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Modeling human gene regulation and function in transgenic mice: role of the anti-inflammatory gene *IL10* in disease

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Abstract

IL-10 plays a central role in limiting inflammation and IL-10 levels are strongly linked to inflammatory disorders in humans. The levels of IL-10 production are reported to be influenced by single nucleotide polymorphisms (SNPs) in the *IL10* promoter and these SNPs are also associated with disease susceptibility. This indicates that inter-individual differences in the regulation of IL-10 production are likely a key factor which determines disease risk. However, the mechanisms that control human IL-10 (hIL-10) production remain unclear due to a lack of appropriate research tools. To address this issue, we generated a transgenic mouse using a bacterial artificial chromosome (hIL10BAC) to model hIL-10 regulation in vivo. Because hIL-10 is biologically active in mice we can evaluate the role of genomically-controlled hIL-10 expression on disease phenotypes. Faithful expression of the hIL10BAC in myeloid cells rescued *Il10*$^{-/-}$ mice from LPS toxicity. However, in the *Leishmania donovani* model of pathogen persistence, Il10$^{-/-}$/hIL10BAC mice did not develop the characteristic IL-10^{+}IFN-□$^{+}$CD4 T cell subset and like *Il10*$^{-/-}$ mice, cleared the parasites. Surprisingly, hIL-10 expression rescued *Il10*$^{-/-}$ mice from colitis and was associated with control of pro-inflammatory cytokine expression in gut tissues. Resistance to colitis was associated with hIL-10-expressing CD4^{+}Foxp3^{+} Tregs in the lamina propria (LP). In addition, LP CD4^{+}CD44^{+} T cells exhibited low H3K27Me3 and high AcH3 levels (marks of repressed and permissive chromatin respectively) in the human *IL10* locus. Thus, modeling human gene regulation in mice may reveal how cell-specific gene expression influences disease and provide a platform to develop/test experimental therapies.

Biography

After completing his Ph.D. at Penn State University, Dr. Bream was a postdoctoral fellow in the Laboratory of Experimental Immunology, Cellular and Molecular Immunology Section at the National Cancer Institute. Dr. Bream then became 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.