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Sending out the cytokine search party

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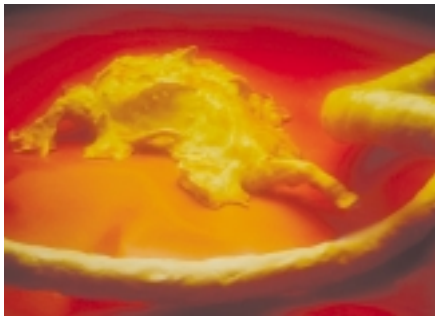
Immunologists investigating a range of inflammatory disorders exacerbated by the notorious macrophage are widening their hunt for therapeutic targets. Several therapies focus on blocking the actions of just one cytokine, but mounting evidence suggests other cytokines – one of which was discovered over 30 years ago – merit further attention.



Macrophages and inflammation

The role of the macrophage in inflammation has long been debated. These cells have roles not only in the initiation but also in the resolution of inflammation, and their actions span both innate and acquired immunity.

A common approach to the treatment of macrophage-mediated disorders, notably rheumatoid arthritis, is to block the actions of the cytokine tumour necrosis factor-α (TNF-α). However, current trials of anti-TNF treatment, although successful, still leave more than 30% of patients without improvement.

In an effort to improve the situation, researchers have looked back through the records and rediscovered an alternative cytokine, macrophage migration inhibitory factor (MIF), which was discovered in 1966. MIF was the first cytokine ever identified, thus earning itself an alternative name, 'interleukin O'. Since its discovery, little research has been done on MIF, but it is now making a comeback. Eric Morand of Monash University, Australia (http://www.monash.edu.au), who was speaking at the *6th World Congress on Inflammation* in Vancouver, Canada (2–6 August 2003; http://www.inflammation2003.com), discussed the latest work on this neglected cytokine.

MIF and the immune response

MIF, in common with the macrophage, has effects on both the innate and acquired immune response and has a proinflammatory action in models of rheumatoid arthritis, glomerulonephritis, multiple sclerosis and inflammatory bowel disease, in which it is overexpressed.

Unlike other cytokines, MIF is also able to antagonize the anti-inflammatory effects of glucocorticoids (GCs), acting through MAP kinases. MIF exerts GC-antagonist effects *in vivo* because its expression is induced by GCs. There is growing evidence of a MAP kinase-dependent, NFκB-independent mode of action of MIF, says Morand, which could be central to its GC-antagonist effects. Data presented by Morand, coupled with the results of others, suggest that antagonism of MIF could be effective in treating a range of inflammatory diseases and could offer similar 'steroid-sparing' benefits as does treatment with anti-TNF.

Proinflammation and GM-CSF

In other work presented at the conference, fellow Australian John Hamilton of the University of Melbourne (http://www.unimelb.edu.au) discussed the proinflammatory role of a third cytokine, granulocyte-macrophage-colony stimulating factor (GM-CSF).

GM-CSF is expressed in inflammatory and immune responses and is present in the synovial fluid of patients with rheumatoid arthritis. Following GM-CSF administration in models of the disease, reports Hamilton, symptoms are exacerbated. Conversely, GM-CSF depletion in disease models results in a greater disease suppression than that observed following TNF-α depletion. Macrophage-colony stimulating factor (M-CSF) also exacerbates disease in models of the disease, heightening the suggestion that CSFs could be effective targets in the treatment of rheumatoid arthritis and possibly other inflammatory diseases.

Clinical experience with anti-TNF therapy suggests that there is room for improvement, therefore, the potential for blocking MIF or GM-CSF is exciting, agreed delegates at the World Congress in Vancouver. However, they warn, current data strongly suggest that a single anti-cytokine treatment will never result in a 100% positive effect.

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