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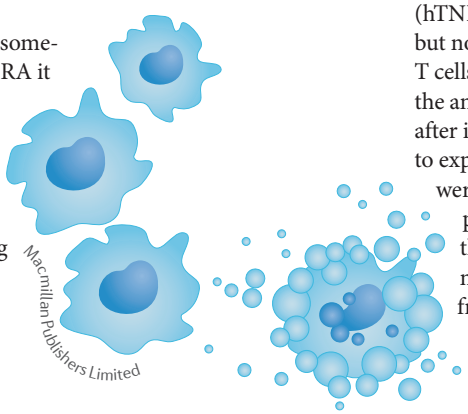
EXPERIMENTAL ARTHRITIS

Anti-TNF kills the macrophage response

Although synovial tissue macrophages are a reliable biomarker of clinical response to treatment in rheumatoid arthritis (RA), the mechanism underlying the reduction of these macrophages following TNF inhibition is unknown. New research published in the *Journal of Immunology* suggests that the initial reduction of macrophages in response to infliximab is attributable, at least in part, to increased apoptosis of macrophages and decreased chemokine secretion by the remaining macrophages.

> “Ly6C$^+$ macrophages … were decreased in the ankles of hTNFtg mice at day 3 after infliximab treatment”

The findings were somewhat unexpected. “In RA it is thought that many of the macrophages in the joints are derived from circulating monocytes,” explains corresponding author Richard Pope. “Our hypothesis was that increased emigration from the joint was the cause of the reduction of macrophages. Using the human TNF transgenic mouse model of arthritis, we were not able to identify increased emigration. In fact, we found decreased migration of monocytes and increased macrophage apoptosis as the cause of the reduction of synovial tissue macrophages shortly after treatment with a TNF inhibitor.”



Treatment with the TNF inhibitor infliximab effectively controlled clinical symptoms of spontaneous arthritis in human TNF transgenic (hTNFtg) mice. Ly6C$^+$ macrophages, but not granulocytes, dendritic cells, T cells or B cells, were decreased in the ankles of hTNFtg mice at day 3 after infliximab treatment. Contrary to expectations, Ly6C$^+$ macrophages were decreased in the draining popliteal lymph nodes, and there was no evidence of CCR7-mediated egress of macrophages from the joints.

Increased apoptosis of Ly6C$^+$ macrophages was observed in both the ankles and the draining popliteal lymph nodes of infliximab-treated hTNFtg mice in comparison with untreated mice at day 3. No difference in necrotic cells was noted at either site, and there was no increase in apoptosis of circulating Ly6C$^+$ macrophages. The researchers also documented decreased migration of monocytes, mediated by a reduction of the classical monocyte chemokine CCL2 in the ankles of hTNFtg mice following infliximab treatment.

“Our data clearly demonstrated the novel observation that the reduction of macrophages in the joints of TNF transgenic mice shortly after starting infliximab was due to decreased migration of monocytes into the joints and to increased apoptosis,” concludes Pope.

Sarah Onuora

ORIGINAL ARTICLE Huang, Q.-Q. *et al.* The role of macrophages in the response to TNF inhibition in experimental arthritis. *J. Immunol.* **200**, 130–138 (2018)