

ICOS Deficiency: News and Views on Clinics and Pathogenesis

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In a worldwide screen we have identified 9 patients from four unrelated families with ICOS (inducible costimulator) deficiency as an autosomal recessive cause of CVID. The defect in all 9 patients is caused by a genomic deletion of exons 2 and 3 of *ICOS*, causing the loss of the ICOS protein on activated T cells.

The clinical phenotype in 6 adults and 3 children comprises, apart the typical bacterial infections in CVID, recurrent viral infections: One patient had herpes keratitis, one had plane warts, and one female patient developed an aggressive carcinoma of the vulva after chronic HPV infection. Interestingly, one patient suffered from neuroborreliosis as diagnosed by *Borrelia*-specific intrathecal IgM antibodies.

The immunological phenotype of the 9 patients showed low peripheral B-cell counts with a profound decrease of memory B-cells and severe hypogammaglobulinemia, especially in IgG and IgA.

Here we addressed the question how ICOS-deficient T cells cause a severe B cell phenotype. We have shown that ICOS-deficient T cells produce diminished levels of IL-10 and IL-17 upon anti-CD3/ICOS as well as anti-CD3/CD28 stimulation. IL-10 is an immunoregulatory cytokine which fosters immunoglobulin class switch and also the generation of regulatory T cells. Decreased IL-10 production may contribute to the disturbed germinal center dependent antibody response. The analysis of a lymph node from one patient with ICOS deficiency confirmed the presence of only rudimentary germinal centers in the absence of ICOS.

In order to reveal further the molecular mechanism of ICOS deficiency, we are reconstituting ICOS in human ICOS ^{-/-} T cells by retroviral gene transfer in order to investigate if the reduced IL-10 and IL-17 production is due to the missing costimulation signal by ICOS.