Tumor necrosis factor in colitis—bad actor or hero?

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Investigators at Children's Hospital Los Angeles have found that a common therapeutic target for the treatment of inflammatory bowel disease (IBD) may actually protect against intestinal inflammation by inhibiting pathogenic T-cells. This discovery, reported in the October 2015 issue of *Gastroenterology*, could lead to new treatment options for the 65 percent of individuals with IBD who do not respond or become resistant to anti-TNF medications.

According to lead author Shivesh Punit of The Saban Research Institute, discovering that tumor necrosis factor receptor 2 (TNFR2) mitigates inflammation in mice was surprising, given that therapies that target tumor necrosis factor (TNF) are the primary treatments for individuals with IBD.

"Understanding this mechanism allows us to target new therapeutic approaches for patients who don't respond to current therapies," said principal investigator Brent Polk, MD, who was senior author on this study. Polk is a pediatric gastroenterologist and director of The Saban Research Institute of Children's Hospital Los Angeles, and is also professor and chairman of pediatrics at the Keck School of Medicine of the University of Southern California.

An autoimmune disorder that causes inflammation of the intestinal tract, IBD is a broad term that includes ulcerative colitis and Crohn's disease. Characterized by severe gastrointestinal symptoms that get worse over time, IBD negatively affects quality of life and increases risk of colon cancer. In the United States, more than one million people are living with IBD with a cost of treatment of over one billion dollars each year. Currently, there is no cure for IBD. For patients with moderate to severe disease, one current therapy acts to blocks TNF. Although anti-TNF medications represent a significant breakthrough in treatment, they are effective in only one third of individuals suffering from IBD. Recent research suggests there are various conditions that lead to the disease including a microbial imbalance in the gut, dysregulated immunity and alterations in the epithelial cells that line the intestinal tract.

In the current study, investigators examined the role of TNFR2 in mice with IBD. Biological activity of TNF is mediated by two cell surface receptors—TNFR1 and TNFR2. TNFR2 is located primarily on immune cells and during inflammation increases in the intestinal epithelial cells. When the investigators blocked this receptor-mimicking the effect of anti-TNF treatment-they noted an increase in severity and decrease in time to onset of colitis. To verify that the effect was mediated by TNFR2, they did bone marrow transfers, and the mice that got TNFR2-deficient bone marrow developed severe disease.

The investigators also noted that loss of TNFR2 increased cytotoxic CD8 T-cells two-fold. When they specifically inhibited CD8 cells, IBD resolved. They also showed that loss of TNFR2 on CD8 cells alone worsened IBD. These observations led the investigators to conclude that CD8 T-cells worsen IBD in this model, and that TNFR2 alleviates IBD by inhibiting these cells.

Provided by Children's Hospital Los Angeles

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