

IL-22 and Psoriasis with

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What is known about IL-22?

Robert Sabat: Interleukin (IL)-22 is a small protein that was discovered in 2000 (1). It is produced and secreted by certain activated immune cell populations, namely T1- and NK-cells (2). IL-22 acts through a receptor complex that is composed of two membrane imbedded chains: IL-22R1 and IL-10R2 (3). The binding of IL-22 to this receptor complex leads in particular to the phosphorylation of transcription factors (mainly STAT 3), which subsequently immigrate into the nucleus and regulate the expression of various genes. Aside from the membrane imbedded receptor chains, a secreted ("soluble") receptor (IL-22BP) also exists and is encoded by a separate gene. IL-22BP binds IL-22 and inhibits its effects *in vitro*, but the biological significance of IL-22BP *in vivo* is not currently known. To our surprise, we found that IL-22R1 is not expressed by resting or

activated immune cells and that this cytokine does not influence the functions of such cells *in vitro* or *in vivo* (4). Instead, the most important target cells of this cytokine are cells in the digestive system, skin, lungs, and kidneys (4).

Our interest in skin is not only linked to the strong expression of the IL-22 receptor complex in this organ but also because we have found high levels of IL-22 in the diseased skin of patients with psoriasis vulgaris, a common skin disorder (4). The difference in IL-22 levels between healthy and diseased skin is greater than the differences for other cytokines such as IFN- γ , IL-1, IL-2, IL-18, or IL-23. Moreover, we found that there are also increased level of IL-22 in the blood of psoriasis patients compared to that of healthy donors. These IL-22 blood levels highly correlate with the severity of disease (5).

Is there any influence of IL-22 on keratinocytes?

Robert Sabat: Keratinocytes belong to the most important target cells of IL-22 (4). They strongly express both chains of the IL-22 receptor complex. Interestingly, IFN- γ (classical T1 cytokine) strengthens the expression of IL-22R1 as well as of IL-10R2 in these cells (4). IL-22 stimulation of keratinocytes led to strong activation of STAT 3, among others, and a weak activation of STAT 1. This stimulation influenced the expression of only a limited number of genes in keratinocytes (5). Through the induction of various anti-

microbial proteins (β -defensin 2, β -defensin 3, psoriasin (S100A7), calgranulin A (S100A8), and calgranulin B (S100A9)), the innate immunity of these cells increases. Moreover, IL-22 inhibits the differentiation of keratinocytes and increases their mobility (5,6). Furthermore, IL-22-stimulated keratinocytes secrete proteases such as collagenase 1 (matrix metalloproteinase 1, MMP 1) and stromelysin 1 (MMP 3), which may play an important role in the remodeling of skin and enable the infiltration of immune cells into the skin.

In which skin diseases does IL-22 have an important role?

Robert Sabat: The currently described effects of IL-22 on keratinocytes let us assume that this cytokine may play an important role in wound healing and the pathological restructuring of the skin, as seen in psoriasis. The changes that IL-22 induces in keratinocytes are identical to the changes of these cells that we observe in wound healing. The inhibition of keratinocyte differentiation and increase in their mobility are essential for these cells to re-epitheliate the wound. Additionally, the induction of anti-microbial proteins by IL-22 in keratinocytes may inhibit bacterial infection of the wound. The assumption that IL-22 does play a role in wound healing is supported by the observation that the wound healing is severely compromised in mice without a functioning STAT 3 (7). The second process in which IL-22 may play an important role is in psoriasis. Psoriasis is a chronic skin disease that is characterized by sharply demarcated, red, and slightly raised lesions with silver-white scales. The micro-

scopic alterations of psoriatic plaques include an infiltration of immune cells and a massively thickened epidermis with atypical keratinocyte differentiation. Despite the fact that the skin's homeostasis is largely malfunctioning, skin infections are rarely seen in psoriasis. Since the early 90's, it was assumed that T1-cells play a dominant role in the pathogenesis of psoriasis. However, recent discoveries made regarding dendritic cells, other T-cell populations, keratinocyte signal transduction, and novel cytokines including IL-22, let us hypothesize that psoriasis is an immunologically induced, overshoot, regeneration-like reaction of the skin in which various cells play a dominant role at different stages. IL-22 may play a role in the distal phases of psoriasis pathogenesis. Our postulated hypothesis regarding the role of IL-22 in psoriasis is supported by the fact that transgenic mice with keratinocytes that express a constitutively active STAT 3 develop a psoriasis-like skin alteration.

Which advantages does IL-22 have as a target?

Robert Sabat: IL-22 is the first example of a new class of immune mediators. It is produced by specific populations of immune cells, but regulates the functions of non-immune tissue cells. For this reason, it is an ideal target for therapeutic intervention. Inhibition/application of IL-22 would not lead to great immunostimulation/immunosuppression, respectively; instead it would regulate the specific functions of tissue cells. Application of IL-22 as a therapy for chronic wounds appears to be a logical conclusion considering the data currently available. Neutralizing IL-22 effects could

be a therapy intervention for psoriasis. From our contacts with pharmaceutical companies, we know that they are currently developing such treatments. Finally, it should be mentioned that IL-22 possibly has a role in other inflammatory T1 diseases such as Morbus Crohn and rheumatoid arthritis.

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