Researchers Discover New Signaling Pathway Linked to Inflammatory Disease

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Scientists at the University of California, San Diego School of Medicine have described for the first time a key inhibitory role for the IL-1 signaling pathway in the human innate immune system, providing novel insights into human inflammatory bowel disease (IBD) and potential new treatments.

The research, led by Jose M. Gonzalez-Navajas, PhD, and Eyal Raz, MD, a professor of medicine at UC San Diego, is published as a Brief Definitive Report in the December issue of *The Journal of Experimental Medicine.*

The researchers report that signaling by the interleukin 1 receptor (IL-1R) controls expression of a protein called DUBA (deubquitinase A), which in turn affects production of anti-inflammatory cytokines reacting to certain bacterial stimuli. Cytokines are molecules that help trigger an immune system response to infections and cancer. Some induce inflammation, some suppress it.

The IL-1R is essential to producing key anti-inflammatory cytokines like IL-10 and type 1 interferon, but genetic alterations, infection and some drugs can disrupt the signaling process, resulting in reduced or increased cytokine production that upsets delicate balances and leads to disease. Laboratory mice deficient in IL-1R type signaling were shown to produce fewer anti-inflammatory cytokines and were more susceptible to a condition similar to human inflammatory bowel disease. Human IBD encompasses a group of disorders affecting the colon and small intestine. The major types are Crohn's disease and ulcerative colitis.

The authors said the research also revealed the deleterious effects of some anti-inflammatory drugs. IL-1 is a pro-inflammatory cytokine implicated in certain conditions like rheumatoid arthritis and gout, the latter a painful inflammation of the toes and feet. The authors propose that several drugs currently used to treat these conditions by blocking IL-1 activity could be harmful to patients suffering from IBD, which generally involves an overwhelming immune response against normal, non-pathogenic gut bacteria.

"Our findings indicate that the use of such drugs can be harmful and therefore should be avoided in such patients," said Raz.

Co-authors include Jason Law, Kim Phung Nguyen, Meha Bhargava, Mary Patricia Corr, Lars Eckmann and Jongdae Lee of the UC San Diego's Department of Medicine, Nissi Varki of the Department of Pathology and Hal M. Hoffman of the Department of Pediatrics.

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