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Transcriptome profiles in sarcoidosis and their potential role in disease prediction

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Abstract

Purpose of review—Sarcoidosis is a systemic disease defined by the presence of non-necrotizing granuloma in the absence of any known cause. While clinically, the heterogeneity of sarcoidosis is well characterized, the transcriptome of the sarcoidosis and underlying molecular mechanisms are not. The signal of all transcripts, small and long non-coding RNAs, can be detected using microarrays or RNA-Sequencing. Analyzing the transcriptome of tissues that are directly affected by granulomas is of great importance to understand biology of the disease and may be predictive of disease and treatment outcome.

Recent findings—Multiple genome wide expression studies performed on sarcoidosis affected tissues were published in the last 11 years. Published studies focused to examine differences in gene expression levels between sarcoidosis vs. control tissues, stable vs. progressive form of sarcoidosis, as well as sarcoidosis vs. other diseases. Strikingly, all these transcriptomics data confirm the key role of TH1 immune response in sarcoidosis and particularly of IFN- γ and type I IFN driven signaling pathways.

Summary—First steps towards transcriptomics of sarcoidosis in precision medicine are taken and highlighted the potentials of this approach. Large prospective follow up studies are required to identify signatures predictive of disease progression and outcome.

Keywords

sarcoidosis; gene expression; transcriptome; transcriptomics; review; human

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Conflicts of interest

NK was a consultant to Biogene, MMI, Pliant and Boehringer Ingelheim, and an inventor of patents regarding novel biomarkers and therapeutics in IPF. The remaining authors have no conflicts of interest.

INTRODUCTION

Multiple genome wide expression studies of sarcoidosis affected tissues were published in the last 11 years. Published studies focused to examine differences in gene expression levels between sarcoidosis vs. control tissues, stable vs. progressive form of sarcoidosis, as well as sarcoidosis vs. other granulomatous and non-granulomatous diseases [1–4].

Understanding the transcriptome of tissues that are directly affected by the presence of granulomas, such as lung, skin or of fluids in the contact with granulomas such as bronchoalveolar lavage (BAL) and peripheral blood is of great importance to understand the biology of sarcoidosis. The signal of all transcripts and the majority of small and long non-coding RNA in humans can be detected by one microarray or RNA-Seq run, then submitted to analysis that allows understanding of intra- and inter-tissues gene networks that underlie the biology of sarcoidosis.

Published transcriptomics studies indicate that numerous specific genes and signaling pathways implicated in inflammatory and immune T-cells and macrophage responses differentiate sarcoidosis from control tissues and other diseased tissues. Specific and common gene expressions, miRNAs and pathways were identified in peripheral blood, BAL and whole lung, orbital and lacrimal tissues lysate.

Methodology

A systematic literature search was performed by searching electronic databases including a database repository of gene expression data (PubMed, Gene Expression Omnibus). We used the following search terms: sarcoidosis, gene expression, transcriptome, transcriptomics. Then, all search results were checked whether the articles contain gene expression data on sarcoidosis.

The transcriptome of sarcoidosis in disease-affected tissues

Crouser et al. used frozen lung tissues and detected 319 differentially expressed genes between sarcoidosis and control lungs [5] (Table 1). Functional analysis revealed genes implicated in cell movement, immune function and Th1 response (e.g. STAT1, IL-5, IL-7, IL-15, CCR5, CXCL9) [5]. Newly identified MMP12 and ADAMDEC1, gene and protein expression, were significantly positively correlated with sarcoidosis severity in lung tissue and in BAL [5]. In addition to analyzing gene profiles in lungs, Crouser et al. identified 60 miRNA (FDR<5%) in lungs and 214 miRNA (FDR<5%) in peripheral blood mononuclear cells (PBMC), as differentially expressed between active pulmonary sarcoidosis and control [6]. Although neither a significant overlap in miRNA expression nor of their chromosomal location was found between lung and PBMC, predicted targets of differentially expressed mRNA were commonly linked to TGF-beta and WNT regulated pathways. These findings support the notion that cell profiles of lung tissues and blood are very different, but at the same time implicated in same pathways that are known to provide links between innate and adaptive immunity [14–16], fibroproliferation [17–19], granuloma formation and resolution [19,20]. Limitations of the study were small numbers of tissues (Table 1) that allowed for limited detection of significant differentially expressed mRNA and miRNA and the lack of a

mechanism that proves the role of miRNA and their targets in TGF-beta and WNT pathways in the context of sarcoidosis development and pulmonary outcome.

Rosenbaum et al. analyzed gene expression profiles of unpaired lung, lymph nodes and peripheral blood from patients with sarcoidosis versus controls[21]. In line with the previously mentioned data, the authors also noticed a strong Th1 immune response, as well as STAT1 and three STAT1 regulated chemokines (CXCL9, CXCL10 and CXCL11) to be commonly up-regulated in sarcoidosis [21]. STAT1 was already shown to be a key inflammatory and INF- γ response transcription factor [22,23].

Lockstone et al. compared the transcriptome of lung tissues of self-limiting versus progressive-fibrotic sarcoidosis patients [1]. 334 genes ($p < 0.01$) were found to be differentially expressed (Table 1), suggesting immune response genes as drivers of fibrotic process in sarcoidosis rather than fibrogenic group of genes characteristic for IPF [24]. However, the findings of this study were based on small sample size, lacking statistical power.

Judson et al. performed a microarray analysis comparing the gene expression in skin tissue from fifteen patients with active cutaneous sarcoidosis to five healthy controls [25]. Ingenuity pathways analysis revealed that interferon (IFN) signaling (type I and II) and the Th17 pathway, including IL-23, IL-23R and IL-21, are significantly dysregulated, however with a limited expression of some hallmark Th17 pathway genes, like IL-17 itself.

Rosenbaum et al. established gene expressions profiles of orbital tissues and peripheral blood from twelve patients with sarcoidosis and six healthy controls with 125 genes being significantly in both orbital tissues and peripheral blood [7]. Upregulated genes included CXCL10, GBP5, STAT1, AIM2, ICAM1, and JAK2, and were modulated by IFN- γ and type I IFNs. Accordingly, enrichment analysis of transcription factor binding sites established that the transcription factors, interferon-response factor 1 and 2 (IRF-1 and IRF-2), as well as nuclear factor κ B, are involved in the transcriptional modulation in sarcoidosis.

The BAL cell transcriptome

Gharib et al. identified over 1500 differentially expressed genes when BAL cell gene expression was compared between sarcoidosis and healthy subjects [8] (Table 1). Gene set enrichment analysis (GSEA) of those genes revealed pathways associated with adaptive immune system, T-cell signaling (Th and CD8+) and IFN- γ , IL-12, -17, and -23 signaling, and identified a novel gene network linkage between immunoproteasome subunits (PSMB-8, -9, -10). Barna et al. performed another BAL cells gene expression microarray study and found Twist1 to be up-regulated, amongst many macrophage M1 – characteristic genes (e.g. IFN- γ , CCL5, CXCL9), in sarcoidosis patients compared to control [9]. Furthermore, Twist1 protein was proposed to serve as a biomarker of M1, but not M2-activation (Table 1). The same group performed microarray analysis on BAL samples from severe (requiring systemic treatment) vs. non-severe (never requiring treatment) stage of sarcoidosis [10]. Reduced expression of Cathelicidin (CAMP) mRNA was observed in severe sarcoidosis stage, and experimental findings suggested that TNF mediates repression of steroid receptor co-

activator-3 (SRC3) and contributes to CAMP deficiency, which further may impede resolution of inflammation [10]. Comparison of BAL cells from patients with progressive and stable sarcoidosis by microarrays demonstrated increased expression of protein kinase TYK2 and cell cycle inhibitor p21Waf1/Cip1 genes confirming association of BAL cells with Th1 and INF- γ immune responses [11].

The peripheral blood transcriptome in sarcoidosis

Several studies looked into differentially expressed genes in peripheral blood samples from healthy subjects and sarcoidosis patients and attempted to define a sarcoidosis specific gene signature and to define biomarkers of disease progression. Zhou et al. identified a 20 gene signature in PBMC that performed with an accuracy of 86.0% (sensitivity = 88.2%, specificity = 83.3%) to distinguish healthy subjects from those with sarcoidosis, while the accuracy was 81.4% (sensitivity = 87%, specificity = 74.2%) when distinguishing complicated vs. non-complicated sarcoidosis cases [12]. The same signature performed less well (75.9% and 78.3%) when validated in replication cohorts of UCSF (whole blood) and Oregon (PBMC) data sets to distinguish healthy control from sarcoidosis. Interestingly, the 20 gene signature was not composed of genes belonging to T-cell, JAK/STAT or cytokines pathways. To evaluate this signature, a genome-wide association study (GWAS) including 407 sarcoidosis patients was performed. 30 SNPs from 6 genes of the 20 gene signature were found to be significantly associated with sarcoidosis in either African American or European American (Caucasians) cases. The concerning point could be the presence of SNP in the gene signature that can potentially act as cis-expression quantitative trait loci and might contribute to variations in expression of signature genes when tested in larger cohorts. Nonetheless, it is a great attempt to find universal and racial specific gene signature to serve as a biomarker of presence of sarcoidosis and development of complicated sarcoidosis.

Whole blood gene expression signature distinguished sarcoidosis from healthy control in UCSF and Oregon cohorts with an error rate 12.1% (92% sensitivity and 92% specificity) [13]. 38 genes were found concordant between blood signature and lung biopsies, and sarcoidosis vs. healthy control [5,13]. These genes belonged to Th1-type inflammation, such as INF signaling pathway (INF- α , - β , - γ , STAT1), and T-cell homeostasis and survival (IL-15 and IL-7R). 21 genes were found to be concordant between the blood signature and lung biopsies classified as progressive vs. self-limiting sarcoidosis [1,13]. This study suggests that blood transcriptional profile reflects lung transcriptional profile in sarcoidosis especially in specific inflammatory pathways.

Monast et al. analyzed the gene expression of whole blood samples of skin and lung sarcoidosis patients (n=164) participating in a large clinical trial of golimumab and ustekinumab in sarcoidosis (NCT00955279 [26]), and of healthy controls (n=45) [27]. They identified a core signature of 497 genes differentiating from healthy controls, which was shared by all three phenotypes (skin, lung, and skin&lung combined). Pathway analysis revealed that the T-cell receptor (TCR) signaling was down-regulated in each phenotype compared to healthy controls, potentially due to peripheral T-cell lymphopenia. Interestingly, the INF signaling (type I and II) pathway was more up-regulated in the

combined lung and skin phenotype than in the skin phenotype, while no change in pathway regulation in the lung phenotype was observed.

Sarcoidosis-specific gene signature

Bloom et al. compared the whole blood transcriptional profiles of sarcoidosis to TB and found that whole blood transcriptional profiles of sarcoidosis were similar to TB, and associated with type I IFN signaling (type I and II) and immune response pathway, but distinct from pneumonia and lung cancer that are mostly associated with inflammatory pathways [4]. Gene expression from active sarcoidosis clustered with TB, whereas non-active sarcoidosis clustered with controls. Significant increase in transcriptional activity and production of more inflammatory transcripts was seen in sarcoidosis patients that respond to glucocorticoids therapy. Type I IFN-inducible genes were most abundant in neutrophils, than in monocyte (CD14+), and lastly in lymphocytes (CD4+- and CD8+T-cells). A signature of 144 transcripts was developed using class prediction methods and performed with >80% sensitivity and >90% specificity to distinguish TB from sarcoidosis, healthy controls, cancer and pneumonia. While this signature performed well on the cohort from Maertzdorf et al. [2], the 100 and 50 gene signatures, proposed to distinguish TB and sarcoidosis by Maertzdorf et al. [2], and Koth et al. [13], performed with much lower sensitivity (50–70%) and specificity (>87%) when tested on the Bloom et al. [4] cohort. Although there were only a few overlapping transcripts between the three mentioned gene signatures, the discrepancy can be explained by the small size of cohorts, the difference in the patients and other technical issues [4].

Both sarcoidosis and tuberculosis (TB) share the pathological hallmark of granuloma, being caseating in tuberculosis opposed to non-caseating epithelioid in sarcoidosis. Two research groups, Koth et al. [13] and Maertzdorf et al. [2], independently explored the gene expression in peripheral blood in TB and sarcoidosis. Maertzdorf et al. compared peripheral blood cell transcriptomes and miRNA expression in 18 healthy, IGRA-negative controls, eight patients with active TB and 18 patients with sarcoidosis [2]. Compared to healthy controls, gene expression in TB and sarcoidosis patients overlapped in 9045 genes. Both diseases showed an upregulation of IFN-signaling (type I and II) and IFN-inducible genes. Further common pathways were systemic lupus erythematosus, complement and coagulation cascades, toll-like receptor signaling, Fc γ -receptor-mediated phagocytosis and even a TB pathway itself. Gene expression in sarcoidosis and TB differed only in 691 genes.

Koth et al. analyzed gene expression of 20 healthy controls and 38 patients with sarcoidosis [13]. As an additional comparator two publicly available data sets composed of gene expression of TB patients, were utilized. The top 50 gene discriminating sarcoidosis and healthy controls showed an impressive overlap to active tuberculosis gene expression pattern with DHRS9 and CCR7 having the most indistinguishable expression pattern. Using a gene module strategy, Koth et al. found as well a profound overlap of activated type I and II IFN pathways in sarcoidosis and TB. Thus, TB and sarcoidosis show an enormous transcriptional overlap with the huge majority of genes being concordantly regulated. Especially lymphocyte derived genes are commonly expressed like IFN-signaling and IFN-inducible genes, suggesting a shared transcriptional program. In TB, but not in sarcoidosis, an elevated

gene expression of genes involved in microbiological host defense and other neutrophil specific genes was observed.

Peripheral blood transcriptome and disease outcome

Only one study used cross-sectional derivation transcriptomics data together with a longitudinal cohort to follow sarcoidosis disease outcome [28]. Lymphopenia and genes from IFN-signaling (STAT1, STAT2, GBP1), pattern recognition (TLR2, TLR4, TLR8) and T-cell receptors (CD28, ITK, LEF1), and CXCL9 initially identified in derivation cohort (whole blood), were analyzed for the capacity to predict and track sarcoidosis outcome longitudinally. TCR genes and CXCL9 outperformed lymphopenia in discriminating chronic vs. non-progressive patients within sarcoidosis subjects who enrolled early in their disease course or were not on immunosuppression.

CONCLUSION AND PERSPECTIVE

Transcriptomic studies identified large numbers of differentially expressed genes and pathways distinguishing sarcoidosis patients from healthy controls and from patients with other diseases. Interpreting the interactome of mRNA and miRNA, including *in silico* modelling, led to the identification of immune and inflammatory pathways relevant for blood and BAL cells activation, granuloma formation and correlation with diseases severity [2,6,29]. Impressively, all these transcriptomic data confirm the key role of IFN- γ driven STAT1 signaling as well as type I IFN signaling in sarcoidosis. The main limitations of most of the published transcriptomics studies are a) limited sample size, less than 20 patients in most studies, b) the lack of African Americans participants, c) the absence of time course data and d) the use of cellular admixtures as input samples. The recently completed Genomics Research in Alpha-1 Antitrypsin and Sarcoidosis (GRADS) study used a multi 'omics' approach in analysis of three compartments (blood, BAL, stool), and included a large sample size with multiethnic participants, and proteomics, metabolomics and microbiomics but did not include prospective time course analysis and cellular subpopulations [30]. Thus, future studies should include cutting-edge technologies that identify changes in specific cell subpopulations, potentially at the level of the single cells, and should provide prospective follow up and repeated sampling to address disease dynamics and heterogeneity.

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Key points

- Genome-wide expression studies of sarcoidosis affected tissues reveal novel gene profiles underlying the biology of sarcoidosis.
- In the last 11 years, several genome-wide expression studies comparing sarcoidosis vs. control tissues, stable vs. progressive form of sarcoidosis, as well as sarcoidosis vs. other diseases were published.
- Most transcriptomic studies confirm a key role of TH1 immune response in sarcoidosis and particularly of IFN- γ and type I IFN driven signaling pathways.
- While present transcriptomic studies mainly focused on identifying differences between sarcoidosis and control tissues, large prospective follow up studies, time course sampling and single cell analysis while focusing on the sickest patients are critically needed to identify signatures predictive of disease progression and outcome.

Table 1**Overview of transcriptomics data sets**

Overview of transcriptomics data sets on sarcoidosis vs. healthy controls or on different sarcoidosis stages.

Study	Comparator	Sample size	Data set/Platform	Sample type	Number of DEGs (Level of Significance)
Lockstone et al., 2010[1]	progressive vs. self-limiting sarcoidosis	7 vs. 8	GSE19976/Affymetrix	Lung tissue	384 (p<0.01)
Maertzdorf et al., 2012[2]	sarcoidosis vs. tuberculosis vs. control	18 vs. 8 vs. 18	GSE34608/Agilent	PBMC	2451 (FDR<1%)
Bloom et al., 2013[4]	sarcoidosis vs. tuberculosis	25 vs. 38	GSE42834/Illumina iScan	PBMC	1391 (FDR<1%)
Crouser et al., 2009[5]	sarcoidosis vs. control	6 vs. 6	GSE16538/Affymetrix	Lung tissue	319 (p<0.02, FDR<3%)
Crouser et al., 2012[6]	sarcoidosis vs. control	4 vs. 4	NA/Axon 4000B	Lung & lymph node tissue	60 (five false discoveries per analysis)
Crouser et al., 2012[6]	sarcoidosis vs. control	10 vs. 5	NA/Axon 4000B	PBMC	214 (see above)
Rosenbaum et al., 2009[7]	sarcoidosis vs. control	12 vs. 12	GSE18781/Affymetrix	PBMC	1911 (FDR<5%)
Rosenbaum et al., 2009[7]	sarcoidosis vs. control	7 & 5 vs. 6	GSE58331/Affymetrix	Orbital & lacrimal gland tissue	1522 & 2001 (FDR<5%)
Gharib et al., 2016[8]	sarcoidosis vs. control	15 vs. 12	GSE75023/Affymetrix	BAL	>1500 (FDR<1%)
Barna et al., 2013[9]	sarcoidosis vs. control	12 vs. 10	NA/Affymetrix	BAL	NA (FDR<5%)
Barna et al., 2012[10]	severe vs. non-severe sarcoidosis	5 vs. 4	NA/Affymetrix	BAL	NA (FDR<5%)
Schischmanoff et al., 2006[11]	progressive vs stable sarcoidosis	3 vs. 3	NA/Atlas BD Bioscience Clontech	BAL	14 (FDR<13%)
Zhou et al., 2012[12]	progressive & non-progressive sarcoidosis vs. control	26 & 17 vs. 35	GSE37912/Affymetrix	PBMC	1124 & 316 (FDR<5%)
Koth et al., 2011[13]	progressive sarcoidosis vs. control	38 vs. 20	GSE19314/Affymetrix	PBMC	NA (FDR<5%)

Abbreviations: BAL: bronchoalveolar lavage, DEGs: differentially expressed genes, FDR: false discovery rate, NA: not applicable, PBMC: peripheral blood mononuclear cell.