CCR9 is critical for control of inflammatory bowel disease by regulatory T cells

HL Evans-Marin, A Cao and Y Cong

Univ. of Texas Medical Branch, Galveston, TX

CCR9 is a gut-trophic chemokine receptor expressed by lymphocytes, DCs, and macrophages. It binds non-promiscuously with CCL25, which is expressed by endothelial cells in the small intestine. Both CCR9 and CCL25 are upregulated in the inflamed intestine during inflammatory bowel disease. We examined the role of CCR9 on pathogenesis of colitis using CBir1 Tg T cell adoptive transfer model, which uses TCR transgenic T cells specific for CBir1 flagellin to induce colitis. When mice received CD4+ T cells from WT CBir1 or CCR9-/- CBir1, knockout of CCR9 had no effect on the disease. However, when mice received WT CBir1 or CCR9-/- CBir1 Tregs along with naïve cells CBir1 T cells, mice receiving the CCR9-/- Tregs had more severe disease. We then examined the distribution of CCR9 on FoxP3 positive versus FoxP3 negative cells from the spleen, MLN, small intestine, and large intestine. We found that in all organs, CCR9 was expressed at higher levels in the FoxP3 positive cells. We also examined CCR9 was expressed on Tregs generated in vitro. We found that retinoic acid, a vitamin A metabolite involved in tolerance and gut trophism, was required to induce CCR9 expression and induced CCR9 expression at a higher rate in FoxP3+ cells than FoxP3- cells in these cultures. Our data indicate that CCR9 plays an important role in the regulation of gut inflammation, which may overshadow its role in driving inflammation.