T-CELL SIGNALLING

Aiding and abetting

DOI:
10.1038/nri1941

A new paper from the laboratory of Michael Lenardo reports that the movement of caspase-8 to lipid rafts following T-cell receptor (TCR) stimulation is facilitated by tumour-necrosis-factor-receptor-associated factor 6 (TRAF6).

TCR stimulation initiates a complex signalling pathway that is not yet fully understood but culminates in the activation of transcription factors, including nuclear factor-κB (NF-κB). Recent reports indicate that caspase-8, better known for its role in apoptosis, also has an important role in TCR-induced NF-κB activation. In response to these reports, Lenardo and colleagues studied caspase-8 and TRAF6 (a signal-transduction mediator that is known to activate transcription factors such as NF-κB) during TCR stimulation.

The authors found a direct interaction between caspase-8 and TRAF6 following TCR stimulation. Two putative TRAF6-binding sites were identified in the sequence of caspase-8, and after mutating specific residues in these sites, the authors found that TRAF6 was unable to bind caspase-8, resulting in reduced TCR-induced NF-κB activation.

An essential step in TCR-mediated signal transduction is the enrichment of crucial molecules in plasma-membrane compartments known as lipid rafts. These molecules include caspase-8, TRAF6, protein kinase C-θ (PKCθ), caspase-recruitment domain membrane-associated guanylate kinase protein 1 (CARMA1) and B-cell lymphoma 10 (BCL-10). 'Knockdown' experiments indicated that caspase-8 first forms a complex with BCL-10 in a PKCθ-dependent manner in the cytosol, leading to transient activation of caspase-8. Subsequently, TRAF6 and CARMA1 participate in the shuttling of activated caspase-8 to lipid rafts, where (as part of a larger signalosome) caspase-8 propagates NF-κB signalling.

These data indicate that the association of activated caspase-8 with TRAF6 is crucial for the translocation of caspase-8 to lipid rafts and for the subsequent TCR-induced activation of NF-κB. Further questions remain, such as why transient activation of caspase-8 is required for this process, but these results help to shed light on the complex molecular pathways that are involved in mounting a successful immune response.

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ORIGINAL RESEARCH PAPER Bidère, N., Snow, A. L., Sakai, K., Zheng, L. & Lenardo, M. J. Caspase-8 regulation by direct interaction with TRAF6 in T cell receptor-induced NF-κB activation. *Curr. Biol.* **16**, 1666–1671 (2006)