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Title: Anti-commensal IgG and FcRs play a pivotal role in intestinal inflammation

Abstract: IgG antibodies are the major soluble effector molecules of humoral immunity and play an important role in defence against infection and susceptibility to some autoimmune diseases. Inflammatory bowel disease is a chronic, relapsing condition with two subtypes, Crohn's disease and ulcerative colitis (UC). Genetic studies in UC implicate an IgG antibody receptor variant, but why this affects inflammation in an IgA-dominated organ is unclear. We have identified a profound induction of anti-commensal IgG and of activating FcγR signaling in the colonic mucosa in UC. We find that commensal-IgG immune complexes engage gut-resident FcγR-expressing macrophages, inducing NLRP3- and reactive oxygen species-dependent production of IL-1β and neutrophil-recruiting chemokines, and that this is modulated by *FCGR2A* genotype. *In vivo,* manipulation of macrophage FcγR signal strength determined the magnitude of intestinal inflammation and IL-1β-dependent type 17 immunity. Together, our data reveal the specific molecular pathway mediating IgG-FcγR dependent inflammation in UC, with therapeutic implications

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