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TRAF6-NFκB pathway in cell growth and differentiation

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Signals emanating from IL-1R, some members of the TLR family, RANK, CD40 and XEDAR, activate transcription factors AP-1 through MAP kinase (MAPK) activation and NFkB through IkB kinase (IKK) activation. These kinases are thought to be activated by tumor necrosis factor receptor-associated factor 6 (TRAF6) via some adapter molecules or other kinases. Hence, TRAF6 is required for osteoclast formation, B cell differentiation, lymph node organogenesis, and formation of skin appendices. Furthermore, TRAF6 is involved in signals from LMP1 protein, an oncoprotein of EB virus. Therefore, TRAF6 plays pivotal roles in the regulation of cell growth and differentiation *in vivo*. To understand the molecular mechanisms of TRAF6-mediated signals, we have identified a novel TRAF6-interacting protein, TIFA, a TRAF-interacting protein with a forkhead-associated (FHA) domain, and its inhibitor protein TIFAB. The FHA domain is a motif known to bind directly to phosphothreonine and phosphoserine. In transient transfection assays, TIFA activates NFκB 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 NFκB and JNK. Functional interaction of TRAF6 and these proteins will be discussed. In addition, an unique function of the RANK-TRAF6 pathway in formation of osteoclasts, which play a role in bone metastasis of tumor cells will also be presented.