Medical Xpress

Novel function of lymphotoxin in mucosal immunity

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This study was initiated almost 10 years ago, even before our group has moved to Berlin, says Sergei Nedospasov, the senior author of the study. We have generated a panel of mice with ablation of TNF, LTα and LTβ in various types of cells, and noted anatomic phenotypes in mice which lacked one of these three genes in RORγt+ ILC. These partial knockouts recapitulated defects in lymphoid organs development, including Peyer's patches (PP), in mice with complete knockouts of the same genes.

When in 2007 our group was invited to join Sonderforschungsbereich (SFB) 633, funded by the German Science Foundation (DFG), which is focusing on mucosal immunity, we thought that we had a good model system in hand to address the mechanisms of immunity in the absence of organized lymphoid tissues in the gut. Surprisingly, mice with ablation of membrane-bound lymphotoxin β (LTα1β2) produced by RORγt+ ILC were still able to mount normal IgA levels in the lamina propria, in spite of the absence of PP and isolated lymphoid follicles.

However, the most interesting result was obtained in mice with ablation of LTα in RORγt+ cells – such animals showed abrogated IgA production in the gut and grossly altered microbiota composition. This study may change the existing paradigm for T-cell-dependent and T-cell-independent pathways in the contol of IgA production in the gut. For cytokine experts it will be interesting to learn about distinct TNF-like function of soluble sLTα in vivo, as the controversy about biological functions of this particular form of lymphotoxin has been going on for over 20 years.

Although this study was done in mice and not in patients, the discovery reported in *Science* may be of relevance for anti-TNF therapy using Etanercept, as this drug can block not only TNF but also soluble lymphotoxin. It would be interesting now to evaluate possible effects of such treatment on IgA levels and gut microbiota in patients, especially because Etanercept, unlike other anti-TNF drugs, is ineffective in inflammatory bowel disease.

The German Rheumatism Research Centre (DRFZ) Berlin, a Leibniz Instiute, investigates rheumatic diseases in an interdisciplinary manner. 25 research groups study immunology, experimental rheumatology and epidemiology of rheumatic diseases. A hallmark of the DRFZ is the close connection to the Charité - Universitätsmedizin Berlin. A benefit for both physicians and scientists: this unique setting enables the development of experimental research to meet the clinical challenges and the application of modern technologies and methods in the clinic.

More information: Kruglov, A. et al. (2013), Nonredundant Function of Soluble LTa3 Produced by Innate Lymphoid Cells in Intestinal Homeostasis. *Science*, DOI: 10.1126/science.1243364

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