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Overline: Autoimmunity

Title: When a double-negative is not a positive: autoantibodies against IL-10 in inflammatory bowel disease patients

One sentence summary: IL-10 autoantibodies are detected in 2 patients with severe inflammatory bowel disease.

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Inflammatory Bowel Disease (IBD) affects almost 2.4 million Americans and countless numbers of people worldwide. However, the underlying causes of IBD remain largely a mystery. Griffin et al. uncover a new trigger for severe IBD in two patients: autoantibodies against Interleukin-10 (IL-10). IL-10 plays key roles in limiting inflammation by reducing release of tumor necrosis factor and promoting development of T regulatory cells, among other mechanisms. To understand the role of IL-10 in the gut immune system, one can look to patients with genetic mutations in the IL-10 or IL-10 receptor genes. These patients' symptoms begin as infantile-onset enterocolitis.

In the two patients highlighted in the author's study, the IL-10 autoantibodies appear to phenocopy the genetic mutations. After screening for infectious and genetic causes of patients' symptoms, the authors performed an assay to determine whether the patients' cells were capable of responding to exogenous IL-10. The patients exhibited normal ability to suppress lipopolysaccharide-induced production of tumor necrosis-factor, and thus the authors screened for the presence of autoantibodies against IL-10 as well as autoantibodies against a large panel of immunomodulatory cytokines. In these cases, the presence of high titers of autoantibodies against IL-10 led the authors to initiate immunosuppressive therapy on these patients. Resolution of symptoms correlated with decreased titers of anti-IL-10 autoantibodies; relapse of symptoms occurred upon weaning of immunosuppression. How broadly these autoantibodies are associated with IBD remains unknown, but the presence of them in these two patients, along with the resolution upon treatment with immunosuppression, highlights the need to include IL-10 autoantibodies among the potential pathogenic mechanisms of IBD.

Griffin H, Ceron-Gutierrez L, Gharahdaghi N, Ebrahimi S, Davies S, Loo PS, Szabo A, Williams E, Mukhopadhyay A, McLoughlin L, Irwin S, Travis S, Klenerman P, Bunn S, Cant AJ, Hambleton S, Uhlig HH, Doffinger R. Neutralizing Autoantibodies against Interleukin-10 in Inflammatory Bowel Disease. *N Engl J Med.* 2024 Aug 1;391(5):434-441. doi: 10.1056/NEJMoa2312302. PMID: 39083772.

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