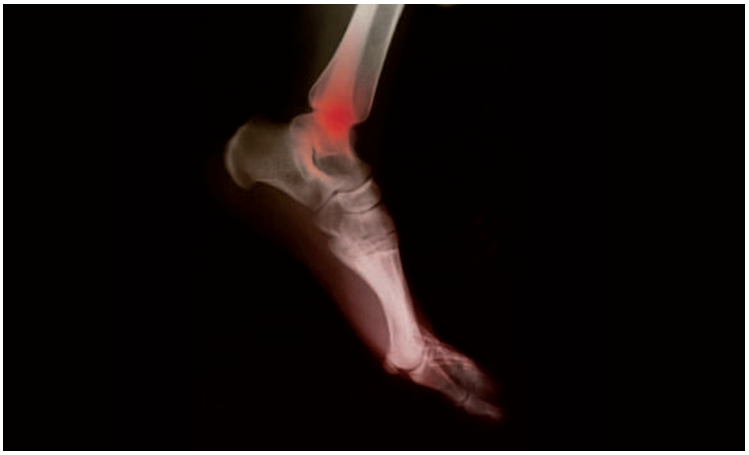

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# Joint damage without antigen

The development of various autoimmune diseases, including rheumatoid arthritis, is thought to be due to a breakdown in $CD4^+$ T cell tolerance for a tissue-specific antigen. However, several lines of evidence have suggested that cognate antigen recognition by $CD4^+$ T cells may not always be necessary. Murakami *et al.* now show that initiation of $CD4^+$ T cell-dependent arthritis in $gp130^{F759/F759}$ mice involves the local accumulation of activated T helper 17 ($T_H17$) cells in the absence of cognate antigen recognition. This triggers an interleukin-17A (IL-17A)-dependent IL-6 amplification loop, which the authors termed the 'IL-6 amplifier'.

$gp130^{F759/F759}$ mice have enhanced IL-6 receptor-mediated signalling and spontaneously develop a rheumatoid arthritis-like disease as they age. In this study, the authors found that $gp130^{F759/F759}$ mice engineered to express a single T cell receptor that recognizes a non-joint antigen also develop arthritis, indicating that cognate antigen recognition was not involved. These mice had a higher number of $T_H17$ cells in lymphoid tissues, and the concentrations of IL-6 and IL-17A in the blood were increased.

The authors hypothesized that local events in the joint (such as microbleeding) may contribute to joint inflammation by triggering the accumulation of activated $T_H17$ cells, so they transferred *in vitro* differentiated $T_H17$ cells to $gp130^{F759/F759}$ or control C57BL/6 mice that had undergone experimental microbleeding in one leg. Arthritis developed in the leg in which microbleeding was induced (but not the other leg) in $gp130^{F759/F759}$ mice following $T_H17$ cell transfer, but did not occur in control mice, suggesting that the enhanced sensitivity to IL-6 in $gp130^{F759/F759}$ mice is required for disease. Microbleeding in the joint induced the localized expression of CC-chemokine ligand 20 (CCL20), which is a chemoattractant for CC-chemokine receptor 6 $(CCR6)^+$ $T_H17$ cells. In addition, IL-6-mediated signalling in type I collagen-expressing cells and local IL-17A production by $T_H17$ cells were shown to be important for disease pathogenesis in this mouse model.

So, putting these observations together, the following model emerges. A local event in the joint, such as microbleeding, induces the accumulation of $T_H17$ cells through increased CCL20 expression, resulting in the activation of the IL-6 amplifier and disease development. The authors propose that in humans, the availability of $T_H17$ cells for such a model could be due to the known age-dependent increase in memory or activated phenotype T cells. Also, several factors, such as infection, may increase sensitivity to IL-6 in the tissue.

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