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EXPERIMENTAL ARTHRITIS

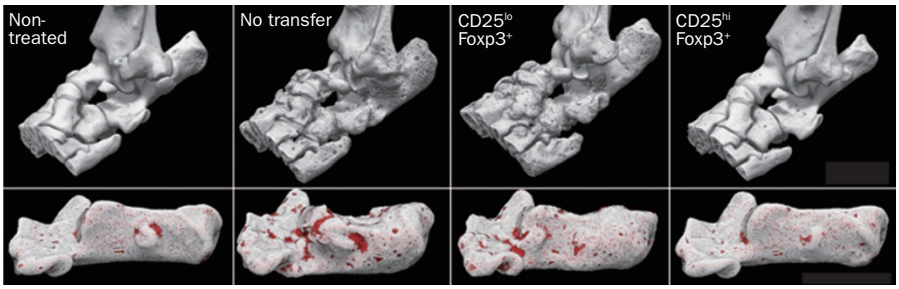
Tipping the balance: conversion of Foxp3$^+$ T cells to T_H17 cells is crucial in autoimmune arthritis

The fine balance between suppressive and immune-activating responses is important in the development of autoimmune disease. In a new study published in *Nature Medicine*, researchers have shown that the conversion of forkhead box protein P3 (Foxp3)$^+$ T cells into pathogenic type 17 helper T (T_H17) cells has a key role in the development of autoimmune arthritis in animal models. The plasticity of Foxp3$^+$ T cells might, therefore, be a determinant in the balance between autoimmunity and self-tolerance.

Rheumatoid arthritis is a multisystem inflammatory autoimmune disease that typically results in cartilage and joint destruction owing to chronic inflammation in the synovial membranes. An area of research interest has been the balance between regulatory T (T_{REG}) cells and IL-17 producing T_H17 cells as an important determinant of autoimmune disease. Speaking to *Nature Reviews Rheumatology*, authors Hiroshi Takayanagi and Noriko Komatsu explain the rationale for their new study: "Imbalance between T_H17–T_{REG} cells may cause the disease, but it remains unknown how pathogenic T_H17 cells are generated in arthritis."

Furthermore, whether the stability of Foxp3 expression, a key T_{REG}-cell transcription factor, has a crucial role in autoimmune disease is debated, with poor understanding of whether T cells with unstable Foxp3 expression are pathologically relevant. As such, Takayanagi, Komatsu and colleagues questioned the importance of these Foxp3-unstable T cells (CD25^{lo}Foxp3$^+$) versus Foxp3-stable T cells (CD25^{hi}Foxp3$^+$) in the context of arthritis.

The investigators examined the stability of Foxp3$^+$ cells in a collagen-induced arthritis (CIA) mouse model and assessed whether Foxp3 expression affected the development of arthritis. Only adoptive transfer of Foxp3-stable T cells (that is *bona fide* T_{REG} cells) led to reduced joint swelling and bone destruction in CIA mice; transfer of Foxp3-unstable T cells resulted in arthritis. Upon tracking these Foxp3-unstable T cells in arthritic mice, they found that Foxp3 expression was lost and the cells switched to IL-17 expression and an activated T_H17 phenotype—an important change given that T_H17 cells are known to be involved in the development of arthritis.



Microcomputed tomography of calcaneus in ankle joints in a mouse model of arthritis. Bone destruction is observed upon adotive transfer of Foxp3-unstable T cells, but is reduced with transfer of Foxp3-stable T cells. Image taken from Komatsu, N. *et al. Nat. Med.* doi:10.1038/nm.3432 © Nature Publishing Group.

Upon further characterization under pathological conditions *in vivo*, these switched Foxp3-to-T_H17 T cells (named exFoxp3 T_H17 cells by the study authors) were shown to accumulate in the inflamed synovium of CIA mice. Moreover, genome-wide expression analysis, CpG methylation analysis and examination of cell-surface markers indicated that these exFoxp3 cells might be result from peripherally-derived T_{REG} cells. "We found that exFoxp3 T_H17 cells express some T_H17 marker genes and at the same time express certain T_{REG} marker genes, as well as some specific genes including *Sox4* and *Tnfsf11* [encoding RANKL], which is distinct from any known pathogenic T_H17 subsets," add Takayanagi and Komatsu.

They found that exFoxp3 T_H17 cells were potent osteoclastogenic T cells, more so than naive CD4$^+$-derived T_H17 cells, and antigen-specific exFoxp3 T_H17 cells were highly arthritogenic *in vivo*, leading to accelerated onset and increased severity of arthritis. In addition, co-culture studies revealed that the interaction (via IL-6) of synovial fibroblasts with the Foxp3$^+$ T cells was shown to promote the switch to a T_H17 phenotype.

"The most important implication of this paper, and of the area in general, is that control of inflammation is vital to ameliorate diseases such as rheumatoid arthritis," says Michael Ehrenstein, University College London, who was not involved in the new study. "If inflammation is not controlled, then cells that normally control inflammation such as T_{REG} cells can be subverted to produce pathogenic cytokines," he notes.

"We showed that unstable Foxp3$^+$ T cells convert to T_H17 cells, but it remains unclear whether the unstable cells are completely identical to T_{REG} cells, and further studies are necessary to investigate the fate of autoantigen-specific T_{REG} cells *in vivo*," say Takayanagi and Komatsu. The researchers postulate that the fate of the unstable Foxp3 cells is a critical determinant of self tolerance versus autoimmunity, and hope that further characterization of these exFOXP3 T_H17 cells in humans could help to improve diagnosis and management of autoimmune disease.

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