Inhibition of Lymphotoxin-beta Receptor (LTbR)-mediated Cell Death by Survivin-deltaEx3

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摘要

Abstract

TNFSF14/LIGHT is a member of the tumor necrosis factor superfamily that binds to lymphotoxin-beta receptor (LTbetaR) to induce cell death via caspase-dependent and caspase-independent pathways. It has been shown that cellular inhibitor of apoptosis protein-1 inhibits cell death by binding to LTbetaR-TRAF2/TRAF3 complexes and caspases. In this study, we found that both Kaposi's sarcoma-associated herpesvirus K7 (KSHV-K7), a viral inhibitor of apoptosis protein, and the structurally related protein survivin-DeltaEx3 could inhibit LTbetaR-mediated caspase-3 activation. However, only survivin-DeltaEx3 could protect cells from LTbetaR-mediated cell death. The differential protective effects of survivin-DeltaEx3 and KSHV-K7 can be attributed to the fact that survivin-DeltaEx3, but not KSHV-K7, is able to maintain mitochondrial membrane potential and inhibit second mitochondria-derived activator of caspase/DIABLO release. Moreover, survivin-DeltaEx3 is able to inhibit production of reactive oxygen species and can translocate from nucleus to cytosol to associate with apoptosis signal-regulating kinase 1 after activation of LTbetaR. Furthermore, survivin-DeltaEx3 protects LTbetaR-mediated cell death in caspase-3-deficient MCF-7 cells. Thus, survivin-DeltaEx3 is able to regulate both caspase-dependent and caspase-independent pathways, whereas inhibition of caspase-independent pathway is both sufficient and necessary for its protective effect on LTbetaR-mediated cell death