

---

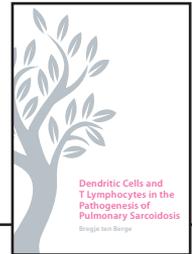
## PROMOTION

# *Dendritic cells and T lymphocytes in the pathogenesis of pulmonary sarcoidosis*



*Bregje ten Berge started her study Medicine at the University of Antwerp, Belgium in 1997. After graduating in 2004, she worked as a resident for one year at the department of Internal Medicine of The Amphibia Hospital, Breda, The Netherlands. Thereafter, she started her research dedicated to dendritic cell – T cell interactions in pulmonary sarcoidosis at the Erasmus Medical Centre Rotterdam, the Netherlands. In 2010 she started her training for pulmonary physician at the Erasmus Medical Centre under the supervision of prof. dr. H.C. Hoogsteden. e-mail: bregjetenberge@hotmail.com. September the 21<sup>st</sup> 2011 has Dr. Bregje ten Berge success-*

*fully defended her PhD thesis at the Erasmus University, Rotterdam.*



**A**lthough advances in understanding the immunopathogenesis of sarcoidosis have been made, the cause remains unclear. The prevailing theory holds that sarcoidosis develops in genetically predisposed hosts from a cell mediated immune response to one or more unidentified antigens characterized by activity of cellular immunity, T-lymphocyte infiltration and formation of noncaseating granuloma in various organ systems. T lymphocytes may be activated via several mechanisms. Interactions between macrophages and T cells are essential for T-cell activation and initiation and development of granulomas. An antigen induces antigen-specific, CD4 type 1 helper T cells (Th1)-mediated, granulomatous inflammation with production of Th1 cytokines. Among others tumor necrosis factor alpha (TNF- $\alpha$ ) is an important cytokine. To become activated T cells need to be stimulated by antigen-presenting cells (APCs) in the lung. Dendritic cells (DCs) are APCs at sites with high antigen exposure like the lungs. It was hypothesized that DCs might play a role in the pathogenesis of sarcoidosis. Additionally, the role of other T helper cells in the pathogenesis of sarcoidosis was evaluated.

### **Dendritic cells in sarcoidosis**

An increased number of DCs was found in bronchoalveolar lavage fluid (BALF), blood and in bronchial granulomas-containing biopsies of sarcoidosis patients. The DCs in BALF and the biopsies showed also increased maturation. These

results suggest an associated between granuloma formation and an increased number together with an increased maturation of DCs. In addition, cultured DCs showed a capacity to induce more TNF- $\alpha$  expression by T cells.

### **T helper cells in sarcoidosis**

Human T helper 17 (Th17) cells contain heterogeneous subsets. The pro-inflammatory cytokine IL-17A plays a role in the pathogenesis of various granulomatous diseases. We found an increased number of IL-17A producing T cells in blood of sarcoidosis patients together with IL-17 producing cells in BALF and in bronchial biopsies. Cells in our immune system capable of suppressing the Th1/Th17 inflammation present in sarcoidosis are the regulatory T cells (Tregs). In sarcoidosis we found increased percentages of Tregs. In contrast, functional in vitro tests show that Tregs of sarcoidosis patients have a reduced suppressive effect on T cell proliferation compared to healthy control Tregs. These results indicate IL-17 involvement besides the known Th1 inflammation in sarcoidosis, as well as an impaired suppressive effect of Tregs in sarcoidosis. A more detailed description of the results of this study is presented in the thesis.

### **Conclusion**

Besides Th1 cells, other cells contribute to the pathogenesis of sarcoidosis and biological agents targeting mechanisms involving these cells may provide more effective, better tolerated therapies.