Identifying Novel Biomarkers in Sarcoidosis Using Genome-Based Approaches

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KEYWORDS

• Sarcoidosis • Biomarkers • Molecular signature • GWAS • Microarray • Sequencing

KEY POINTS

- The use of biomarkers to support diagnosis and predict disease activity remains a focal point in routine clinical care of sarcoidosis.
- Monitoring subclinical disease activity and likelihood of progression or remission in a longitudinal fashion remains a challenge.
- Genome-wide gene expression signature strategies and genetic variation data represent a new venue to generate useful biomarkers in sarcoidosis.
- Recent advances in genome-wide expression profiling techniques, such as gene expression microarray and RNA sequencing in blood provide a highly useful, non-invasive method to assess inflammatory activities in sarcoidosis.

SARCOIDOSIS: OVERVIEW AND NEED FOR BIOMARKERS

Sarcoidosis is a systemic heterogeneous inflammatory disease characterized by the presence of noncaseating epithelioid granulomas in one or multiple organs, with the lung affected in ~90% of cases. Lung involvement is commonly manifested as bilateral hilar lymphadenopathy (BHL) and pulmonary infiltration with more severe cases developing pulmonary fibrosis. Ocular and skin lesions may become sight threatening or disfiguring, requiring aggressive treatment. Cardiac and neurologic involvement may cause morbidity and death.[1,2] Löfgren syndrome, an acute presentation of sarcoidosis, is characterized by erythema nodosum, BHL, and polyarthralgia and is associated with spontaneous regression.[3,4] In addition, more

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than 50% of sarcoidosis patients will experience remission within 3 years after diagnosis, with more than 66% of patients experiencing remission within 10 years.[5,6] It is clear that although certain disease phenotypes and chest radiograph stages portend a good prognosis, a large proportion of patients would benefit from technological advances in biomarker development.

The need to develop useful biomarkers in the diagnosis and prognosis of subjects with sarcoidosis has long been recognized because sarcoidosis is a diagnosis of exclusion and may mimic multiple other rheumatologic illnesses.[7,8] Furthermore, a significant percentage of patients with sarcoidosis (about one-third) develop complications with granulomatous involvement of vital organs with progressive disease. Thus, monitoring subclinical disease activity and likelihood of progression or remission in a longitudinal fashion remains a challenge. Finally, significant racial and gender differences in disease development and prognosis have been reported in African American,[9] Irish, Scandinavian, and Hispanic populations. Again, these differences represent a compelling need for racial and ethnic-selective biomarkers to assess disease progression and response to therapy in diverse populations. In this article, traditional biomarkers in sarcoidosis as well as biomarkers emerging from technology-driven strategies are reviewed. Discussed are the integration of genome-wide gene expression signature strategies and genetic variation data as additional opportunities to generate useful biomarkers in sarcoidosis, particularly in assessment of personal risk for developing complicated sarcoidosis.

Traditional Biomarkers in Sarcoidosis

Despite limitations, the use of biomarkers to support diagnosis and predict disease activity remains a focal point in routine clinical care. Multiple methodologies have been applied to detect biomarkers in serum, lung tissue, bronchoalveolar lavage fluid (BALF), and exhaled breath condensate (EBC) using enzyme-linked immunosorbent assays, proteomic analysis, and mass spectrometry.[10] Traditionally, clinical biomarkers measured in sarcoidosis were limited to soluble factors measured in blood, bronchoalveolar lavage (BAL), or cerebral spinal fluid (**Table 1**). Data remain inconsistent regarding the validity of EBC biomarkers.[11] As technology improves, biomarker panels generated from array data will continue to emerge.

SOLUBLE BIOMARKERS ASSOCIATED WITH MONOCYTE-MACROPHAGE ACTIVATION

Although specific biomarkers have been suggested as useful tools in sarcoidosis, reduced specificity has been a major limitation with angiotensin-converting enzyme (ACE), the most commonly used biomarker in sarcoidosis. ACE is derived from activated macrophages in granulomatous pulmonary remodeling[12] and is useful in supporting a diagnosis and monitoring disease activity in some patients.[12,13] ACE levels are increased in approximately two-thirds of patients with sarcoidosis with elevated levels reported in neurosarcoidosis.[14] However, elevated ACE levels are not specific for sarcoidosis and are observed in granulomatous diseases such as tuberculosis,

Table 1
Conventional sarcoidosis biomarkers and their clinical association

Biomarker	Origin and Clinical Association
ACE	Monocyte-macrophage origin; acute stage, levels influenced by polymorphisms
sIL-2R	Lymphocyte associated; disease severity, extrapulmonary organ involvement
SAA	Monocyte-macrophage origin; higher level in tissue and serum in sarcoidosis
α-1-antitrypsin (BALF)	Cytokine associated; downregulated only in patients without LS; associated with spontaneous resolution
Protocadherin-2 precursor (BALF)	Cell adhesion; upregulated in sarcoidosis across all studied phenotypes
Chitotriosidase	Monocyte-macrophage origin; disease progression
Tenascin-C (BALF)	Fibrosis and ECM associated; levels correlated with infiltrates on chest radiographs in sarcoidosis
IL-17RC	Lymphocyte associated; elevated expression in retinal tissues
TGF-β1	Fibrosis and ECM related; associated with pulmonary fibrosis

Abbreviations: ECM, extracellular matrix; LS, Lofgren syndrome.