host factors, infectious processes, and non-infectious environmental exposures that results in a final common pathway to systemic granulomatous inflammation. A plausible hypothesis is that multiple different antigens, when introduced to a host with a susceptible genetic background and appropriate immunologic milieu, may be capable of inducing this aberrant immune response. Further studies are necessary to understand the etiology of sarcoidosis, and we are hopeful that future work will help unravel the pathophysiology of this highly complicated and mysterious disorder.

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