GM-CSF: New Hope for Multiple Sclerosis Patients?

GM-CSF, the neutralization of this cytokine could halt the development of multiple sclerosis. This was demonstrated by the research team of the immunologist Burkhard Becher at the University of Zurich in an animal model. Unlike other known cytokines, they write in the journal *Nature Immunology*, this messenger substance is essential for the development of the disease. By the end of this year, a clinical trial will be launched in which GM-CSF is to be neutralized in MS patients.

The immune systems main task is to protect us from pathogenic microorganisms. To do so, an armada of immune cells is diligently instructed to search for invading pathogens. The ability of immune cells to communicate with one another is vital to this protection. Mistakes in the communication can lead to ‘misunderstandings' and an erroneous attack against ones own tissues. Such is the case in autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis and juvenile diabetes, where the immune system inadvertently attacks the body. So-called helper T cells are chiefly responsible for the fatal immune response.

There are various sub-classes of helper T cells with different tasks and responsibilities. Clinicians and researchers have long been trying to ascertain which sub-class the rogue T cells that attack the body's own organs in autoimmune diseases actually belong to. T cells release certain messenger substances, known as cytokines, which in turn coordinate the appropriate immune response. Until now, the type of T-cell and, above all, the relevant cytokine that causes the inflammation in the brain and spinal cord were not known.

The research team of Professor Burkhard Becher has spent six years testing the relevant cytokines by a process of elimination in transgenic mouse models of multiple sclerosis. Over the years, they were able to cross many factors off the list before eventually hitting the jackpot with GM-CSF (granulocyte macrophage colony-stimulating factor). GM-CSF is produced by a newly discovered subclass of helper T cells. "The MS-like disease could not be induced in mice without GM-CSF," says Becher.
"What's more, the disease could even be cured in MS mice if the cytokine was neutralized."

GM-CSF is not a new cytokine; we already knew that it can cause or aggravate inflammation. Apart from GM-CSF, however, all the other cytokines studied thus far only played a minor role. "GM-CSF is therefore the first T-cell cytokine that's essential for the initiation of an inflammatory reaction," says Becher. Furthermore, the researchers were able to demonstrate that the GM-CSF delivered to the brain by T cells activates the recruitment of tissue-damaging scavenger cells. "Without scavenger cells like these, the inflammation can't really get going in the first place and the neutralization of GM-CSF can even reverse the inflammatory process," says the immunologist.

Patients suffering from rheumatoid arthritis are currently being treated with neutralizing antibodies against GM-CSF in a clinical trial. A trial with MS patients is due to begin at the end of 2011. "We're extremely hopeful," says Becher enthusiastically. "But whether this form of therapy will actually help MS patients remains to be seen. Quiet optimism is the way to go," he explains.

Irrespective of the clinical trial, the team expects the study to have a significant impact on basic and clinical research. "We're really making headway; we now understand much better how an inflammatory lesion can develop in the brain."

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Codarri, L., Gyülveszi, G., Magnenat, L., Hesske, L., Fontana, A., Suter, T., and Becher, B. RORgt drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation. *Nature Immunology*, doi: 10.1038/ni.2027

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