# Unexpected molecular partners may offer new way to counter inflammatory diseases

December 16 2015

When overactive or off target, certain cells in the immune system that normally fight infection instead attack a person's own tissue. This process fuels inflammation as part of autoimmune diseases. Now, a study from researchers at NYU Langone Medical Center publishing on December 16 in *Nature* has revealed a new way to curtail these mechanisms that could shape the design of future drugs.

The researchers, led by immunologist Dan Littman, MD, PhD, found that a specific enzyme - DDX5 - must first unfurl a snippet of genetic material called Rmrp to activate T helper 17 (Th17) cells. These cells are known to play important roles in autoimmune and inflammatory diseases.

"Our study results suggest a surprising, new way to control the contribution of Th17 cells to abnormal inflammation," says Littman, the Helen L. and Martin S. Kimmel Professor of Molecular Immunology in the Department of Pathology at NYU Langone. "This is crucial given the limited efficacy of currently available treatments for diseases that affect millions," adds Littman, also a member of the Kimmel Center for Biology and Medicine of the Skirball Institute.

The new study centers on T lymphocytes, immune cells that react to infections by expanding into a cellular army that attacks the bacterium or fungus at hand. A subset of T cells, Th17 cells, produce interleukin 17 (IL-17), a signaling protein (cytokine) that amplifies normal immune responses - but is also closely linked to autoimmune disease.

Current treatments that block the actions of IL-17 have been effective against the autoimmune skin disease psoriasis, but make worse inflammatory bowel diseases, including Crohn's disease. Evidence suggests that IL-17 may have several functions in the gut, some protective, but others that contribute to inflammation. Th17 cells also make other cytokines that may encourage disease.

Instead of targeting any one cytokine with drugs, a better way to counter inflammatory gut disease, says Littman, may be to prevent some Th17 cells from becoming mature and active in the first place. For this reason, immunologists are excited by the idea of shutting down with drugs a protein called retinoid-related orphan receptor gamma t (RORγt). It signals Th17 cells to mature and produce cytokines.

Older, experimental treatment approaches that broadly target RORγt, however, may interfere with the formation of new T cells or add to risk for one kind of lymphoma, Littman says. The current finding suggests a new way to block RORγt action through its partners, and only in Th17 cells.

The newly published study found two new partners with RORγt that, when working together, latch onto genes that control Th17 cell maturity at the right spots. The first is a DEAD-box RNA helicase (DDX5) required for expression of genes controlling Th17 maturation. Helicases like DDX5 unwind RNA chains as part of passing on genetic messages, but had never been seen to influence Th17 cell genes. The other newfound RORγt partner is a long, noncoding RNA called Rmrp, part of a class of material that some experts once called "junk DNA" - and thought to have no function in the body.

The researchers showed that DDX5 causes Rmrp to change shape and attach to RORγt, which equips a larger complex to attach to its target sites as it turns on genes. In experiments, the team found that mouse

versions of key autoimmune diseases do not occur if this mechanism is not in place, or if you change even a single unit in the Rmrp molecular structure. Th17 cells still mature in mice engineered to lack functional DDX5 or Rmrp, but they are frozen in a poised state. They never take a second step that arms them to protect the gut from harmful bacteria, or when they misfire, to drive autoimmune disease.

While the study is in mice, a rare genetic disease called Cartilage-Hair Hypoplasia provides evidence that similar mechanisms are at work in humans. Patients with the condition have defective immune systems based on coding errors in Rmrp, and researchers hope the work will lead to new treatments for them, says Littman, also a Howard Hughes Medical Institute investigator.

Beyond autoimmunity, the study has implications for human complexity. Genes are DNA chains that encode instructions for the building of proteins, which make up the body's structures and carry its signals. As a first step in protein-building, DNA is converted into a related nucleic acid in RNA. Despite being more complex, humans have fewer genes than wheat. The explanation is that human cells put the same genes to many uses thanks to regulatory mechanisms that govern when and where genetic material is accessed. Some of these functions are performed by myriad non-gene RNA snippets, with more being discovered regularly and the DDX5/Rmrp/RORγt partnership as the latest example.

**More information:** Wendy Huang et al. DDX5 and its associated lncRNA Rmrp modulate TH17 cell effector functions, *Nature* (2015). DOI: 10.1038/nature16193

Provided by New York University