Modulation of cellular immune responses by bacterial products. Implications for Crohn's disease

Christian Lodberg Hvas, MD

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Official opponents: Thomas Ledet, Jørn Brynskov, and Lena Öhman, Sweden.

Supervisors: Jens F. Dahlerup, Jørgen Agnholt, and Per Höllsberg.

Correspondence: Christian Lodberg Hvas, Department of Medicine V (Hepatology and Gastroenterology), Aarhus University Hospital, Noerrebrogade 44, 8000 Århus C. Denmark

E-mail: clhvas@dadlnet.dk

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ABSTRACT

The work was carried out at Department of Medicine V, Aarhus University Hospital, Institute of Medical Microbiology and Immunology, University of Aarhus, and Institute for Clinical Molecular Biology, Christian-Albrecht-University in Kiel, Germany.

Crohn's disease (CD) is a chronic inflammatory disorder of the intestine. It arises in the genetically susceptible host as the result of an imbalanced immune response towards resident intestinal bacteria. Sustained activation of memory CD4+ T cells is pivotal in disease pathogenesis. Probiotics may beneficially affect T cell function, but data from clinical trials in CD are controversial. Genetic variants among CD patients may give rise to different disease phenotypes and to different responses to therapy. In particular, mutations in the gene encoding for the pattern recognition receptor Nucleotide-binding Oligomerization Domain (NOD)2 may affect the immune response.

We hypothesized that intestinal T cells react to probiotic bacteria in CD in ways other than in healthy volunteers. We therefore investigated the functional role of NOD2 in CD4+ T cells and compared responses to pattern recognition receptor ligands in CD patients with or without NOD2 mutations.

First, we found a disturbed balance between the pro-inflammatory cytokine interferon (IFN)-γ and the regulatory cytokine interleukin (IL)-10 in CD intestinal CD4+ T cells. The imbalanced T cell function was enhanced in the presence of dendritic cells and persisted despite stimulation with probiotics or autologous intestinal bacteria.

Next, we found that NOD2 expression in CD4+ T cells from healthy volunteers was upregulated by tumour necrosis factor (TNF)-α and muramyl dipeptide (MDP) which is a specific NOD2 ligand. Stimulation of CD4+ T cells with MDP increased IL-8 and IFN-γ productions. Apoptosis induction was independent of MDP while MDP increased CD4+ T cell proliferation.

Finally, we found that CD patients who carried two mutations in the NOD2 gene had an impaired production of granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF-α, and IL-1β in response to MDP, but also that they had a defect down-regulation of TNF-α responses to Toll-like receptor 2 following MDP stimulation.

In conclusion, our findings point to a possible regulatory T cell defect in CD, and they provide a further molecular basis for the direct crosstalk of innate and adaptive immune responses in CD.