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PAIN

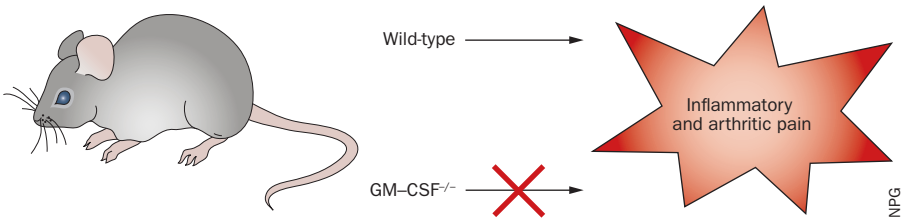
Granulocyte-macrophage colony-stimulating factor required for inflammatory and arthritic pain

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is known to be important in the pathogenesis of a number of inflammatory and autoimmune conditions; indeed, results from clinical trials targeting this cytokine in rheumatoid arthritis highlight its role as an inflammatory mediator. New research, led by Andrew Cook of the University of Melbourne, emphasize the contribution of GM-CSF as a mediator of inflammatory and arthritic pain.

The investigators first sought to determine whether GM-CSF could modulate pain, using the complete Freund's adjuvant (CFA) model—a widely used model of inflammatory pain—in mice deficient for the gene encoding GM-CSF (*Csf2*$^{-/-}$). A single intraplantar injection of 20 μl CFA produced inflammation, indicated by ipsilateral paw swelling, to a similar degree in *Csf2*$^{-/-}$ and in wild-type (WT) mice. Whereas WT mice developed pain (measured as differential distribution of weight) 24–72 h post-CFA injection, *Csf2*$^{-/-}$ mice did not. Notably, in the WT mice, administration of the NSAID indomethacin, which is a nonselective cyclooxygenase inhibitor, relieved the pain observed in WT mice but had no effect on swelling. Thus, inflammatory pain is GM-CSF-dependent in the CFA model.

Next, in order to determine whether GM-CSF could control pain in models of inflammatory disease involving tissue remodelling, the investigators used two different models of monoarticular inflammatory arthritis: antigen-induced arthritis (AIA) and a model of IL-1-driven arthritis. Histology was used to assess arthritic disease in both models.

To induce AIA, which is widely used as a model of rheumatoid arthritis, systemic priming with methylated bovine serum albumin (mBSA) was followed by induction of arthritis via intra-articular injection of mBSA into the right knee and saline into the left knee.



Levels of pain were substantially higher in WT mice than in *Csf2*$^{-/-}$ mice in the AIA model. In the acute, inflammatory stage of AIA, at 1 week after injection of mBSA, swelling and inflammatory cell infiltration was greater in the affected joints of WT mice than in those of *Csf2*$^{-/-}$ mice. *Csf2*$^{-/-}$ mice also showed less severe disease in the chronic, destructive phase of arthritis: at 6 weeks post-injection, joint destruction (including bone erosion) was more pronounced in the WT than the *Csf2*$^{-/-}$ mice.

In the second inflammatory arthritis model, IL-1-driven arthritis was induced in a similar fashion to AIA, but with a subcutaneous injection of IL-1β or saline into the scruff of the neck of the mice up to 2 days after antigen challenge. After this systemic administration of IL-1, WT mice developed pain by day 4 in mBSA-injected knees whereas *Csf2*$^{-/-}$ mice where completely protected from pain development. mBSA-injected knees of *Csf2*$^{-/-}$ mice also displayed less inflammatory cell infiltration, synovitis and cartilage damage than those of WT mice. Treatment with indomethacin completely attenuated the pain in WT mice, but had no effect on disease severity.

Together, these results suggested an important role for GM-CSF in inflammatory and arthritic pain. "We demonstrated for the first time that GM-CSF was absolutely required for pain development in both the inflammatory pain and arthritis models," says Cook, "including for IL-1-dependent arthritic pain."

But does GM-CSF itself induce inflammatory pain? This question was assessed by use of a model of GM-CSF-driven arthritis, in which GM-CSF, rather than IL-1 as in the model described earlier, was administered systemically following intra-articular injection of mBSA. The GM-CSF-driven arthritis was then treated with indomethacin. "This approach enabled us to determine whether GM-CSF itself could induce inflammatory pain, and whether such pain was cyclooxygenase-dependent," explains Cook.

Injection with GM-CSF induced arthritis to a similar extent as IL-1 administration. Indomethacin treatment was able to reverse GM-CSF-induced pain, but had no effect on severity of arthritis, indicating that pain and arthritis could be under separate control downstream of GM-CSF. "The complete suppression by indomethacin of pain, but not arthritis development, is similar to what is often reported clinically with NSAIDs," says Cook.

Much remains to be learned about the role of GM-CSF within the cytokine network in inflammatory arthritis, and the nature and timing of its algesic effects. The authors argue however, that the current study implicating GM-CSF as a key mediator of inflammatory pain could have major implications for the study of this cytokine in a wide range of diseases, in which pain is a major feature and remains an unmet clinical need.

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