New factor in the development of psoriasis discovered

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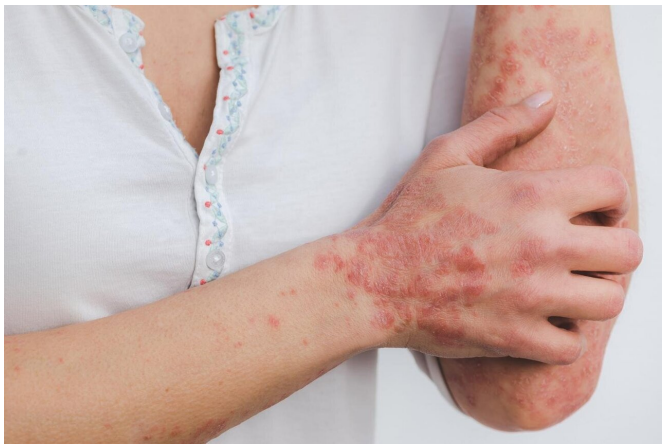

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Psoriasis is a common inflammatory skin condition. The underlying genetic factors have not yet been sufficiently researched. The skin inflammation is usually triggered by external factors such as infections or stress. A research team at the Institute of Cancer Research of the Medical University of Vienna has now managed to identify a new factor in signal transmission of the immune system that plays a major role in the development of a psoriatic episode. The scientists have shown that symptoms can be alleviated by inhibiting the "c-Jun" protein in signal transmission.

The common clinical manifestation of psoriasis is a pinkish-gray thickening of the epidermis in distinct foci of infection, so-called plaques. Biomedical research into the molecular processes involved has shown that a disruption in the normal interaction between the immune system and dermal epithelial cells is responsible for the inflammation. However, it was hitherto unclear which signaling pathways regulate the activation of immune cells, thus contributing to pathogenesis.

Function deciphered

In the recent study published in the leading journal *Embo Molecular Medicine*, it was demonstrated using patient data and animal models that a protein known as "c-Jun" in a particular immune cell, the dendritic cell, plays a major role in promoting psoriatic skin inflammation. "Inhibiting signal transmission by c-Jun alleviates symptoms in the animal model," says lead author of the study Philipp Novoszel from MedUni Vienna's Institute of Cancer Research. The protein that was studied, c-Jun, belongs to a larger family of transcription factors, DNA-binding factors, known as Activator Protein-1 (AP-1). Previous studies have already identified a significant role of these AP-1 proteins in psoriasis in dermal epithelial cells but its function in immune cells was not yet clear.

"In order to answer this question, we examined whether AP-1 proteins in immune cells have a role in the pathogenesis of psoriasis. We identified elevated values of c-Jun in dendritic cells in skin sections of psoriasis patients," explains Novoszel. "To further investigate the role of c-Jun, we deactivated the gene specifically in dendritic cells." When psoriasis-like skin inflammation was now triggered, we found that the deactivation of c-Jun reduced epidermal thickening and decreased the infiltration of immune cells.

Treatment option

Pharmacological inhibition of the c-Jun activating protein, known as JNK (c-Jun N-terminal Kinase) was likewise effective. "That represents a potential treatment option, since highly effective, selective JNK inhibitors are available and could be investigated," stresses Novoszel. A further analysis using human dendritic cells showed that c-Jun controls the secretion of a key molecule in the development of psoriasis, cytokine interleukin-23 (IL-23). High values are characteristically found in psoriasis patients and lead to activation of disease-triggering T cells. "The inhibition of c-Jun-dependent signal transmission could improve the

clinical picture of psoriasis by reducing pathogenic IL-23."

"Our study findings describe a previously unknown, pro-inflammatory role of c-Jun in dermal dendritic cells. This occurs, on a molecular level, through the control of the cytokine interleukin-23. A therapeutic blockade of c-Jun-JNK signal transduction might therefore be a promising therapeutic approach for the treatment of psoriasis," says the study author in summary.

More information: Philipp Novoszel et al. Psoriatic skin inflammation is promoted by c?Jun/AP?1?dependent CCL2 and IL?23 expression in dendritic cells, *EMBO Molecular Medicine* (2021). DOI: 10.15252/emmm.202012409

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