

Identification of signal transduction pathways involved in formation of skin appendices including hair follicles, sweat glands and sebaceous gland.

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Tumor necrosis factor receptor (TNFR)-associated factor 6 (TRAF6) transduces signals from members of the Toll/interleukin-1 (IL-1) receptor and members of the TNF receptor super family including CD40 and RANK. We have reported recently that TRAF6 deficiency results in defective development of epidermal appendices including guard hair follicles and sweat glands. Furthermore, our results suggest that this defect may be due to the impaired signaling of EDAR, XEDAR or TROY, members of the TNFR super family expressed in skin. Although TRAF6 plays a crucial role in formation of the skin appendices, the molecular mechanisms underlying regulation of TRAF6 are largely unknown. Thus, we began to search for proteins that bind to and activate TRAF6. We have identified TIFA, a TRAF-interacting protein with a forkhead-associated (FHA) domain. The FHA domain is a motif known to bind directly to phosphothreonine and phosphoserine. In transient transfection assays, TIFA activates NF κ B and JNK. However, TIFA carrying a mutation that abolishes TRAF6 binding or mutations in the FHA domain that are known to abolish FHA domain binding to phospho-peptide fails to activate NF κ B and JNK. TIFA, when overexpressed, binds both TRAF6 and IRAK-1 and significantly enhances the IRAK-1/TRAF6 interaction. Furthermore, analysis of endogenous proteins indicates that TIFA associates with TRAF6 constitutively, whereas it associates with IRAK-1 in an IL-1 stimulation-dependent manner *in vivo*. Thus, TIFA is likely to mediate IRAK-1/TRAF6 interaction upon IL-1 stimulation. These results suggest that TIFA may be involved in signaling that leads to the development of skin appendices. In such a case, TIFA could be important target molecule for drugs that affect skin condition. Inhibition of TIFA or TRAF6 may reduce the number of hair follicles. In contrast, activation of TIFA or TRAF6 may increase their number. Thus, TIFA and TRAF6 could be target molecules for developing compounds that could be used by hairy or bald-headed persons.