CCR9 REGULATES COLITIS DEVELOPMENT BY INHIBITING REGULATORY T CELL DEVELOPMENT

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CD4+ T cells reactive to microbiota regulate the pathogenesis of inflammatory bowel disease (IBD). As T cell trafficking to intestines is regulated through interactions between highly specific chemokine-chemokine receptors, efforts have been made to develop intestine-specific immunosuppression based on blocking these key processes. CCR9, a gut-trophic chemokine receptor expressed by lymphocytes and dendritic cells, has been implicated in regulation of IBD through mediating recruitment of T cells to inflamed sites. However, the role of CCR9 in inducing and sustaining inflammation in the context of IBD is poorly understood. In the current study, we demonstrate that CCR9 inhibits Treg cell development, which contributes to its regulation of intestinal inflammation. While CCR9-/- mice are more resistant to disease compared to wild type (WT) mice upon DSS insults, CCR9 deficiency does not affect effector or regulatory T cell induction of colitis in a microbiota antigen specific T cell-mediated model. Interestingly, CCR9-/- mice demonstrate a high level of Foxp3+ Tregs, and ligation of CCR9 by its ligand CCL25 inhibited Treg cell differentiation in vitro. Furthermore, partial depletion of Tregs in CCR9-/- mice increased susceptibility to DSS insults to a level similar to WT mice. Collectively, our data indicates that CCR9 signaling inhibits Treg cell development, which contributes to its regulation of colitis development, in addition to acting as a gut-homing molecule.