**Clinical Connections**

**Association of Increased F4/80\(^{\text{high}}\) Macrophages With Suppression of Serum-Transfer Arthritis in Mice With Reduced FLIP in Myeloid Cells**


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**SUMMARY**

Macrophages are increased in number in inflamed rheumatoid joints. The number of sublining macrophages correlates with disease activity, and neutralization of mediators produced by these cells is effective therapy in many patients. Under usual circumstances, inflammation resolves in part due to programmed cell death, or apoptosis. In trying to understand why joint macrophages in rheumatoid arthritis (RA) are resistant to apoptosis, Huang and colleagues found that the FLIP protein, which protects against death receptor–mediated apoptosis, was greatly increased in these cells. When FLIP was reduced experimentally, macrophages underwent apoptotic cell death. To determine if FLIP reduction might be an effective therapeutic approach, mice deficient in FLIP in myeloid cells (*Flip\(^{f/f}\)Lys\(^{c/+}\)*) were generated and found to demonstrate a reduced number of macrophages but increased neutrophils. When serum-transfer arthritis was induced in these mice, the arthritis resolved more quickly; however, macrophage numbers in the inflamed joints were increased. In the *Flip\(^{f/f}\)Lys\(^{c/+}\)* mice, it was found that macrophages survived most likely due to an increase in other antiapoptotic proteins resulting from the inflammation. Notably, the surviving macrophages demonstrated an increase in the number of F4/80\(^{\text{high}}\) macrophages, which were polarized toward an antiinflammatory phenotype. These observations suggest that polarizing macrophages by modulating the expression of FLIP may be an effective therapy in patients with RA.

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**KEY POINTS**

- FLIP is required for macrophage survival in the steady state and is increased during inflammation.
- During inflammation, macrophages survive the forced reduction of FLIP.
- When FLIP is reduced in macrophages under inflammatory conditions, there is an increase in F4/80\(^{\text{high}}\) macrophages with an antiinflammatory phenotype.
- The increased number of F4/80\(^{\text{high}}\) macrophages is highly associated with enhanced resolution of arthritis.
Expression of HLA–B27, a major histocompatibility complex (MHC) molecule, is strongly associated with spondyloarthritides such as ankylosing spondylitis. Current theories suggest that initiation of disease requires gastrointestinal (GI) inflammation, which is influenced by host (e.g., HLA–B27) and microbial (dysbiosis) factors. Transition to a systemic inflammatory state results in disease establishment and the classic clinically observed skeletal changes. Although the influence of GI inflammation has been appreciated for decades, we still do not fully understand the interaction between the GI microbiota and the systemic immune response. In the human HLA–B27–transgenic rat model of spondyloarthritis, a germ-free state inhibits the development of both colitis and arthritis, while normal microbiome colonization alters the myeloid compartment, such that myeloid precursors with osteoclastogenic potential have an exacerbated response to tumor necrosis factor (TNF). Ansalone and colleagues found that a combination of deep immune profiling and treatment with broad-spectrum antibiotics in this rat model revealed that perturbation of the GI microbiota not only had profound effects on GI inflammation, but also altered the systemic expression of interleukin-1α (IL-1α) and chemokine ligand 2 (CCL2). These observed changes in the systemic response also corresponded to a decrease in the number of monocytes primed to respond to TNF and proceed to an osteoclast lineage. This study illustrates the interaction between the GI environment and innate immunity and how the latter may drive the characteristic pathology of the spondyloarthritides. Further study of how manipulation of the GI microbiome may be used to treat this disease may provide insight into alternative approaches, which could include fecal transplants, diet modifications, and/or targeting of specific bacterial strains.