NAPA OF BORRELLIA BURGDORFERI DRIVES TH17 INFLAMMATION IN LYME ARTHRITIS

G. Codolo¹,², A. Amedei³, A.C. Steere⁴, E. Papinutto², A. Polenghi², G. Del Prete³, C.T. Baldani¹, G. Zanotti⁶, C. Montecucco¹, M.M. D'Elios², M. de Bernard²

¹Dept of Experimental Biomedical Sciences, University of Padua, ²Venetian Institute of Molecular Medicine, Padua, ³Dept of Internal Medicine, University of Florence, Florence, Italy. ⁴Center for Immunology and Inflammatory Diseases, Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, ⁵Dept of Evolutionary Biology, University of Siena, Siena, ⁶Dept of Chemistry, ⁷Dept of Biology, University of Padua, Padua, Italy

Objective: This study was undertaken to evaluate the role of the innate and acquired immune responses elicited by the protein NAPA of Borrelia burgdorferi in Lyme arthritis, which is characterized by an inflammatory infiltrate, consisting mainly of neutrophils and T cells. Th1 cells were proposed to play a central role in Lyme arthritis; more recently Th1 cells were shown not to be essential in inducing Lyme arthritis suggesting that other mediators and T cells are involved. In particular the attention was focused on Th17 cells.

Methods: The cytokine profile of synovial fluid T cells specific for NAPA was investigated in 5 patients with Lyme arthritis. It was also evaluated the cytokine and chemokine profile induced by NAPA in neutrophils, monocytes/macrophages and endothelial cells. Finally, the effect of protein administration in vivo, in rat synovia, was considered.

Results: T cells from synovial fluid of patients with Lyme arthritis produced IL-17 in response to NAPA. In agreement with these data, NAPA was found to induce the expression of IL-23 in neutrophils and monocytes, and IL-6, IL-1b and TGF-b in monocytes, all cytokines crucial for the differentiation of the Th17 subset. Finally, we demonstrated in vivo that NAPA is able to recruit lymphocytes in rat synovia. Accordingly, it was found to promote the release of monocytes- and lymphocytes-attractive chemokines from endothelial cells and macrophages.

Conclusion: Collectively our results suggest that NAPA might be one of the major bacterial products of Borrelia burgdorferi responsible for triggering and sustaining inflammation within synovia, with a strong ability to recruit monocytes and lymphocytes from the blood. Moreover, we found that NAPA is able to drive the expression of IL-6, IL-1b, IL-23, and TGF-b by innate immune cells and, in virtue of such an activity, to elicit a synovial T helper 17 response which, in turn, is expected to play a crucial role in the pathogenesis of Lyme arthritis.