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# Chronic skin inflammation alleviated with lymphatic vessel growth stimulation

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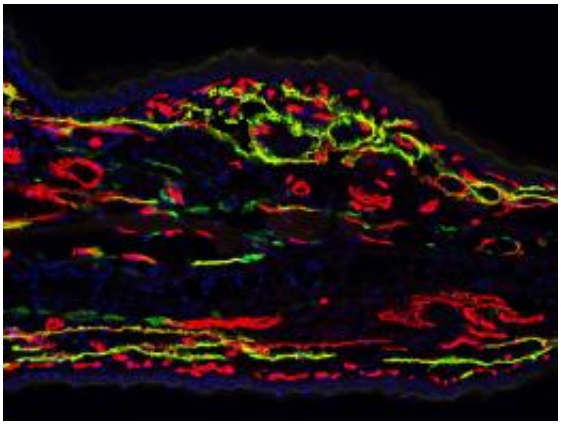

The immunofluorescence image shows lymphatic vessels (yellow), blood vessels (red) and cell nuclei (blue) in the skin of a transgenic mouse, 28 days after inducing chronic inflammation. (Photo: R. Huggenberger, Institute of Pharmaceutical Sciences).

ETH Zurich pharmacists have discovered an astonishing mechanism that could help alleviate the suffering of patients with chronic skin inflammation, by stimulating lymphatic vessel growth.

Bad luck can sometimes turn into good fortune for researchers. A working hypothesis or idea may turn out to be wrong, but the absolute opposite yields the correct result. That is what happened in the research work of Reto Huggenberger, who is studying for a doctorate with Professor Michael Detmar at the Institute of Pharmaceutical Sciences.

The researchers wanted to know what role lymphatic vessels play in chronic inflammatory conditions, particularly skin inflammations such as psoriasis. All chronic inflammatory diseases are associated with the growth of both the blood and lymphatic vessels. The latter are involved in immune responses because they mediate the migration of immune cells from the site of inflammation, e.g. the skin, to the local lymph nodes and can directly produce substances that trigger or maintain the body's inflammatory response.

## Signals like a lock and key

A signal is needed to enable blood vessels and lymphatic vessels to grow. This signal operates on a lock and key principle. The keys are the so-called growth factors, which fit exactly into the corresponding locks, the receptors. These receptors are located on the surfaces of the two types of vessels. Thus the growth factor VEGF-A stimulates blood vessels by docking onto the VEGFR-1 and VEGFR-2 receptors, which are mainly found on blood vessels. Lymphatic vessels, on the other hand, respond mainly to the activation of "their" lock, the VEGFR-3 receptor, whose keys are the factors VEGF-C and VEGF-D.

## Growth stopped, inflammation increased

The researchers then followed the idea of inhibiting the lymphatic vessels so that fewer immune cells can reach the local lymph node and fewer inflammation-promoting substances are produced. They hoped the inflammation would subside as a result.

The researchers inhibited lymphatic vessel activation in a mouse model created for chronic skin inflammation. This pathway runs via the growth factor VEGF-C and its receptor, VEGFR-3, on the surface of the lymphatic vessels. They specifically inhibited the growth of lymphatic

vessels by blocking VEGFR-3 with an antibody. The researchers were astonished by what they subsequently observed: instead of subsiding, the inflammation became more intense.

## Salutary experience

This gave the ETH Zurich pharmacists the idea of testing the opposite effect. They developed a mouse model in which the animals produce excessive amounts of the growth factor VEGF-A, which causes chronic inflammation, and of VEGF-C, which stimulates the VEGFR-3, in their skin. This quite specifically triggered lymphatic vessel growth, i.e. exactly the opposite of what had originally been intended by blocking VEGFR-3.

“The difference was dramatic,” says Huggenberger. Not only was the inflammation reduced, but it regressed entirely within four weeks. The mice’s skin injuries healed. “We didn’t expect that,” he stresses.

## Natural substance as a lymph activator?

The principle that the ETH Zurich researchers were able to demonstrate is not limited to chronic skin inflammation. Similar processes occur in rheumatoid arthritis, a chronic inflammation of the joints, and in chronic inflammatory diseases of the intestine.

However, the growth factors used in the model are unsuitable for use in humans. These proteins are too large for that purpose. “All we have done is proving the principle,” says Detmar. However, he and his group have already examined around 600 extracts of natural substances to find active ingredients that stimulate the lymphatic vessels. They have found one potential candidate. According to the ETH Zurich professor, with a bit of luck this will be therapeutically usable. In initial experiments the

researchers even observed that the effect of the plant extract was more powerful than the growth factor VEGF-C.

## Inhibiting and stimulating

However, Detmar hopes for an optimal treatment of inflammatory responses if blood vessels are inhibited and lymphatic vessels activated. In fact, the inflammation subsides noticeably if blood vessels can be prevented from growing into the foci of inflammation.

Up to now the medical profession has often used cortisone against inflammation. Psoriasis is often treated with cortisone, especially in the USA, even though unwanted side effects sometimes occur. Detmar hopes his research group's new strategy could provide a long-term replacement for this therapy.

**More information:** Huggenberger R, et al: Stimulation of lymphangiogenesis via VEGFR-3 inhibits chronic skin inflammation. J. Exp. Med. www.jem.org/cgi/doi/10.1084/jem.20100559

Provided By ETH Zurich

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