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Helicobacter-induced colitis is reversed in "humanized" IL-10 transgenic mice

Jay H. Bream
Johns Hopkins Bloomberg School of Public Health, USA

Abstract

IL-10 is an anti-inflammatory cytokine that is produced by a variety of cell types. Studies in mice suggest that the regulation of IL-10 expression in different cellular subsets may determine the outcome of infections. In humans however, the relationship between cell type-specific IL-10 production and the response to microbial pathogens, remains unclear. To this end, we generated a transgenic mouse system to model hIL-10 regulation in vivo using a bacterial artificial chromosome (hIL10BAC). Because hIL-10 is physiologically active in mice we can evaluate the role of genomically-controlled hIL-10 expression on disease phenotypes. We found that hIL-10 expression rescued $Il10^{-/-}$ mice from Helicobacter-typhlonius induced colitis and was associated with control of pro-inflammatory cytokine expression and T_H17 cell accumulation in gut tissues. Resistance to colitis was associated with an accumulation of hIL-10-expressing $CD4^+Foxp3^+$ T regulatory cells specifically within the lamina propria. In agreement with an enhanced capacity to express IL-10, $CD4^+CD44^+$ T cells isolated from the lamina propria exhibited lower levels of the repressive histone mark H3K27Me3 and higher levels of the permissive histone mark AcH3 in both the human and mouse IL10 locus compared to the spleen. Therefore, the hIL10BAC mouse is a model of human gene regulation and function revealing cell- and tissue-specific regulatory requirements for hIL-10 expression which impacts microbial pathogenesis.

Biography

After completing his Ph.D., Dr. Bream was a postdoctoral fellow in the laboratory of Dr. Howard Young in the Laboratory of Experimental Immunology, Cellular and Molecular Immunology Section at the National Cancer Institute. Dr. Bream then joined the laboratory of Dr. John O'Shea as a Research Fellow in the Molecular Immunology and Inflammation Branch at the National Institute of Arthritis, Musculoskeletal and Skin Diseases. Currently, Dr. Bream is an Associate Professor of Molecular Microbiology and Immunology and Co-director of the Becton Dickinson Immune Function Laboratory at the Johns Hopkins Bloomberg School of Public Health.