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The production and responsiveness to skin interferon (IFNλ1) are regulated by TNF-α

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IL-29 (IFNλ1) is a type III IFN that is highly expressed in lesional skin of lupus patients. IL-29 is produced mainly by tissue cells and cutaneous responsiveness to the cytokine is most pronounced in keratinocytes. TNF alpha (TNF-α) is well known to be highly expressed in inflamed tissue. As such, biologics targeting TNF-α have proved extremely successful in treating psoriasis and other inflammatory diseases. However, TNF-α also has major regulatory functions. It is well known to counter-regulate the expression of type I interferons (IFNα/β). The effects of TNF-α on IL-29 is not well understood but of clinical relevance regarding patients who fail to respond to, or develop cutaneous side effects in the context of TNF blocking therapies. We here demonstrate, that TNF-α potently regulates the biological function and expression of IL-29 in the skin compartment. In cultured, human adult skin-derived fibroblasts and keratinocytes, TNF-α failed to induce the expression of IL-29 on its own or in combination with nucleic acids known to induce antiviral responses. Furthermore, IFN-γ dependent induction of the receptor for IL-29, IL-28R, was abrogated in the presence of TNF-α, causing a significantly reduced functional responsiveness of these cells with regard to anti-viral molecules expression, including MxA, GBP-1 and IFI16. In addition, TNF had a profound inhibitory effect on IL-29 expression by human fibroblasts in both non-stimulated or IFNα stimulated cells. Patients receiving anti-TNF therapy in form of infliximab or adalimumab showed increased plasma concentration of IL-29 under anti-TNF therapy. Our project demonstrates that IL-29 mediated anti-viral response by keratinocytes and fibroblasts is abrogated in the presence of TNF-α. Anti-TNF therapy increases systemic levels of IL-29. Further investigation is necessary to correlate IL-29 to different therapeutic responses or cutaneous side effects under anti-TNF therapy.