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Research suggests new way to treat inflammatory gut disease and prevent rejection of bone marrow transplants

October 31 2017

A new study explains how a widely used drug is effective against inflammatory bowel disease and rejection of bone marrow transplants, while suggesting another way to address both health issues.

Researchers at NYU School of Medicine found that the value of the drug infliximab, marketed as Remicade, in both applications proceeds from its ability to block the contribution of the protein tumor-necrosis factor alpha, or TNF alpha, to problem-causing inflammation.

TNF alpha expands the rush of immune cells to the site of an infection, where they seek to destroy foreign invaders like bacteria. However, these same inflammatory responses can become part of a disease if they mistakenly target the body's own cells, such as occurs in the case of autoimmune conditions like Crohn's disease.

Published in the *Journal of Experimental Medicine* online Oct. 31, the new study found that infliximab prevents TNF alpha from speeding the death of Paneth cells, which protect the gut from microbes. The research team also found that the action of a gene, ATG16L1, kept TNF alpha-driven inflammation from triggering the self-destruction of too many Paneth cells, by an explosive process called necroptosis.

In experiments with mice, the researchers found that Paneth cells engineered to lack a functional ATG16L1 gene were five times more

likely to die in the face of rising TNF-alpha signals than normal cells.

Furthermore, the study authors found that the action of ATG16L1 protected tissue against the spikes in TNF-alpha levels seen in graft-versus-host disease, a frequently occurring complication of bone marrow transplants in blood cancer patients. As the immune cells in the recipient recognize transplanted cells as foreign, they mount an inflammatory response that can lead to the body rejecting the transplant. In mice undergoing a bone marrow transplant, ATG16L1-deficient mice were three times more likely to die or show signs of transplant rejection than mice with the protective action of ATG16L1 in place.

"Our study results are the first to argue that we may be able to treat inflammatory bowel disease and protect against transplant rejection not only by blocking TNF alpha as is done currently, but also by stimulating ATG16L1 to prevent early death of cells lining the gut," says study senior investigator Ken Cadwell, PhD, an associate professor at NYU School of Medicine and NYU Langone Health's Skirball Institute for Biomolecular Medicine.

Cadwell cautions that such a strategy must await further evidence to confirm his theory that this trend in Paneth cell death occurs in people deficient in ATG16L1 who are, like his study mice, prone to higher risk of inflammatory disease and transplant rejection.

As part of the study, researchers found that mice engineered to develop symptoms of human inflammatory disease, and which also lacked the ATG16L1 gene, developed gut damage. The ATG16L1-deficient mice had shorter intestines, reduced number of Paneth cells, and rising TNF-alpha levels. But mice with a working version of the gene suffered little to no damage to their gut-lining cells. When TNF-alpha action was blocked in the mice lacking ATG16L1, their damaged guts underwent repair and the mice survived. All untreated mice died.

More information: *Journal of Experimental Medicine* (2017). jem.rupress.org/cgi/doi/10.1084/jem.20170558