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OX40/gp34 (OX40L) And Adult T-cell Leukemia (ATL)

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Abstract

ATL is a T-cell leukemia that develops in a minor population of HTLV-I-infected individuals after a long (usually more than 50 years) latent period. One of the clinical characteristics of ATL is marked infiltration of leukemic cells into various organs including lymphoid tissue, liver and skin. When we studied on the mechanism of in vivo cell growth of leukemic cells in ATL focusing on cell adhesion molecules, we noticed a cell adhesion pathway mediated by unknown molecule(s). We cloned cDNA encoding the molecule by expression cloning using monoclonal antibodies that blocked the cell adhesion. The cloned molecule turned out to be OX40 that was originally reported as a rat T-cell activation antigen. The results from our study on OX40 and its ligand, gp34 are summarized as follows: 1) OX40 and gp34 directly mediate cell adhesion between ATL cells and vascular endothelial cells, 2) OX40 is expressed on ATL cells and gp34 is expressed on vascular endothelial cells, 3) gp34 stimulation induces *c-fos* and *c-jun* activation, 4) gp34 signaling induces vascular endothelial cells to produce a CC chemokine RANTES, 5) OX40 stimulation by gp34 activates NF-kB through TRAF2, TRAF5, NIK and IKK, whereas TRAF3 negatively modulates NF-kB activation, 6) OX40 stimulation enhances cell proliferation and produces anti-apoptotic effects in ATL cells. It was reported by others that Tax of HTLV-I induced OX40 and gp34 expression. Taken together, we consider that OX40/gp34 may play a key role not only in proliferation and survival of ATL cells but also in tissue infiltration of ATL cells.