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Original Article

A Targetable, Noncanonical Signal Transducer and Activator of Transcription 3 Activation Induced by the Y-Less Region of IL-22 Receptor Orchestrates Imiquimod-Induced Psoriasis-Like Dermatitis in Mice

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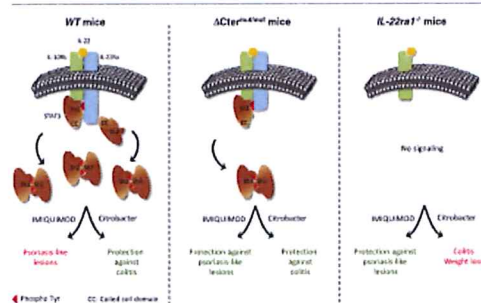
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<https://doi.org/10.1016/j.jid.2021.04.016>

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Exacerbated IL-22 activity induces tissue inflammation and immune disorders such as psoriasis. However, because IL-22 is also essential for tissue repair and defense at barrier interfaces, targeting IL-22 activity to treat psoriasis bears the risk of deleterious effects at mucosal sites such as the gut. We previously showed in vitro that IL-22 signaling relies on IL-22 receptor alpha (IL-22Rα) Y-dependent and -independent pathways. The second depends on the C-terminal Y-less region of IL-22Rα and leads to a massive signal transducer and activator of transcription 3 (STAT3) activation. Because STAT3 activation is associated with the development of psoriasis, we hypothesized that the specific inhibition of the noncanonical STAT3 activation by the Y-less region of IL-22Rα could reduce psoriasis-like disease while leaving intact its tissue defense functions in the gut. We show that mice expressing a C-terminally truncated version of IL-22Rα ($\Delta\text{Cter}^{\text{mut/mut}}$ mice) are protected from the development of psoriasis-like dermatitis lesions induced by imiquimod to a lesser extent than $\text{IL22ra}^{-/-}$ mice. In contrast, only $\text{IL22ra}^{-/-}$ mice lose weight after *Citrobacter rodentium* infection. Altogether, our data suggest that specific targeting of the noncanonical STAT3 activation by IL-22 could serve to treat psoriasis-like skin inflammation without affecting IL-22-dependent tissue repair or barrier defense at other sites.

Graphical abstract



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Abbreviations