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Bacterial Burden, Innate Immunity, and Specific Response against *Propionibacterium acnes* in Sarcoidosis

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A role of microbial factors in the pathogenesis of sarcoidosis is assumed and toll-like receptors (TLR) may be involved in the initiation of a first immune response. Nevertheless, against bacteria of pathogenetic relevance a specific immune response should exist.

Next generation sequencing of the 16S DNA was applied to sarcoid bronchoalveolar lavage (BAL) samples and the microbial composition was characterized on the basis of operational taxonomical units and analyzed for diversity and indicator species. TLR9 expression by BAL cells was analysed by real-time RT-PCR and cell surface expression by flow cytometry. In sarcoid BAL specific immunoglobulin against *P.acnes* and BAL-cell cytokine release after *P.acnes* stimulation was measured.

The microbial composition differed significantly between sarcoidosis samples and controls. *Atopobium spec.* and *Fusobacterium spec.* were detected in 68% of the sarcoidosis samples, but not in controls. *Mycobacteria* and *Propionibacteria* were not found to be imbalanced between sarcoidosis samples and controls in BAL. Host-genotype analysis revealed an association of the *BTNL2* risk allele with a decrease in bacterial burden. We found increased TLR9 mRNA expression in sarcoid BAL cells and an increased and exaggerated chemokine release after stimulation with the TLR9 ligand CpG. In sarcoid BAL IgG and IgA against *P.acnes* was elevated and heat-killed *P.acnes* stimulated increased GM-CSF and TNF release by sarcoid BAL cells.

Our results indicate disease subtype dependent microbiota in sarcoidosis BAL samples containing *Atopobium spec.* and *Fusobacterium spec.* as novel candidates for sarcoidosis associated bacteria. TLR9 ligands delivered by these and other bacteria contribute to the immunopathogenesis of the disease by macrophage activation. Although *P.acnes* have not been found elevated in sarcoid BAL increased antibody levels and cytokine production in response to *P.acnes* suggest an involvement of these bacteria in the pathogenesis of sarcoidosis which depends most likely on the individual genetic background of the patient.