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The Roles of T Helper 1, T Helper 17 and Regulatory T Cells in the Pathogenesis of Sarcoidosis

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ABSTRACT

Sarcoidosis is a systemic granulomatous disorder of unidentified etiology, with a heterogeneous clinical presentation. It is characterized by a reduced delayed-type hypersensitivity to tuberculin and common antigens. The balance between Th1, Th17 and Regulatory T(Treg) cells controls T-cell proliferation and activation.The Th17/Treg ratio in the peripheral blood and bronchoalveolar lavage fluidis increased in patients with active sarcoidosis. Amplified IL-17A expression in granulomas and the presence of IL-17A$^+$, IL-17A$^+$IL-4$^+$ and IL-17A$^+$IFN-γ$^+$ memory T helper cells in the circulation and BAL indicate Th17 cell involvement in granuloma induction and/or maintenance in sarcoidosis. Sarcoidosis should therefore be considered as a Th1/Th17 multisystem disorder and anti-IL-17/Th17 approaches that control and reduce IL-17Amay be an option, therefore, for the treatment of sarcoidosis.Here we provide a short overview as to the role of Th17 cells as critical cells in the pathogenesis of sarcoidosis.

Keywords: Granuloma; Interleukin 17; Sarcoidosis; Th17 cell

INTRODUCTION

Sarcoidosis is a systemic granulomatous disorder of unidentified etiology, with a heterogeneous clinical presentation.

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The majority of patients have lung and intrathoracic lymph node involvement. In most cases sarcoidosis is sub-acute and self-limiting; however, highmorbidity and mortalitymay result from pulmonary fibrosis or cardiac or neurological involvement.[1] Although disease remission occurs in up to two-thirds of patients, others have chronic constant sarcoidosis which may lead to lung fibrosis.[2] The lungs are involved in >90% of patients[3] and histopathologically, sarcoidosis is the

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existence of noncaseatingepithelioid granulomas with mononuclear cell infiltration and microarchitecture damage.[3] Sarcoidosis is usually defined according to clinical and radiological definitions[1]although the detection of CD4 and CD8 T cells by flow cytometry is being increasingly used as a diagnostic tool.[4] The heterogeneity of the disease ranges from no symptoms to severe respiratory insufficiency, cardiac death, neurological disease, and blindness.[5]Chest radiographis reported as abnormalin 95% of sarcoidpatients[6]with the most characteristic featurebeing bilateral hilar lymphadenopathy (BHL) which is seen in 50-80% of patients.[7]

Granulomas are generated whenever macrophages are not able to degrade and completely eradicatean antigen. More specifically, in sarcoidosis multinucleated giant cells and epitheloid cells are present. Activated mononuclear cells and T cells accumulate around a granuloma and surrounding tissue indicating that ongoing immune stimulation is occurring.[8] These immunoinflammatory processes are compartmentalized since enhanced immune cell activation is seen in organs with inactive or only modestly activated cells in the peripheral blood.[9] As such, sarcoidosis can bedescribed as an "immune paradox" with the presence of peripheral anergy,as demonstrated by a reduced delayed-type hypersensitivity to tuberculin and common antigens[10],despiteenhanced inflammation at disease sites.[11]

A disequilibrium between effector and regulatory lymphocytes (Treg cells), notably $CD4^+$ $CD25^{bright}FoxP3^+$ cells may underpin this paradox.[11]Treg cells accumulate intheperipheryof the granuloma andperipheral bloodof patients with active sarcoidosis and exert anti-proliferative effects on and weakly suppress TNF-α production from naive T cells.[12] Treg inactivation may lead to enhanced Th1 cytokine patterns and an increase in Th17cell activity resulting inamplified T cell proliferation and activation.[13] This review summarizes the evidence for arole of T cell subsets notably Th17 cells in the pathogenesis of sarcoidosis.

T Helper 1(Th1) Cells

Clinically sarcoidosis is characterized by peripheral blood T cell lymphopenia, accompanied by cutaneous anergy to tuberculin and other skin tests. However, there is a clear differentiation between local and systemic immune activation. There are increasednumbers of $CD3^+CD4^+$ T cells observed in bronchoalveolar lavage (BAL) resulting in an increased CD4/CD8 ratio. Increased levels of Th1 cytokines are found in the BAL fluid (BALF) and sites of inflammation in sarcoidosis patients.[14, 15] This is reflected in the presence of $Th1CD4^+$ T cells characterized by high TCR expression and by IFN-γ and Tbx21 gene expression in sarcoid tissue. Lung T cells in sarcoid patients are highly activated, expressing the IL-2 receptor (CD25), CD69 and CD26[16,17] Thus, sarcoidosis bears the hallmarks of a Th1-mediated disease in which activated T cells and cytokines are associated with diseasepathogenesis.[18]

Regulatory T Cells

In addition to Th1 and Th2 subsets, recent reports have identified $CD4^+CD25^{high}Foxp3^+$ regulatory T cells (Tregs) and Th17 cells as the two new distinct subsets of $CD4^+$T cells.[19,20] Tregs are observed in and around kidney and lymph node granulomas in sarcoidosis patients where they proliferate as evidenced by elevated Ki-67 expression.[21] However, their presence in blood and BAL of sarcoidosis patients presentsconflicting results. Idahli et al.[21] found a decreased expression of Foxp3 mRNA in $CD4^+$ BAL T cells and a reduced number of $Foxp3^+CD4^+$ T cells inthe BAL and blood of patients with sarcoidosis. In contrast, Miyara et al.[22] found an increased number of$CD4^+CD25^{bright}$Tregs in blood and BAL.In addition, an increase in activated/memory Tregs and a decrease inresting/naive Tregs in the blood of sarcoidosis patients has been reported.[23] However, functional tests usingTregs from sarcoidosis patients have shown a decreased ability to suppress IFN-γ and TNF-α production by effector T cells.[24]

T Helper17 (Th17) Cells

There is a lack of data concerning human Th17 cell function compared to the vast array of knowledge associated with human Th1 and Th2 cell function in human immunopathology.[25-27] Since recent studies have shown an altered Treg and Th17 cell ratio in many immune-mediated diseases including autoimmune arthritis, psoriasis, inflammatory bowel disease, systemic lupus erythematous,[28-30] it was no surprise that there is an increased Th17/Treg ratio in the peripheral blood and BALFof patients with active sarcoidosis.[31]Importantly, a good response to

corticosteroid treatmentin sarcoidosis patients is associated with a shift in this ratio towards baseline. These results indicate that an immune imbalance between Th17 and Treg cells may play a key role in the pathogenesis of sarcoidosis and suggest that strategies designed to favoureither Treg cell expansion or the suppression of Th17 cell differentiation may be helpfulapproaches for the treatment of sarcoidosis.[31]

The recruitment of IL-17-producing Th17 cells to granulomas is due to the release of cytokines and chemokines such as IL-1β, IL-6, IL-23, IL-12, IL-18, and CCL20 by locally and systemically activated macrophages[32-34](Figure1). Recent studies have found an increase in$IL\text{-}17A^{+}CD4^{+}$ memory T cells in the peripheral blood and BAL of pulmonary sarcoidosis patients,[35] implicating Th17 cells in the pathogenesis of sarcoidosis.[34, 36]

IL-17 is emerging as an essential player in the host defence in several mammalian organs including the human lung [37, 38] particularly during the chronic inflammation seen with mycobacterial infection, autoimmune disorders and also with granuloma formation.[39,40] IL-17 is required not only to clear the primary infection but also to establish effective memory cell responses and may be produced by CD4+ T cells and by γδT cells which produce IL-17 rapidly after infection.[41] Increased levels of IL-17 have been reported in sarcoidgranulomas[42] where it is thought to play a role in the formation and maturation of granulomas.[39, 43] In addition, to its presence in granulomas, increased levels of IL-17A and of IL-17-producing cells are seen in peripheral blood of patients with sarcoidosis.[42, 44] As a consequence it has been proposed that IL-17-producing cells may be useful biomarkers for the prognosis of sarcoidosis.[44]It is hoped, therefore, that targeting IL-17 may have a similar therapeutic efficacy in some sarcoidosis patients as that seenin patients with rheumatoid arthritis orpsoriasis.[45]

IL-6 is known to promote the differentiation of T cells to Th17cells[46,47] and there is a significant upregulation of IL-6, IL-17 as well as of IFN-γ in BALFof sarcoidosis patients.[51] This is associated with the presence of $IL\text{-}17A^{+}$, $IL\text{-}17A^{+}IL\text{-}4^{+}$ and $IL\text{-}17A^{+}IFN\text{-}\gamma^{+}$ memory Th cells in the circulation and BAL of these patients.[48] Peripheral blood Th17 cells have decreased expression of IFN-γ upon TCRstimulation[49] which mediatesthe recruitment of $CXCR3^{+}$ T cells into the lung following the production of the chemokinesCXCL9, CXCL10, and CXCL11.IFN-γ is a key mediator in the acquired immune response and is closely associated with Th1 cells. The reduced expression of IFNγ fromTh1 and Th17 cells from sarcoidosis patients suggests that the resulting levels of IFN-γmay not be sufficient for the clearance of the antigenic agents driving sarcoidosis.[49] Overall, based on the presence of $IL\text{-}17^{+}CD4$ T cells in sarcoid lung tissue and the clear links with pathogenic mechanisms it may be better to describe sarcoidosis as a Th1/Th17multi-system disorder with the implication that targeting these cells that may treat thedisease.[13]

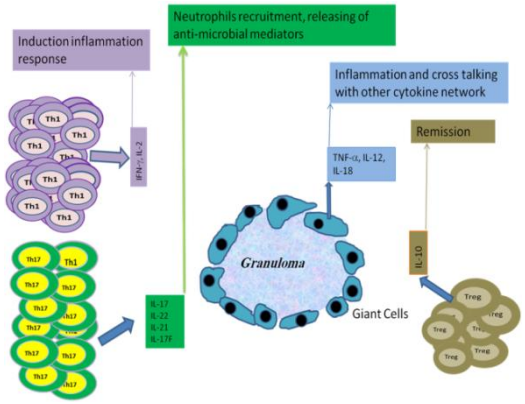

Figure1. Schematic summary of cell interactions in sarcoid tissue. The granulomatous infiltrate is a highly inflammatory microenvironment, which promotes the differentiation of Th0 to Th1 and Th17. IL-12 is instrumentalinbiasingTcellstowardtheTh1 lineage; IL-6,TGF-β, andIL-23providesignalsforTh17differentiation.

Other IL-17-Associated Cytokines

IL-23 is a key cytokine for the induction ofTh17[56] and its gene expression is increased in cutaneous sarcoidosis.[50] IL-23 mRNA expression is also up-regulated in two thirds of pulmonary sarcoidosis patients despite no significant expression ofIL-17 mRNA.[51] IL-23 and TGF-β play a role in the proliferation and differentiation of Th17 cells, which produce IL-17A, IL-17F, IL-21, and IL-22. Whilst IL-17 is animportant member of the Th17 pathway, there are data suggesting that IL-21and IL-23 can act independently of IL-17 mRNA induction. This may explain the absence of IL-17 mRNA expression despite the presence of other Th17 pathway molecules.[52,53] STAT3 has also been linked to the generation of Th17 cells and the expression of IL-21 and its overexpression in peripheral blood in sarcoidosis indicates activation of the Th17pathway.[54] The enhanced expression of the Th17 pathway genes including IL-23 and IL-21, but not of IL-17 mRNA, differentiates sarcoidosis from several other immune-mediated disorders such as psoriasis and Crohn'sdisease.[55] Judson et al.[56] confirm the upregulation of IL-12, IL-2, IL-23 and IFNγ in sarcoidosis. A clinical trial has been recently initiated to test an anti-IL-12p40 monoclonal antibody in sarcoidosis.[57]

SUMMARY AND CONCLUSION

There are several lines of evidence implicating an involvement of pro-inflammatory Th17-lineage cytokines in sarcoidosis: (1) elevated numbers of circulating IL-17A$^+$ memory Th cells, (2) increased presence of IL-17A$^+$ cells, particularly IL-17A$^+$IFN-γ$^+$ and IL-17A$^+$IL-4$^+$ cells in BAL samples of sarcoidosis patients, (3) enhanced numbers of IL-17A-producing T cells in the lamina propria of sarcoidlung, (4) increased numbers of IL-22$^+$ cells, especially in subepithelial regions, in granuloma-containing biopsies, (5) differential distribution of IL-17A$^+$ and IL-22$^+$ T cells in local granulomas, BAL and the circulation of sarcoidosis patients and (6) no evidence of increased IL-17A production by other Tγδ or CD8$^+$ T cells.[34] As such sarcoidosis may be considered as a Th1/Th17 disorderthat affects many organs.[13] Th1 and Th17 cells are the main T cell subtypes involved in the immunopathogenesis of sarcoidosis and it is becoming evident that IL-17Aplays a significant role in disease progression. This suggests that the control and reduction of IL-17Aor the suppression of Th17 cells should be investigated as an option for the treatment of sarcoidosis.Clinical trials of the fully humanized anti-IL-17A antibody, AIN457, reduced theinflammation and decreasedthe disease activity in RA, psoriasis and non-infectious uveitishighlighting the efficacy and safety of this approach.[58] In conclusion, modulation of Th17 cells and cytokines may be an attractive alternative method for the future treatment of sarcoidosis.

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