EXPERIMENTAL ARTHRITIS

How T_{reg} cells lose FOXP3

"*Ptpn2* haploinsufficiency increases development of arthritis in mice through an effect on regulatory T (T_{reg}) cells," says Mattias Svensson, first author of a new study that might account for the association of human autoimmune diseases with loss-of-function single nucleotide polymorphisms (SNPs) in *PTPN2* (which encodes the phosphatase PTPN2).

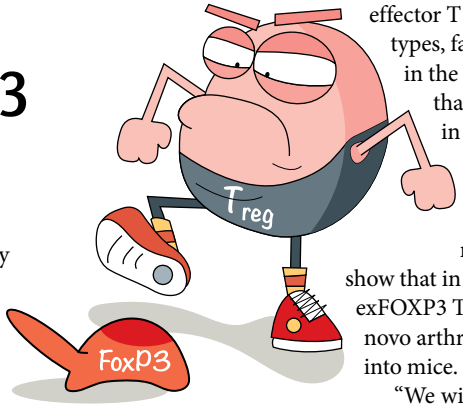
Loss of stability of the transcription factor FOXP3 can result in transdifferentiation of FOXP3$^+$ T_{reg} cells into so-called exFOXP3 T_{reg} cells that are pro-inflammatory and contribute to autoimmune disease partly by producing IL-17A.

Although IL-6 was already thought to contribute to the loss of FOXP3 stability, underlying mechanisms were unclear. "We show that PTPN2 is of critical importance in retaining T_{reg} cell stability during autoimmune inflammation," notes Svensson. "PTPN2 does this by controlling IL-6-induced STAT3 signalling."

The new data show that severity of disease in two arthritis mouse models that are dependent on innate immune cells (the K/B × N passive serum transfer and collagen antibody-induced models) is not substantially different in *Ptpn2*$^{+/-}$ mice versus wild-type mice. By contrast, spontaneous or mannan-induced arthritis is exacerbated by haploinsufficiency of *Ptpn2* in the T cell-dependent SKG model.

Furthermore, T_{reg} cells transferred into mice (which were then subjected to mannan-induced arthritis) more readily transdifferentiated into exFOXP3 T_{reg} cells if they were sourced from *Ptpn2*$^{+/-}$ mice, rather than from wild-type mice.

Although the severity of disease in the SKG mice might be affected by the level of expression of *Ptpn2* by effector T cells or other cell types, fate-mapping data in the new article support that haploinsufficiency in the T_{reg} population is sufficient to modulate disease. Importantly, the researchers also show that in vitro-generated exFOXP3 T_{reg} cells drive de novo arthritis when injected into mice.



Credit: Springer Nature Limited

> "haploinsufficiency in the T_{reg} population is sufficient to modulate disease"

"We will continue our studies to further understand the mechanism by which PTPN2 regulates T_{reg} cell stability," adds Nunzio Bottini, corresponding author of the study. "Hopefully an understanding of this biology might be used in the design of personalized therapies for patients with *PTPN2* variants that predispose them to autoimmune diseases."

Nicholas J. Bernard

ORIGINAL ARTICLE Svensson, M. N. D. et al. Reduced expression of phosphatase PTPN2 promotes pathogenic conversion of Tregs in autoimmunity. *J. Clin. Invest.* https://doi.org/10.1172/JCI123267 (2019)

IMMUNOLOGY

Unmasking the double life of ELMO1

Defects in the clearance of apoptotic cells are linked to inflammation and autoimmunity, and single nucleotide polymorphisms (SNPs) in the genes of several components of cell clearance pathways have been linked with rheumatoid arthritis (RA). However, investigations into one such cell clearance molecule, engulfment and cell motility protein 1 (ELMO1), have revealed an unexpected non-canonical role that questions conventional wisdom about conserved protein functions.

"We initially hypothesized that loss of ELMO1 would worsen inflammatory arthritis, as ELMO1 promotes apoptotic cell engulfment," explains corresponding author Kodi Ravichandran. "Surprisingly, *Elmo1*-deficient mice had reduced joint inflammation in two arthritis models." Further investigations using conditional knockout mice and the K/B × N serum transfer model of arthritis revealed that it was the loss of ELMO1 function specifically in neutrophils that attenuated the development of arthritis.

> "the loss of ELMO1 function specifically in neutrophils … attenuated the development of arthritis"

A comparison of the protein interaction partners of ELMO1 in neutrophils and macrophages uncovered several neutrophil-specific interaction partners that had known associations with RA. Many of these proteins are involved in responses to inflammatory stimuli and cell migration, functions that were also restricted in *Elmo1*-deficient neutrophils. Knocking out total *Elmo1* using an inducible system in mice with early, but not established, arthritis reduced disease severity compared with mice in which *Elmo1* deletion was not induced, suggesting a role for ELMO1 in neutrophil recruitment during the early stages of arthritis.

"Neutrophils from the peripheral blood of human donors that carry an RA-associated SNP in *ELMO1* had increased migratory capacity to chemokines linked to arthritis," says lead author Sanja Arandjelovic. "These data suggest a neutrophil-specific ELMO1-dependent signalling nexus that could be a new target for therapeutic intervention in RA."


Credit: bortonia/DigitalVision Vectors/Getty

Given the interest in the potential to therapeutically target apoptotic pathways in RA, such cell type-specific, non-canonical functions of evolutionarily conserved components of cell clearance pathways seem to be deserving of further attention.

Joanna Collison

ORIGINAL ARTICLE Arandjelovic, S. et al. A noncanonical role for the engulfment gene ELMO1 in neutrophils that promotes inflammatory arthritis. *Nat. Immunol.* **20**, 141–151 (2019)