The Role of Apoptosis Signal-regulating Kinase 1 in Lymphotoxin-beta Receptor-mediated Cell Death

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摘要

Abstract

LIGHT (homologous to lymphotoxins, shows inducible expression, and competes with herpes simplex virus glycoprotein D for herpesvirus entry mediator, a receptor expressed by T lymphocytes) is a member of the tumor necrosis factor superfamily that caninteract with lymphotoxin-beta receptor (LTbetaR), herpes virus entry mediator, and decoy receptor (DcR3). In our previous study, we showed that LIGHT is able to induce cell death via the non-death domain containing receptor LTbetaR to activate bothcaspase-dependent and caspase-independent pathway. In this study, a LIGHT mutein, LIGHT-R228E, was shown to exhibit similar binding specificity as wild type LIGHT to LTbetaR, but lose the ability to interact with herpes virus entry mediator. By usingboth LIGHT-R228E and agonistic anti-LTbetaR monoclonal antibody, we found that signaling triggered by LTbetaR alone is sufficient to activate both caspase-dependent and caspase-independent pathways. Cross-linking of LTbetaR is able to recruit TRAF3and TRAF5 to activate ASK1, whereas its activity is inhibited by free radical scavenger carboxyfullerenes. The activation of ASK1 is independent of caspase-3 activation, and kinase-inactive ASK1-KE mutant can inhibit LTbetaR-mediated cell death. Thissuggests that ASK1 is one of the factors involved in the caspase-independent pathway of LTbetaR-induced cell death.