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Th17-lineage cells in pulmonary sarcoidosis and Löfgren's syndrome: Friend or foe?

Jelle R. Miedema [a, 1], Ylva Kaiser [b, 1], Caroline E. Broos [a], Marlies S. Wijsenbeek [a], Johan Grunewald [b], Mirjam Kool [a, *, 1]

[a] Department of Pulmonary Medicine, Erasmus MC, Rotterdam, The Netherlands
[b] Department of Medicine, Solna and Center for Molecular Medicine, Karolinska Institutet and Karolinska University Hospital, Solna, Stockholm, Sweden

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ABSTRACT

Sarcoidosis, a multisystem granulomatous disorder, has historically been classified as Th1-driven disease. However, increasing data demonstrate a key role of Th17-cell plasticity in granuloma formation and maintenance.

In Löfgren's syndrome (LS), an acute and distinct phenotype of sarcoidosis with a favorable outcome, differences in Th17-lineage cell subsets, cytokine expression and T-cell suppressive mechanisms may account for differences in clinical presentation as well as prognosis compared to non-LS sarcoidosis. In contrast with LS, up to 20% of non-LS sarcoidosis patients may progress to irreversible pulmonary fibrosis. In non-LS sarcoidosis patients, IFN-γ-producing Th17.1-cells appear to be more pathogenic and possibly linked to disease progression, while a broader range of cytokines is found in bronchoalveolar lavage fluid (BALF) in LS patients. Differences in Cytotoxic T-lymphocyte antigen 4 (CTLA-4) expression on Th17-cells and regulatory T-cells (Treg) could contribute to Th17-cell pathogenicity and consequently to either disease resolution or ongoing inflammation in sarcoidosis. Furthermore, several genes and SNPs are associated with disease susceptibility and outcome in sarcoidosis, the majority of which are involved in antigen presentation, T-cell activation or regulation of T-cell survival. Novel insights into the role of Th17-cells in the pathogenesis of both LS and non-LS sarcoidosis will unravel pathogenic and benign Th17-lineage cell function and drivers of Th17-cell plasticity. This will also help identify new treatment strategies for LS and non-LS sarcoidosis patients by altering Th17-cell activation, suppress conversion into more pathogenic subtypes, or influence cytokine signaling towards a beneficial signature of Th17-lineage cells.

In this review, we summarize new insights into Th17-cell plasticity in the complex pathogenesis of sarcoidosis and connect these cells to the different disease phenotypes, discuss the role of genetic susceptibility and autoimmunity and focus on possible treatment strategies.

Contents

* Corresponding author.
E-mail address: m.kool@erasmusmc.nl (M. Kool).
[1] Shared first authorship.

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1. Sarcoidosis pathophysiology and heterogeneity

Sarcoidosis is a complex systemic disease, heterogeneous in both clinical presentation and disease course. A key pathological feature is the presence of non-necrotizing granulomas in the affected organs. These aggregates of differentiated immune cells contain a core of alveolar macrophages, converted into epithelioid cells and multinucleated giant cells (MGCs) [1] and a shell comprised of T-cells and a few B-cells [2]. These granulomas are primarily found in lungs and lung-draining mediastinal lymph nodes (MLN), but can also be present in for example the eyes, skin, central nervous system and heart [3]. The development of granulomas involves the close interaction between T-cells and antigen-presenting cells (APCs) such as macrophages and dendritic cells (DCs) (Fig. 1). The exact cause and triggers of sarcoidosis are still unknown, but the current concept is an exaggerated antigen-driven immune response inducing the formation of disease-typical granulomas [4]. The increase of oligoclonal $CD4^+$ T helper (Th)-cells specifically in the lung implicates these cells as the primary drivers of inflammation [5]. Historically, sarcoidosis has been considered a Th1-mediated disease, defined by a typical increase in interferon (IFN)-γ production by Th-cells in bronchoalveolar lavage fluid (BALF) [6], as well as the presence of Th1-skewing cytokines interleukin (IL)-12 and IL-18 in both granulomatous tissue and BALF [7,8]. Recently, the perception of sarcoidosis as a purely Th1-driven disease has shifted to a general understanding that a combination of Th1- and Th17-associated factors contribute to disease progression and outcome. Furthermore, the high prevalence of IFN-γ-producing Th17-cells in sarcoidosis BALF and the presence of all Th17-lineage cells (Table 1) in T-cell-priming MLN have contributed to our understanding of Th17-cell plasticity. In addition, interesting differences were identified in the involvement of Th17-cells between Löfgren's syndrome (LS), a specific subtype of sarcoidosis, and non-LS sarcoidosis. Therefore this review will also include a comparison of the clinical and immunological features of these two types of sarcoidosis.

1.1. Clinical presentation of sarcoidosis

Symptomatic presentation, histological identification of granulomas and exclusion of other diagnoses are the main criteria for evaluation of all sarcoidosis patients. Although sarcoidosis can affect virtually any part of the body, pulmonary involvement is present >90% of cases (Table 2). Approximately half of all sarcoidosis patients show disease regression within 2 years, others will develop chronic disease (duration ≥ 3–5 years) [9], but in up to 20% of non-LS patients [10,11] granuloma formation persists and progresses to pulmonary fibrosis. This permanent organ damage may lead to disabling symptoms like progressive dyspnea and cough [12] and impaired quality of life. Other commonly affected extra-pulmonary organs are the liver (20–30%), eyes (10–30%), and skin (15%). Less prevalent but potentially catastrophic are cardiac (2–5%) or central nervous system involvement (5%) [9]. Pulmonary fibrosis, cardiac or CNS involvement are the main reasons for an increased risk of mortality in sarcoidosis [13].

When sarcoidosis is suspected based on clinical and radiological presentation, confirmation of granulomatous tissue in a biopsy sample is often required (Table 2). Moreover, a thorough effort to exclude alternative causes of granulomas (e.g. infections such as aspergillosis, beryllium exposure, environmentally, malignancy- or drug-induced sarcoid-like reactions) is mandatory before the diagnosis of sarcoidosis can be made. Lymphocytosis marked by an elevated BALF CD4/CD8 ratio (>3.5) can support the diagnosis [9,14].

The incidence and clinical presentation of sarcoidosis varies greatly depending on ethnicity, geographic location, genetic background and gender. In parts of Europe, a specific acute disease phenotype termed Löfgren's syndrome (LS) is characterized by a usually favorable outcome, even without treatment [15,16] (Table 2). In contrast, the non-acute form or non-LS sarcoidosis may lead to chronic inflammation and eventually pulmonary fibrosis. Constituting a much more heterogeneous patient group than LS, non-LS patients often present with a broader range of sometimes unspecific symptoms. With current methodology, it is difficult to detect patients at risk for developing progressive organ damage [10].

1.2. Clinical perspective: Löfgren's syndrome

LS is a clinically distinct phenotype of sarcoidosis, first described in 1946 by Swedish pulmonologist Sven Löfgren. Similarly to non-LS sarcoidosis, the hallmark pathophysiological finding is non-caseating granulomas in the affected organs and an elevated BALF CD4/CD8 ratio [13,14]. In contrast to the often-insidious onset, slow disease progression and heterogeneous phenotype of non-LS sarcoidosis, LS patients typically experience an acute disease presentation (Table 2). Moreover, LS usually manifests with characteristic clinical symptoms of fever, erythema nodosum and/or ankle arthritis, in addition to bilateral hilar lymphadenopathy on chest radiography, either with or without parenchymal infiltrates [17–19]. Erythema nodosum is significantly more common in women and arthritis in men [20,21], suggesting hormonal and/or genetic influence on symptomatic appearance.

Gender differences are also observed in terms of incidence. While LS generally arises in young adults of both sexes between 25 and 40 years of age, a second peak of incidence is also observed in women around menopause, at the age of 45–60 [15,21]. Global incidence of LS is highly varied, with LS patients constituting up to a third of all sarcoidosis patients in Scandinavia, the Netherlands and Spain [22–24], but radically less, down to one percent, in e.g. the UK, the US, and Asia [24–27].

The perhaps most striking distinction between LS and non-LS sarcoidosis lies in disease outcome. Despite the acute onset and often pronounced symptoms, LS is normally a self-limiting

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