The bile acid receptor GPBAR1 regulates M1/M2 phenotype of intestinal macrophage and its activation rescues from murine colitis

1)Biagioli M. 2)Carino A. 3)Cipriani S. 4)Francisci D. 5)Marchianò S. 6)Scarpelli P. 7)Sorcini D. 8)Zampella A. 9)Fiorucci S.

University of Perugia

GPBAR1 (TGR5 or M-BAR) is a G-protein coupled receptor for secondary bile acids highly expressed in monocytes/macrophages. Here, we aimed to determine the role of GPBAR1 in mediating leukocyte trafficking in chemically induced models of colitis and investigate the therapeutic potential of BAR501, a small molecule agonist for GPBAR1. Results of these studies demonstrated that GPBAR1 gene ablation enhanced the recruitment of M1 macrophages in the colonic lamina propria and worsened the severity of inflammation. In contrast, GPBAR1 activation by BAR501 reversed intestinal inflammation in both TNBS and oxazolone models by reducing the trafficking of Ly6C+ monocytes from blood to intestinal mucosal. Exposure to BAR501 shifted intestinal macrophages from a M1 (CD11b+, CCR7+, F4/80-) to M2 (CD11b+, CCR7-, F4/80+) phenotype, reduced the expression of inflammatory genes (TNF-α, IFN-γ, IL-1β, IL-6 and CCL2 mRNAs) and attenuated the wasting syndrome and severity of colitis (≈70% reduction of CDAI). The protective effect was lost in Gpbar1-/-. Exposure to BAR501, increased the colonic expression of IL-10 and TGF-β mRNA and the percentage of CD4+/ FoxP3+ cells. The beneficial effects of BAR501 were lost in Il-10-/- mice. In a macrophage cell line, regulation of IL-10 by BAR501 was GPBAR1-dependent and mediated by the recruitment of CREB to its responsive element in the IL-10 promoter. In conclusion, GPBAR1 is expressed in circulating monocytes and colonic macrophages and its activation promotes a IL-10-dependent shift toward a M2 phenotype. The targeting of GPBAR1 may offer therapeutic options in inflammatory bowel diseases.