Etiology of Sarcoidosis: Does Infection Play a Role?

Shiv Saidha, MRCPI\textsuperscript{a}, Elias S. Sotirchos, MD\textsuperscript{a}, Christopher Eckstein, MD\textsuperscript{b}\textsuperscript{*}

\textsuperscript{a}Richard T. Johnson Division of Neuroimmunology and Neurological Infections, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland; \textsuperscript{b}Division of Neuroimmunology, Department of Neurology, University of South Alabama College of Medicine, Mobile, Alabama

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

---

\textsuperscript{*To whom all correspondence should be addressed: Dr. Christopher Eckstein, 2451 Fillingim Street, Suite 10F, Mobile, AL 36617, Tel: 251-445-9717, Fax: 251-445-8249, Email: ceckstein@usouthal.edu.}

\textsuperscript{†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.}

Keywords: sarcoidosis, etiology, immunology, Mycobacterium, infection
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/μL. 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-γ, IL-2, IL-12, TNF-α, 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-γ production and thus plays a key role in the immune response of sarcoidosis. Furthermore, administration of IL-2 or IFN-α (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-γ 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-α), 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-α and IFN-γ appear to drive granuloma formation, and inhibition of either of these cytokines results in diminished capacity for granuloma formation [26,27]. Thus, TNF-α has been proposed as a target for therapy in sarcoidosis, and the use of TNF-α inhibitors has been investigated for the treatment of sarcoidosis, but results of clinical trials are conflicting [28]. Understanding the role of TNF-α in the pathophysiology of sarcoidosis and TNF-α inhibitors as potential therapeutic agents is further complicated by multiple cases of paradoxical development of granulomatous disease following therapy with TNF-α 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, sinuating 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 antimi-
crobial 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 trans-
missible. Bone marrow transplants from pa-
tients with sarcoidosis have resulted in
granulomatous inflammation in recipients
[59,60]. Donor macrophages also have been
shown to be the origin of granulomatous in-
flammation in the allograft of a heart trans-
plant recipient who subsequently developed
recurrent cardiac sarcoidosis [61]. While
these examples do not directly indicate ac-
tive infection, they do suggest that the incit-
ing agent in sarcoidosis may be an antigen
contained within mononuclear phagocytes.
One plausible explanation of these pheno-
mena is that the immune system effectively
overcomes an inciting infection, but is un-
able to completely clear the organism, leav-
ing behind organism remnants (which may
be intracellular) to serve as antigens and po-
tentially act as niduses for granuloma for-
mation.

NON-INFECTIONIOUS ETIOLOGIES

There are several proposed non-infec-
tious causes for sarcoidosis, notably ex-
posures to various environmental agents.
Multiple environmental and occupational ex-
posures have been reported to confer in-
creased 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 fol-
lowing the World Trade Center disaster, New
York City firefighters developed sarcoidosis
at significantly higher than normal rates [63].
Some of these exposures however, are asso-
ciated with increased environmental microbe
exposure and thus are not specific for non-
infectious agents. The ACCESS study iden-
tified modestly positive and negative rela-
tionships 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 pul-
monary 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 po-
tential etiologic agents in sarcoidosis remains
possible. One hypothesis is that sarcoidosis
may be caused by a dysregulated immune re-
sponse to nanoparticulates (<1μm) derived
from common metals and minerals in the en-
vironment [66]. It is proposed that due to
their size, their presence cannot be reliably
demonstrated in sarcoid lesions with avail-
able methods. The shortcomings of dusts as
a sole cause of sarcoidosis are primarily re-
lated 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, de-
finitive etiologic agents or specific patho-
physiologic 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 predis-
position to the disease, many occupational
and environmental exposures confer an in-
creased risk for developing sarcoidosis, and
the underlying inflammatory process is an
antigen-driven, strongly polarized Th1 im-
mune response. A large body of evidence
supports the role of a mycobacterial organ-
ism 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 eluci-
dated. 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.

REFERENCES

1. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007;357(21):2153-65.
2. Rybicki BA, Iannuzzi MC, Frederick MM, Thompson BW, Rossman MD, Bresnitz EA, et al. Familial aggregation of sarcoidosis. A case-control etiologic study of sarcoidosis (ACCESS). Am J Respir Crit Care Med. 2001;164(11):2085-91.
3. Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol. 1997;145(3):234-41.
4. Sverrild A, Backer V, Kyvik KO, Kaprio J, Milman N, Svendsen CB, et al. Heredity in sarcoidosis: a registry-based twin study. Thorax. 2008;63(10):894-6.
5. Smith G, Brownell I, Sanchez M, Prystowsky S. Advances in the genetics of sarcoidosis. Clin Genet. 2008;73(5):401-12.
6. Grunewald J. Review: role of genetics in susceptibility and outcome of sarcoidosis. Semin Respir Crit Care Med. 2010;31(4):380-9.
7. Newman LS, Rose CS, Bresnitz EA, Rossman MD, Barnard J, Frederick M, et al. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. Am J Respir Crit Care Med. 2004;170(12):1324-30.
8. Barnard J, Rose C, Newman L, Canner M, Martyny J, McCammon C, et al. Job and industry classifications associated with sarcoidosis in A Case-Control Etiologic Study of Sarcoidosis (ACCESS). J Occup Environ Med. 2005;47(3):226-34.
9. Rosen Y. Pathology of sarcoidosis. Semin Respir Crit Care Med. 2007;28(1):36-52.
10. Hunninghake GW, Crystal RG. Pulmonary sarcoidosis: a disorder mediated by excess helper T-lymphocyte activity at sites of disease activity. N Engl J Med. 1981;305(8):429-34.
11. Morris DG, Jasmer RM, Huang L, Gotway MB, Nishimura S, King TE Jr. Sarcoidosis following HIV infection: evidence for CD4+ lymphocyte dependence. Chest. 2003;124(3):929-35.
12. Grunewald J, Eklund A. Role of CD4+ T cells in sarcoidosis. Proc Am Thorac Soc. 2007;4(5):461-4.
13. Logan TF, Bensadoun ES. Increased disease activity in a patient with sarcoidosis after high dose interleukin 2 treatment for metastatic renal cancer. Thorax. 2005;60(7):610-1.
14. Rubinowitz AN, Naïdich DP, Alsonorin C. Interferon-induced sarcoidosis. J Comput Assist Tomogr. 2003;27(2):279-83.
15. Moller DR, Forman JD, Liu MC, Noble PW, Greenlee BM, Vyas P, et al. Enhanced expression of IL-12 associated with Th1 cytokine profiles in active pulmonary sarcoidosis. J Immunol. 1996;156(12):4952-60.
16. Antoniou KM, Tzouvelekis A, Alexandrakis MG, Tsiliogiani I, Tzanakis N, Sfridaki K, et al. Upregulation of Th1 cytokine profile (IL-12, IL-18) in bronchoalveolar lavage fluid in patients with pulmonary sarcoidosis. J Interferon Cytokine Res. 2006;26(6):400-5.
17. Macatonia SE, Hosken NA, Litton M, Vieira P, Hsieh CS, Culpepper JA, et al. Dendritic cells produce IL-12 and direct the development of Th1 cells from naive CD4+ T cells. J Immunol. 1995;154(10):5071-9.
18. D’Andrea A, Rengaraju M, Valiante NM, Chehimi J, Kubin M, Aste M, et al. Production of natural killer cell stimulatory factor (interleukin 12) by peripheral blood mononuclear cells. J Exp Med. 1992;176(5):1387-98.
19. Sypek JP, Chung CL, Mayor SE, Subramanyam JM, Goldman SJ, Sieburth DS, et al. Resolution of cutaneous leishmaniasis: interleukin 12 initiates a protective T helper type 1 immune response. J Exp Med. 1993;177(6):1797-802.
20. Hsieh CS, Macatonia SE, Tripp CS, Wolf SF, O’Garra A, Murphy KM. Development of TH1 CD4+ T cells through IL-12 produced by Listeria-induced macrophages. Science. 1993;260(5107):547-9.
21. Gazzinelli RT, Hayashi S, Wysocka M, Carrera L, Kuhn R, Muller W, et al. Role of IL-12 in the initiation of cell mediated immunity by Toxoplasma gondii and its regulation by IL-10 and nitric oxide. J Eukaryot Microbiol. 1994;41(5):98.
22. Locksley RM. Interleukin 12 in host defense against microbial pathogens. Proc Natl Acad Sci USA. 1993;90(13):5879-80.
23. Lammas DA, De Heer E, Edgar JD, Novelli V, Ben-Smith A, Baretto R, et al. Heterogeneity in the granulomatous response to mycobacterial infection in patients with defined genetic mutations in the interleukin 12-dependent interferon-gamma production pathway. Int J Exp Pathol. 2002;83(1):1-20.
24. Baughman RP, Strohofer SA, Buchsbaum J, Lower EE. Release of tumor necrosis factor by alveolar macrophages of patients with sarcoidosis. J Lab Clin Med. 1990;115(1):36-42.
25. Bachwich PR, Lynch JP 3rd, Larrick J, Spencer M, Kunke SL. Tumor necrosis factor production by human sarcoid alveolar macrophages. Am J Pathol. 1986;125(3):421-5.
26. Hansch HC, Smith DA, Mielke ME, Hahn H, Bancroft GJ, Ehlers S. Mechanisms of granuloma formation in murine Mycobacterium avium infection: the contribution of CD4+ T cells. Int Immunol. 1996;8(8):1299-310.
27. Smith D, Hansch H, Bancroft G, Ehlers S. T-cell-independent granuloma formation in response to Mycobacterium avium: role of tumour necrosis factor-alpha and interferon-gamma. Immunology. 1997;92(4):413-21.
28. Morgenthal AS, Iannuzzi MC. Recent advances in sarcoidosis. Chest. 2011;139(1):174-82.
29. Clementine RR, Lyman J, Zakem J, Mallepalli J, Lindsey S, Quinet R. Tumor necrosis factor-alpha antagonist-induced sarcoidosis. J Clin Rheumatol. 2010;16(6):274-9.
30. Grunewald J, Wahlstrom J, Berlin M, Wigzell H, Eklund A, Olerup O. Lung restricted T cell receptor AV283+ CD4+ T cell expansions in sarcoidosis patients with a shared HLA-DRbeta chain conformation. Thorax. 2002;57(4):348-52.
31. Forman JD, Klein JT, Silver RF, Liu MC, Greenlee BM, Moller DR. Selective activation and accumulation of oligoclonal V beta-specific T cells in active pulmonary sarcoidosis. J Clin Invest. 1994;94(4):1533-42.
32. Forrester JM, Wang Y, Ricilton N, Fitzgerald JE, Loveless J, Newman LS, et al. TCR expression of activated T cell clones in the lungs of patients with pulmonary sarcoidosis. J Immunol. 1994;153(9):4291-302.
33. Silver RF, Crystal RG, Moller DR. Limited heterogeneity of biased T-cell receptor V beta gene usage in lung but not blood T cells in active pulmonary sarcoidosis. Immunology. 1996;88(4):516-23.
34. Siltzbach LE. The Kveim test in sarcoidosis. A study of 750 patients. JAMA. 1961;178:476-82.
35. Klein JT, Horn TD, Forman JD, Silver RF, Teirstein AS, Moller DR. Selection of oligoclonal V beta-specific T cells in the intradermal response to Kveim-Siltzbach reagent in individuals with sarcoidosis. J Immunol. 1995;154(3):1450-60.
36. Holter JF, Park HK, Sjoerdsma KW, Kataria YP. Nonviable autologous bronchoalveolar lavage cell preparations induce intradermal epithelioid cell granulomas in sarcoidosis patients. Am Rev Respir Dis. 1992;145(4 Pt 1):864-71.
37. Friou GJ. A study of the cutaneous reactions to oidiomycin, triphophytin, and mumps skin test antigens in patients with sarcoidosis. Yale J Biol Med. 1952;24(6):533-9.
38. Morell F, Levy G, Orriols R, Ferrer J, De Gracia J, Sampol G. Delayed cutaneous hypersensitivity tests and lymphopenia as activity markers in sarcoidosis. Chest. 2002;121(4):1239-44.
39. Miyara M, Amoura Z, Parizot C, Badoual C, Doghram K, Trad S, et al. The immune paradox of sarcoidosis and regulatory T cells. J Exp Med. 2006;203(2):359-70.
40. Chen ES, Moller DR. Sarcoidosis—scientific progress and clinical challenges. Nat Rev Rheumatol. 2011;7(8):457-67.
41. Alavi HA, Moscovic EA. Immunolocalization of cell-wall-deficient forms of Mycobacterium tuberculosis complex in sarcoidosis and in sinus histiocytosis of lymph nodes draining carcinoma. Histol Histopathol. 1996;11(3):683-94.
42. Hann gren A, Odham G, Eklund A, Hoffner S, Stjernberg N, Westerdahl G. Tuberculostearic acid in lymph nodes from patients with sarcoidosis. Sarcoidosis. 1987;4(2):101-4.
43. Gupta D, Agarwal R, Aggarwal AN, Jindal SK. Molecular evidence for the role of mycobacteria in sarcoidosis: a meta-analysis. Eur Respir J. 2007;30(3):508-16.
44. Song Z, Marzilli L, Greenlee BM, Chen ES, Silver RF, Askin FB, et al. Heterogeneity in the granulomatous response to Mycobacterium tuberculosis complex in sarcoidosis and in sinus histiocytosis of lymph nodes draining carcinoma. Histol Histopathol. 1996;11(3):683-94.
45. Drake WP, Dhasilos SN, Nadaf M, Shepherd BE, Vadivelu S, Hajizadeh R, et al. Cellular recognition of Mycobacterium tuberculosis ESAT-6 and KatG peptides in systemic sarcoidosis. Infect Immun. 2007;75(1):527-30.
46. Oswald-Richter KA, Beachboard DC, Zhan X, Gaskill CF, Abraham S, Jenkins C, et al. Multiple mycobacterial antigens are targets of the adaptive immune response in pulmonary sarcoidosis. Respir Res. 2010;11:161.
47. Chen ES, Moller DR. Etiology of sarcoidosis. Clin Chest Med. 2008;29(3):365-77, vii.
48. Minami J, Eishi Y, Ishige Y, Kobayashi I, Ishige I, Kobayashi D, et al. Pulmonary granulomas caused experimentally in mice by a recombinant trigger-factor protein of Propionibacterium acnes. J Med Dent Sci. 2003;50(4):265-74.
49. Eishi Y, Suga M, Ishige I, Kobayashi D, Yamada T, Takemura T, et al. Quantitative analysis of mycobacterial and propionibacterial DNA in lymph nodes of Japanese and European patients with sarcoidosis. J Clin Microbiol. 2002;40(1):198-204.
50. Homma JY, Abe C, Chosa H, Ueda K, Sae- gusa J, Nakayama M, et al. Bacteriological investigation on biopsy specimens from patients with sarcoidosis. Jpn J Exp Med. 1978;48(3):251-5.
51. Hiramatsu J, Kataoka M, Nakata Y, Okazaki K, Tada S, Tanimoto M, et al. Propionibacterium acnes DNA detected in bronchoalveolar lavage cells from patients with sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2003;20(3):197-203.
52. Iishi Y, Eishi Y, Takemura T, Kobayashi I, Nakata K, Tanaka I, et al. Propionibacterium acnes is the most common bacterium commensal in peripheral lung tissue and mediastinal lymph nodes from subjects without sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2005;22(1):33-42.
53. Nikoskelainen J, Hannukela M, Palva T. Antibodies to Epstein-Barr virus and some other herpesviruses in patients with sarcoidosis, pulmonary tuberculosis and erythema nodosum. Scand J Infect Dis. 1974;6(3):209-16.
54. Mitchell DN, McSwiggan DA, Mikhail JR, Heimer GV, Sutherland I. Antibody to herpes-like virus in sarcoidosis. Am Rev Respir Dis. 1975;111(6):880-2.
55. Brown ST, Brett I, Almenoff PL, Lesser M, Terrin M, Teirstein AS. Recovery of cell wall-deficient organisms from blood does not distinguish between patients with sarcoidosis and control subjects. Chest. 2003;123(2):413-7.
56. Fite E, Fernandez-Figueras MT, Prats R, Querol M, Morera J. High prevalence of Mycobacterium tuberculosis DNA in biopsies from sarcoidosis patients from Catalonia, Spain. Respiration. 2006;73(1):20-6.
57. Labro MT. Antibiotics as anti-inflammatory agents. Curr Opin Investig Drugs. 2002;3(1):61-8.
58. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. J Am Acad Dermatol. 2006;54(2):258-65.
59. Heyll A, Meckenstock G, Aul C, Sohngen D, Borchard F, Hadding U, et al. Possible transmission of sarcoidosis via allogeneic bone marrow transplantation. Bone Marrow Transplant. 1994;14(1):161-4.
60. Sundar KM, Carveth HJ, Gosselin MV, Beatty PG, Colby TV, Hoidal JR. Granulomatous pneumonitis following bone marrow transplantation. Bone Marrow Transplant. 2001;26(6):627-30.
61. Padilla ML, Schileri GJ, Teirstein AS. Donor-acquired sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2002;19(1):18-24.
62. Kajdasz DK, Lackland DT, Mohr LC, Judson MA. A current assessment of rurally linked exposures as potential risk factors for sarcoidosis. Ann Epidemiol. 2001;11(2):111-7.
63. Izbicki G, Chavko R, Banauch GI, Aldrich TK, et al. World Trade Center "sarcoid-like" granulomatous pulmonary disease in New York City Fire Department rescue workers. Chest. 2007;131(5):1414-23.
64. Drent M, Bomans PH, Van Suylen RJ, Lamers RJ, Bast A, Wouters EF. Association of man-made mineral fibre exposure and sarcoid-like granulomas. Respir Med. 2000;94(4):815-20.
65. Rossman MD, Kreider ME. Is chronic beryllium disease sarcoidosis of known etiology? Sarcoidosis Vasc Diffuse Lung Dis. 2003;20(2):104-9.
66. Heffner DK. The cause of sarcoidosis: the Centurial enigma solved. Ann Diagn Pathol. 2007;11(2):142-52.