

X-linked inhibitor of apoptosis regulates T cell effector function.

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J Immunol. 2007 Dec 1;179(11):7553-60.

To understand how the balance between pro- and anti-apoptotic signals influences effector function in the immune system, we studied the X-linked inhibitor of apoptosis (XIAP), an endogenous regulator of cellular apoptosis. Real-time PCR showed increased XIAP expression in blood of mice with experimental autoimmune encephalomyelitis, correlating with disease severity. Daily administration (10 mg/kg/day i.p.) of a 19-mer antisense oligonucleotide specific for XIAP (ASO-XIAP) abolished disease-associated XIAP mRNA and protein expression, and given from day of onset, alleviated experimental autoimmune encephalomyelitis and prevented relapses. Prophylactic treatment also reduced XIAP expression and prevented disease. Random or 5-base mismatched ASO was not inhibitory, and ASO-XIAP did not affect T cell priming. In ASO-XIAP-treated animals, infiltrating cells and inflammatory foci were dramatically reduced within the CNS. Flow cytometry showed an 88-93% reduction in T cells. The proportion of TUNEL(+) apoptotic CD4(+) T cells in the CNS was increased from <1.6 to 26% in ASO-XIAP-treated mice, and the proportion of Annexin V-positive CD4(+) T cells in the CNS increased. Neurons and oligodendrocytes were not affected; neither did apoptosis increase in liver, where XIAP knockdown also occurred. ASO-XIAP increased susceptibility of T cells to activation-induced apoptosis in vitro. Our results identify XIAP as a critical controller of apoptotic susceptibility of effector T cell function.