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TNFR2 activates JNK but not MAPK pathways

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Keywords

c-Jun, kinase, MAPK, signaling, TNF-a, TNF receptor, TRAF

Context

Activation of the two tumor necrosis factor (TNF) receptors, p55 type I (TNFR1) and p75 type II (TNFR2), by TNF binding leads to a variety of cellular responses including inflammatory events, proliferation and cell death. Signals induced by these receptors are complex and involve several extracellular signal-regulated kinases (ERKs), including the mitogen-activated protein kinases (MAPKs), c-Jun N-terminal kinases (JNKs) and p38 MAPK. The type and amplitude of cellular response to TNF interaction is thought to be dependent upon the balance of signaling between the two TNF receptors; however, the specific signaling mechanisms of each have not been fully elucidated. In this report the authors studied the ability of signaling via TNFR1 and TNFR2 to activate MAPKs, JNKs and p38 MAPK and the contribution of the two receptors toward cell death processes.

Significant findings

The effects of TNF receptor stimulation were analyzed in several cell lines. The authors showed that stimulation of the various cell lines with wild-type TNF-a or a TNF-a variant specific for the type I receptor (R1-TNF) resulted in full activation of the JNK, MAPK and p38 MAPK pathways. Conversely, TNFR2 stimulation by a TNF-a variant specific for the type II receptor (R2-TNF) and/or a monoclonal antibody with specific agonist activity for TNFR2 (MR2-1) resulted in activation of JNK but not MAPK or p38 MAPK. Analysis of cell death following incubation of the different cell lines with the various TNF variants and the MR2-1 antibody for 24 hours showed that direct, specific TNFR2 stimulation was capable of achieving a complete response, and that the level of cell death mediated by TNFR2 was directly related to its level of expression on the cell surface.

Comments

It is widely thought that TNFR1 is the primary TNF signaling receptor involved in cell death. However, because much TNF stimulation occurs at the membrane level prior to its processing and release, and because soluble TNF binds poorly to TNFR2, the contribution that TNFR2 plays in programmed cell death may be underestimated. In this work, by using a combination of TNFR2-specific agonist antibody and TNF-a variant, the authors show that the two receptors differentially activate signaling kinases and that TNF-mediated cell death likely is the sum of the contribution of cell signaling from both receptors depending upon their relative levels.

Methods

FACS analysis, confocal microscopy, kinase assays, western blot, cell death measurement

Additional information

References

1. Jupp OJ, McFarlane SM, Anderson HM, Littlejohn AF, Mohamed AA, MacKay RH, Vandenabeele P, MacEwan DJ: Type II tumour necrosis factor alpha receptor (TNFR2) activates c-Jun N-terminal kinase (JNK) but not mitogen-activated protein kinase (MAPK) or p38 pathways. Biochem J. 2001, 359: 525-535.