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ASC-mediated NF-κB Activation Leading to IL-8 Production Requires Caspase-8 and Is Inhibited by CLARP

M. Hasegawa, R. Imamura, T. Kinoshita, N. Matsumoto, J. Masumoto, N. Inohara, and T. Suda

ASC is an adaptor molecule that mediates apoptotic and inflammatory signals from several Apaf-1-like molecules, including CARD12/Ipaf. ASC is also implicated in tumor suppression, because the ASC gene expression is suppressed in various cancer cells. To characterize the signaling pathway mediated by ASC, we established cell lines in which muramyl dipeptide, the bacterial component recognized by another Apaf-1-like molecule, Nod2, induced an interaction between a CARD12-Nod2 chimeric protein and ASC, and elicited cell-autonomous NF-κB activation. This response required caspase-8, and was suppressed by CLARP/FLIP, an inhibitor of caspase-8. The catalytic activity of caspase-8 was required for the ASC-mediated NF-κB activation when caspase-8 was expressed at an endogenous level, although it was not essential when caspase-8 was overexpressed. In contrast, FADD, the adaptor protein linking Fas and caspase-8, was not required for this response. Consistently, ASC recruited Caspase-8 and CLARP but not FADD and Nod2 to its speck-like aggregates in cells. Finally, muramyl dipeptide induced IL-8 production in MAIL8 cells. These results are the first to indicate that caspase-8 plays an important role in the ASC-mediated NF-κB activation, and that the ASC-mediated NF-κB activation actually induces physiologically relevant gene expression.
(Hasegawa M, et al., J. Biol. Chem. 280: 15122-30, 2005.)

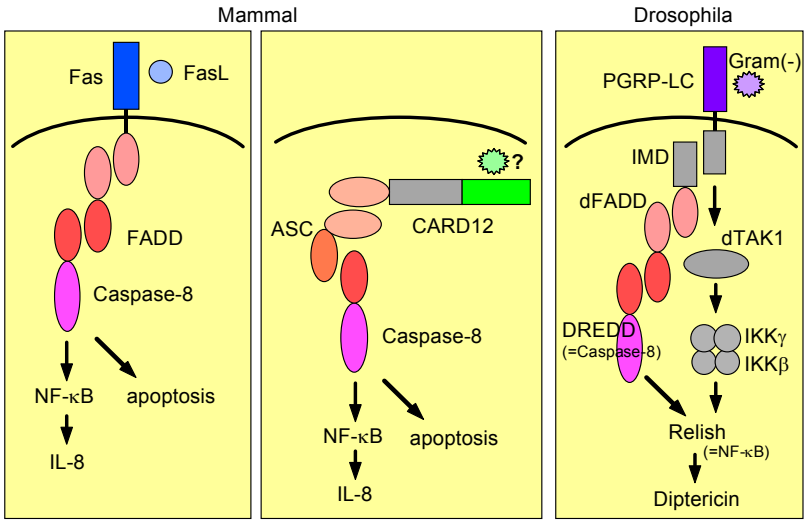

Figure
DREDD, the drosophila homolog of caspase-8 has been shown to play an important role in NF-κB activation. In mammals, caspase-8 also plays an important role in Fas ligand-induced and ASC-mediated NF-κB activation.