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## 2016

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# Antiinflammatory drug HUMIRA enhances specific TNF function in rheumatoid arthritis patients

Published on June 7, 2016 at 6:52 AM

Researchers from University College London have discovered that the widely used antiinflammatory drug HUMIRA doesn't just work by inhibiting its target protein, TNF, but by enhancing a particular function of TNF in rheumatoid arthritis patients. The study, "Anti-TNF drives regulatory T cell expansion by paradoxically promoting membrane TNF-TNF-RII binding in rheumatoid arthritis," which will be published online June 6 in The Journal of Experimental Medicine, may help explain the divergent efficacies of different TNF-targeting drugs.

TNF is an important inflammatory molecule produced by the immune system, and TNF inhibitors are commonly used to treat inflammatory diseases such as rheumatoid arthritis and Crohn's disease. One such inhibitor is the monoclonal anti-TNF antibody adalimumab, commonly marketed under the brand name HUMIRA. Michael Ehrenstein and colleagues at University College London previously found that treating rheumatoid arthritis patients with adalimumab increased the number of regulatory T cells capable of suppressing inflammation. Researchers presumed that this was because, in the absence of adalimumab, TNF blocks the development of these regulatory T cells. Mysteriously, however, another TNF inhibitor, etanercept, doesn't induce the formation of these inflammation-suppressing T cells in rheumatoid arthritis patients.

Ehrenstein and his colleague, Dao Xuan Nguyen, now report that, unlike etanercept, adalimumab actually enhances the ability of TNF to induce the formation of antiinflammatory T cells. In particular, Nguyen and Ehrenstein discovered that adalimumab increases the expression of TNF on the surface of patient monocytes and promotes the association of these TNF molecules with receptor proteins on the surface of regulatory T cells. This activates a signaling pathway that endows the T cells with the capacity to suppress inflammation.

Adalimumab may therefore block the proinflammatory functions of soluble TNF secreted by immune cells, while augmenting the activity of membrane-bound TNF that ultimately helps to resolve inflammation. "These results highlight how a treatment that targets a pivotal inflammatory cytokine not only preserves but actually boosts the pro-resolution forces driven by that pathway, thereby introducing a novel therapeutic paradigm," Ehrenstein says.

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Source:
The Rockefeller University Press

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