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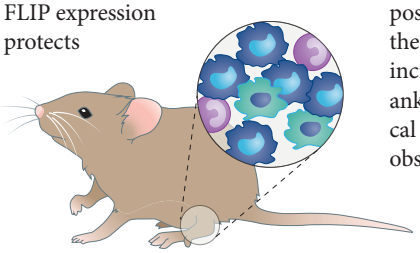
EXPERIMENTAL ARTHRITIS

FLIPping the switch on macrophages

> the number of F4/80^{hi} macrophages and the level of expression of F4/80 inversely correlated with joint swelling

Reducing the expression of anti-apoptosis molecule FLICE-like inhibitory protein (FLIP, also known as CASP8 and FADD-like apoptosis regulator) in macrophages could protect against inflammatory arthritis, according to new findings published in *Arthritis & Rheumatology*. Deleting FLIP in macrophages exacerbated the early stages of serum transfer-induced arthritis in mice, but attenuated the later peak and resolution stages. "Suppression of FLIP in macrophages might be an effective strategy to increase anti-inflammatory macrophages and to treat inflammatory conditions, such as rheumatoid arthritis," states corresponding author Richard Pope.

Previous work by Pope's group demonstrated that FLIP expression protects macrophages from Fas ligand-mediated apoptosis, leading to the hypothesis that deletion of FLIP in myeloid cells would reduce the number of synovial tissue macrophages by increasing apoptosis of these cells, thereby protecting against arthritis. To investigate this hypothesis, Pope and colleagues generated mice that do not express FLIP in their myeloid cells (Flip$^{f/f}$LysM$^{c/+}$ mice). The total numbers of macrophages in the joints were unchanged in these mice compared with their littermate controls, and 9 days after arthritis induction, they showed similar levels of apoptosis and necrosis in synovial macrophages in their ankles compared with their littermate controls.



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Flip$^{f/f}$LysM$^{c/+}$ mice had modestly increased joint swelling at 4 days post-injection compared with their littermate controls, as well as increased inflammation around the ankle joints as assessed by histological analysis. However, the reverse was observed at 9 days following arthritis induction. Surprisingly, the number of resident macrophages in the synovium was increased at day 9, corresponding to an increase in a population of F4/80^{hi} macrophages. These macrophages had an M2-like phenotype, with increased expression of *IL10* and *RETNLA* mRNA and decreased expression of *NOS2* mRNA compared with F4/80^{lo} macrophages. Furthermore, the number of F4/80^{hi} macrophages and the level of expression of F4/80 inversely correlated with joint swelling.

Pope and colleagues speculate that the Flip$^{f/f}$LysM$^{c/+}$ mice had improved resolution of arthritis due to these anti-inflammatory macrophages, and that FLIP suppresses the transition of monocytes to suppressive macrophages. "In future studies we will examine the mechanism(s) by which the level of FLIP regulates macrophage polarization," concludes Pope.

Jessica McHugh

ORIGINAL ARTICLE Huang, Q. Q. *et al.* Increased F4/80^{hi} macrophages is associated with suppression of serum transfer induced arthritis in mice with Flip reduced in myeloid cells. *Arthritis Rheumatol.* http://dx.doi.org/10.1002/art.40151 (2017)