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Granuloma genes in sarcoidosis – what's new?

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Abstract

Purpose of review—Non-necrotizing granulomas in the affected organ are the hallmark of sarcoidosis. This review summarizes most recent genetic findings in sarcoidosis with a focus on genes that might influence granuloma formation or resolution. Specific results in multiple ethnic groups and certain clinical subphenotypes, such as extra-pulmonary organ involvement, are discussed.

Recent findings—Associations of genetic variants in antigen-presenting molecules (*HLA-DRB1*) were shown to confer risk to sarcoidosis and certain disease phenotypes in populations of different ethnic origin. Specific *DRB1* alleles, such as *0301 and *0302, appear to confer protection against chronic disease, but in an ethnic-specific manner illustrating the extensive genetic heterogeneity and complexity at this locus. Mechanistic studies of putative sarcoid antigens lend further credence to a role of *HLA-DRB1* in disease pathogenesis. With relevance to granuloma formation, genes involved in apoptotic processes and immune cell activation were further confirmed (*ANXA11* and *BTNL2*) in multiple ethnicities; others were newly identified (*XAF1*). Linking mechanism to clinical application, a *TNF* variant was shown to correlate with anti-TNF response in sarcoidosis patients.

Summary—The investigation of known and novel risk variants for sarcoidosis and specific clinical phenotypes in various ethnicities highlights the genetic complexity of the disease. Detailed subanalysis of disease phenotypes revealed the potential for prediction of extra-pulmonary organ involvement and therapy response based on the patient's genotype.

Keywords

HLA; apoptosis; prediction; antigens; clinical phenotype

Introduction

In the recent years, our knowledge on the genetic background of sarcoidosis has grown substantially due to modern technology allowing genome-wide association mapping and the investigation of large-size populations of different ethnicities. Many of these sarcoidosis risk variants are assumed to influence the formation of granulomatous structures in the affected

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Conflicts of interest

No conflict of interest exists.

organ, a hallmark of sarcoidosis pathogenesis. This review summarizes most recent genetic findings in sarcoidosis, with a focus on granuloma-relevant factors including HLA-alleles.

1. T cell activation through HLA-alleles

One important aspect in granuloma formation is the activation of T cells by antigen-presenting cells through a molecular interaction of the T cell receptors and antigen presenting molecules. The latter are genetically encoded in the HLA region on chromosome 6p21.3, which is characterized by extreme genetic diversity. Over 7000 specific combinations of HLA variants, so-called HLA-haplotype alleles, are known today ¹. This great diversity evolved as an adaptation to disease pathogens, since allelic variation resulted in HLA molecules with different binding affinities for pathogenic targets. The world-wide distribution of HLA-alleles reflects migration patterns as well as pathogen-driven balancing selection (reviewed in ²). Until recently, the identification of HLA-alleles carried by an individual was costly, applying Sanger sequencing based typing. Imputation of HLA-alleles from genome-wide genotype data as well as next generation sequencing methods now allow for a higher-throughput HLA-typing at lower cost ³⁻⁵.

Certain HLA-alleles are well-known to influence susceptibility to sarcoidosis and disease course (reviewed in ⁶). Of those, *HLA-DRB1*-alleles confer the highest risks on the population level. An excerpt of known HLA-associations with sarcoidosis and its subphenotypes is given in Table 1, with a focus on risk alleles and recent reports comprising rather large study populations.

2. Diagnostic value of HLA information

Besides its functional role in the pathogenesis of sarcoidosis, HLA alleles have potential to aid clinical decisions with regards to sarcoidosis subphenotypes. Extra-thoracic manifestations as well as the course of the disease are associated with specific HLA alleles. For instance, variation at the *HLA-DRB1* locus is associated with disease course ^{13, 18-22} and organ-specific involvement ^{8, 11} in sarcoidosis. Grunewald et al. demonstrated that 95% of *03-positive patients with Löfgren's syndrome experienced disease resolution within two years, whereas disease resolved for only half of *03-negative patients ¹⁴. Subsequent work by Grunewald and his group showed that *DRB1**14 and *DRB1**15 tended to increase the risk for a non-resolving disease, but *DRB1**14 had a more pronounced effect on non-Löfgren syndrome patients, whereas *DRB1**15 has a greater effect on Löfgren syndrome patients with *DRB1**03 predominating over *DRB1**15 in terms of increasing the likelihood of resolving disease ⁹. Interestingly, in a Han Chinese population, it was *HLA-B**51, not *DRB1**03, that most strongly associated with Löfgren syndrome ⁷, suggesting that the *DRB1**03 association with acute disease may be specific to European populations.

Until recently, *DRB1* associations with sarcoidosis phenotypes have never been evaluated in African Americans. Levin et al. examine *DRB1* variation in the context of disease phenotype in 1,277 African Americans patients and 1,468 controls ¹². They found that the *DRB1**03:02 allele conferred a similar likelihood of resolving disease in African American sarcoidosis patients as *03:01-positivity does in Europeans ¹⁴. While the *DRB1**03:01 allele is found less frequently in African Americans ¹¹, the *03:02 allele could have similar clinical

implications as the *03:01 allele in sarcoidosis patients of European ancestry²³. Since *HLA* genes are known to be inherited in haplotype blocks, information about the ancestral background at a *HLA* locus may include more than the risk effect of an allele at that locus. In analyses stratified by local ancestry Levin et al. found that the associations of *HLA-DRB1**03:01 and *03:02 with susceptibility and *DRB1**03:01 with persistent disease were dependent on local ancestry (European or African) at *DRB1*. Replication of *DRB1**03:02 association with resolving disease in African American sarcoidosis patients is needed before any conclusions can be made about its potential impact on disease course.

Levin et al. further showed carriage of *DRB1**03:01 decreased risk for extra-pulmonary manifestations of sarcoidosis in non-thoracic lymph nodes, eyes, skin and liver¹². Alternatively, carriage of *DRB1**03:02 increased risk for skin involvement in African American sarcoidosis patients. In a Scandinavian population, Darlington et al. showed that non-Löfgren syndrome sarcoidosis patients more frequently than Löfgren syndrome patients have extra-pulmonary involvement¹⁶. While this in itself is not a novel finding, the investigators found unique associations with *HLA-DRB1* alleles and risk of extra-thoracic disease manifestations depending upon Löfgren syndrome status. In Löfgren syndrome patients, *DRB1**03 significantly decreased risk for extra-thoracic disease, but in non-Löfgren syndrome patients it was carriage of *DRB1**11, *13, or *14 that decreased risk for extra-thoracic disease and carriage of *DRB1**04 that increased risk for extra-thoracic disease.

As was discussed earlier, ethnicity clearly plays a role in *HLA-DRB1* associations. This is further evidenced by the study of Ozyilmaz et al. who found *DRB1**11 also significantly decreased risk for extra-thoracic disease in a Turkish population¹⁰, in agreement with findings of Darlington et al. in Scandinavian non-Löfgren cases. A nation-wide study of tissue confirmed sarcoidosis in Iceland from 1981 to 2004 found several different significant associations between *HLA* alleles and sarcoid-related arthritis¹⁵. *HLA-B8* and *-B14* were more common among those who suffered from sarcoid arthritis as was carriage of the *HLA-DRB1**03 allele. Alternatively, the *HLA-DRB1**04 allele was significantly less common in sarcoid arthritis sufferers. This is in contrast to the findings of Darlington et al. in terms of *DRB1**04 increasing risk for extra-thoracic disease in Scandinavians. Sato et al.⁸ showed that over 40 percent of English patients that suffer from sarcoid uveitis carry the *DRB1**04 allele. The risk for uveitis for *DRB1**04 carriers is even higher in the Japanese, but because this allele is much less frequent in the Japanese population, the vast majority of sarcoidosis uveitis patients carry other *DRB1* alleles. In general, *HLA* genotype and predicting sarcoid organ involvement is confounded by ethnicity and the attendant genetic background.

3. HLA Class II antigens

Crucial for granuloma formation is the existence and the presentation of an antigen(s) that initiates this process. The class II molecules, such as *HLA-DRB1*, bind peptides on the surface of antigen-presenting cells, which are subsequently recognized by CD4+ T cells. The capacity of docking an antigenic peptide depends on genetically encoded polymorphic residues in the binding pockets^{24, 25}. Investigators have therefore performed studies to

identify the sarcoidosis antigen(s) with a strong binding affinity to specific HLA class II DR epitopes.

In sarcoidosis, T cell-mediated immune responses to mycobacterial antigens have been shown to be dependent upon *DRB1* genotype ²⁶. *In silico* predictions of peptide binding affinities ²⁷ can be used to predict which *DRB1* allele/antigen combinations are likely to initiate the most robust immune response. For example, an *in silico* analysis found that patients with Löfgren's syndrome express *HLA-DR* alleles capable of binding a significantly higher number of bacterial epitopes than other *HLA-DR* alleles ²⁸. Interestingly, *DRB1**03:01, shows the highest predicted binding to *M. tuberculosis* epitopes ²⁹. Given the affinity for *03:01 encoded epitopes to bind to *M. tuberculosis*-derived peptides, a potential model for exposure to this antigen involving effective clearance and subsequent self-limiting Löfgren's disease would seem very credible.

Mechanistic studies have provided additional insight into variation at the HLA class II loci and immune response to putative sarcoidosis antigens. ESAT-6 is a secretory protein and potent T cell antigen produced by *M. tuberculosis*. A high percentage of sarcoidosis patients appear to have been previously exposed to ESAT-6, as evidenced by a positive T-cell response to different ESAT-6 peptides ³⁰. *HLA-DRB1**1101 is a known sarcoidosis risk allele in both Europeans and African Americans ¹¹. Oswald-Richter et al. showed that carriage of *DRB1**1101 was strongly associated with a more robust Th1-response upon exposure to ESAT-6 in both European and African American sarcoidosis patients ²⁶. These findings lay the ground work for gene-environment studies focused on HLA genotypes and targeted antigens known to elicit Th-1 immune responses observed in sarcoidosis.

Another similar line of mechanistic research has used patients that are positive for the *HLA-DRB**03 genotype to study self-antigens that can sustain an inflammatory response in lungs. Wahlstrom et al. ³¹ used lung cells from 16 *HLA-DRB1**0301-positive patients obtained by bronchoalveolar lavage and identified 78 amino acid sequences from self-proteins presented in the lungs of sarcoidosis patients, some of which were well-known auto-antigens such as vimentin and ATP synthase. Subsequent work by this same group examined the antigenic potential of these self-antigens, and found in peripheral blood that strong T cell responses to a peptide derived from the cytoskeletal protein vimentin was present in a majority of *DRB1**0301 positive patients with active disease, but not in patients with other HLA types ³². While the importance of *HLA-DRB1**0301 in acute sarcoidosis cannot be understated, given that most sarcoidosis patients are not *DRB1**0301 positive, further work is needed to better understand the antigens with high binding affinity to other sarcoid-*DRB1* associated alleles that might subsequently stimulate an active immune response.

4. Other granuloma-promoting genetic factors

Genome-wide genetic screening approaches revealed a number of novel susceptibility factors for sarcoidosis, some of which are very likely to affect granuloma formation. A splicing variant in the *BTNL2* gene had first been reported with regards to sarcoidosis by Valentonyte et al. in a German study sample ³³. The protein functions as a negative co-stimulator in T cell activation. In mice, it was shown that *BTNL2* controls mucosal inflammation by promoting FOXP3 expression and thereby the development of regulatory T

cells³⁴. The genetic association of the *BTNL2* variant with sarcoidosis has been confirmed in various populations, including African Americans and Japanese^{17, 35-41}. Most recently, the association was confirmed in a Greek population of 146 sarcoidosis patients and 90 controls⁴². Sequencing of the coding and neighboring intronic regions of the *BTNL2* gene in these individuals revealed the existence of 37 different variants, of which 12 were synonymous and 25 non-synonymous substitutions. Thirteen of the 37 variants were predicted to affect gene function, including four yet unknown variants. In light of the small sample size in this study, it remains to be elucidated, whether one or several of these variants confer additional independent genetic effects.

Annexin 11 is a protein involved in the regulation of apoptosis⁴³ and might influence the stability of sarcoid granulomas. Based on a genome-wide association study (GWAS), variants in the *ANXA11* gene which codes for Annexin 11 were found to be associated with sarcoidosis⁴⁴ and confirmed in independent populations of German, Czech, Portuguese and European and African American origin^{37, 45-48}. Evidence has recently been substantiated by a report on *ANXA11* variants being associated in a Han Chinese population of 412 patients and 418 healthy controls⁴⁹. In a tagging-SNP approach Feng et al. investigated 29 high frequency SNPs (MAF > 0.2) in the *ANXA11* gene region and found significant differences in the allele frequency for three variants. Consecutive multi-SNP modeling showed that the non-synonymous SNP rs1049550 (R230C) completely explains this association, while rs2789679 and rs2819941 did not represent independent signals in this population.

In a sarcoidosis admixture linkage scan, nine regions were suggested to be linked to either West African or European ancestry⁵⁰. Most recently, a refined analysis of those regions by Levin et al. showed the most significant sarcoidosis admixture linkage to a non-HLA loci on chromosome 17p13.1-13.3 could be explained by one SNP, rs6502976, that accounted for the majority of the admixture linkage signal in the region⁵¹. SNP rs6502976 is located in intron 5 of the *XAF1* gene region and is suggested to influence transcriptional expression of *XAF1*, which is a negative regulator of *XIAP*. The *XIAP/XAF1* pathway is known to be involved in apoptotic mechanisms. For sarcoidosis, a differential expression patterns of *XAF1* and *XIAP* in granulomas suggest that this pathway may play a role in granuloma maintenance⁵¹. Due to its novelty, this genetic finding now awaits replication in independent study populations and further functional exploration.

Most thoroughly investigated in candidate gene studies on sarcoidosis, the tumor necrosis factor (*TNF*) gene encodes a well-known pro-inflammatory cytokine that acts on macrophage activation, promotion of cellular migration towards the site of inflammation and leukocyte adhesion (reviewed in⁵²). Further, *TNF* is targeted in sarcoidosis therapy by *TNF*-antibodies, such as infliximab or adalimumab. Summarizing twelve sarcoidosis case-control studies, a very recent meta-analysis including 3,218 participants highlighted the *TNF*-308G/A variant being associated in populations of Asian and Caucasian ethnicity and in sarcoidosis with Löfgren syndrome⁵³, with the A allele conferring increased risk. Regarding the clinically important subphenotype of cardiac sarcoidosis, a very recent publication in a Greek population of 173 patients reported the A allele being significantly associated⁵⁴. This is in line with a long-standing finding in Japanese sarcoidosis patients⁵⁵. The same polymorphism was reported to correlate with the response to *TNF*-inhibitor

treatment⁵⁶. Wijnen et al. followed 111 patients receiving TNF-inhibitor treatment for at least one year. They found that for patients with the GG-genotype, the probability of improving compared with remaining stable or deteriorating was three times higher (risk ratio = 3.09) than in carriers of the A allele. In case of a successful replication, we expect that this finding will be of high importance in clinical management.

Granuloma formation in sarcoidosis might be influenced by a number of additional risk variants, e.g. in the *IL23R* and *NOTCH4* gene regions or in genes encoding toll-like receptors. However since these findings had been reported and reviewed previously⁶, they will not be discussed in detail here.

5. Conclusion

Granuloma formation in sarcoidosis is a complex phenomenon that is most likely influenced by genetic sarcoidosis risk factors in several aspects. As illustrated by this review, antigen presentation (*HLA-DRB1*), immune cell activation (*BTNL2*, *TNF*, *IL23R*) and regulation of apoptosis (*ANXA11*, *XAF1*) might be key players. As demonstrated for HLA class II associations, further investigation of subclassifications of disease phenotypes may provide deeper insights into genetically determined mechanisms that steer the disease pathophysiology down a certain pathway – including the interaction of multiple genes in a pathway - hopefully leading to more targeted and effective disease therapies. While studies of multiple ethnic groups increases the complexity of sarcoidosis genetics, they at the same time can help us to better understand the underlying genetic heterogeneity of certain disease phenotypes. The challenge that lies ahead is teasing apart the genetic heterogeneities that exist across ethnic groups to make a more complete picture of the genetic landscape of this disease and to understand its role in disease pathogenesis. This knowledge can be applied in the upcoming era of precision medicine where a patient's genotype will be an important determinant of his or her treatment strategies.

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Key points

- Granulomatous processes in sarcoidosis are assumed to be influenced by genetic risk factors at the level of antigen-presentation (HLA class II genes), immune cell activation (*TNF*, *BTNL2*, *IL23R*) and apoptosis (*ANXA11*, *XAF1*).
- Genetic associations in sarcoidosis are partly phenotype-specific and depend on the ethnic background of an individual.
- Variants in granuloma-relevant genes may be applied for the prediction of disease phenotype and therapy response in sarcoidosis.

Table 1

HLA-associations with sarcoidosis and its subphenotypes (LS: Löfgren syndrome; EPM: extra-pulmonary manifestation)

Locus	Allele	Phenotype	OR	Reference reporting association	N with phenotype	N without phenotype	N controls	Ethnicity/ Nation
HLA-B	*51	LS	11.11	7	22		122	China
DQB1	*0201	LS	12.50	8	47		218	Dutch
	*0201	LS	17.40	8	47	92		Dutch
DQB1	*0503/4	Sarcoidosis	2.55	8	340		354	UK
	*0503/4	Lung sarcoidosis	2.80	8	233		354	UK
	*0503/4	Lung sarcoidosis	4.40	8	78		218	Dutch
DRB1	*01	Resolving	2.44	9	325	399		Sweden
	*11	Sarcoidosis	6.25	7	131		122	China
	*11	EPM	0.36	10	39	52		Turkey
	*1101	Sarcoidosis	1.98	11	474		474	Mixed US
	*1101	Sarcoidosis	1.69	12	1277		1467	African Americans
	*1101	Persistent	1.41	12	624		308	African Americans
	*12	Sarcoidosis	3.71	8	340		354	UK
	*12	Lung sarcoidosis	4.20	8	233		354	UK
	*12	Lung sarcoidosis	5.30	8	37		168	Japan
	*1201	Sarcoidosis	2.13	11	474		474	Mixed US
	*1201	Sarcoidosis	2.06	12	1277		1467	African Americans
	*14	Sarcoidosis	1.79	9	754		1366	Sweden
	*1401/2	Sarcoidosis	2.54	8	340		354	UK
	*1401/2	Lung sarcoidosis	2.70	8	233		354	UK
	*15	Sarcoidosis	2.37	10	91		145	Turkey
	*1501	Sarcoidosis	1.70	11	474		474	Mixed US
	*1501	Sarcoidosis	1.67	13	188		150	Finland
	*03	Resolving in LS	79.98	14	223	45		Sweden
	*03	LS	12.50	8	47		218	Dutch
	*03	LS	18.60	8	47	92		Dutch
	*03	Sarcoidosis	1.91	9	754		1366	Sweden
	*03	Resolving	5.42	9	325		1366	Sweden
	*03	Resolving	2.22	9	325	399		Sweden
	*03	Löfgren	6.71	9	302		1366	Sweden
	*03	Sarcoid arthritis	3.17	15	39		544	Iceland
	*0301	Resolving	2.22	13	90	98		Finland
	*0301	Sarcoidosis	0.56	12	1277		1467	African Americans
	*0302	Resolving	1.92	12	308	624		African Americans

Locus	Allele	Phenotype	OR	Reference reporting association	N with phenotype	N without phenotype	N controls	Ethnicity/ Nation
	*04	EPM in non-LS	2.35	16	257	360		Sweden
	*04	Sarcoid arthritis	0.27	15	39		544	Iceland
	*0803	Sarcoidosis	2.43	17	237		287	Japan