INFLAMMATORY SKIN DISEASES (OTHER THAN ATOPIC DERMATITIS & PSORIASIS)

FN14-TRAF2-TNFR SIGNALING AXIS MEDIATES THE TWEAK/FN14 REGULATION OF KERATINOCYTE FATE

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Background: The tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK)/fibroblast growth factor-inducible 14 (Fn14) interaction regulates the fate of keratinocytes, depending on the expression profile of the TNF receptor (TNFR). However, the precise mechanism underlying this regulation of TWEAK remains unclear.

Objective: This study was designed to reveal the exact associations among Fn14, TNFR, and other relevant molecules and to elucidate the structural basis for the TWEAK/Fn14 regulation of cell fate.

Materials and Methods: Normal keratinocytes (mainly expressing TNFR1) and TNFR2-overexpressing keratinocytes were stimulated through TWEAK. The associations between protein molecules were analyzed by immunoprecipitation and Western blotting, and surface plasmon resonance.

Results: The associations among Fn14, TNFR-associated factor 2 (TRAF2), cellular inhibitor of apoptosis protein 1 (cIAP1), and TNFR molecules were confirmed using the protein lysates of the keratinocytes. TRAF2 exhibited binding affinities to the Fn14, cIAP1, and TNFR molecules. Moreover, TWEAK induced the apoptosis of normal keratinocytes and the proliferation of TNFR2-overexpressing keratinocytes in a TNF-α-independent manner. Furthermore, TRAF2 inhibition abrogated the effect of TWEAK on keratinocytes. Interestingly, the TWEAK/Fn14 interaction increased the TNFR1-associated death domain protein and caspase 8 expressions in normal keratinocytes and promoted the cytoplasmic import of cIAP1 in TNFR2-overexpressing keratinocytes.

Conclusions: The Fn14-TRAF2-TNFR signaling axis mediated the TWEAK regulation of cell fate in keratinocytes, possibly involving the TNF-α-independent TNFR signal transduction.