23. Psoriasis-like skin lesion induced by Raf-MAPK signaling requires Stat3 activation.

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Raf is one of the downstream effectors of Ras GTPases, and plays a key role in cell proliferation and differentiation through activation of MAPK. We have previously demonstrated that temporal induction of Raf in the epidermis of K14-Raf:ER mice results in development of psoriasis-like phenotype, including epidermal hyperplasia, lymphocyte and neutrophil infiltrates. It has been demonstrated that epidermal Stat3 activation was required for psoriasis development. Here, we investigated whether Stat3 signaling was involved in Raf-MAPK-dependent psoriasis-like lesions. Epidermal hyperplasia of K14-Raf:ER mice following topical tamoxifen (4OHT) application showed Stat3 activation in keratinocytes. We mated them with epidermis-specific Stat3 null mice (K5-Cre.Stat3f/f). Surprisingly, over-expression of Raf by 4OHT treatment in Stat3 deficient background (K14-Raf:ER;K5-Cre.Stat3f/f) demonstrated greatly attenuated epidermal hyperplasia or dermal cell infiltrates, compared to K14-Raf:ER; Stat3f/wt mice. Also, up-regulation of psoriasis-associated cytokine profiles, including VEGF and IL-1β was decreased in the skin from K14-Raf:ER;K5-Cre.Stat3f/f upon 4OHT treatment. These results clearly indicated that Raf-MAPK-dependent psoriatic-skin development required Stat3 signaling in keratinocytes. Topical treatment of K14-Raf:ER mice skin with a Stat3 inhibitor STA-21 resulted in attenuation of epidermal hyperplasia upon 4OHT induction. Whereas K14-Raf:ER;IL17A-/- mice upon 4OHT treatment did not suppress Raf induced skin changes. Further analysis of the mechanistic crosstalk of these two important signalings in developing psoriasis is currently being undertaken.