Molecular Mechanism of Fas ligand-induced IL-8 Production

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It has been believed that apoptosis does not induce inflammation. However, there are remarkable similarities between the molecular mechanisms of apoptosis and inflammation. Fas (CD95) is not an exception and recent studies revealed that Fas ligand (FasL)-Fas system possesses inflammatory activity. We recently found that FasL induces production of the inflammatory chemokine IL-8 in human cell lines and FasL-induced NF-κB and AP-1 activation is required for this IL-8 production. Our further analyses revealed that the death domain of Fas, FADD, and caspase-8, which are essential for the apoptosis signaling, are required for both NF-κB and AP-1 activation by FasL. However, rsponses of NF-κB and AP-1 activation are independent of each other. In the NF-κB signaling pathway, we also showed that TRADD and RIP, which are essential for the TNF-α-induced NF-κB activation, were not involved in the FasL-induced NF-κB activation and CLARP/FLIP inhibited the FasL- but not the TNF-α-induced NF-κB activation. More interestingly, our results revealed that enzymatic activity of caspase-8 is required for both NF-κB and AP-1 activation induced by FasL. Further characterization of these pathways will help us to understand and, hopefully, to control the FasL-induced inflammation. (Imamura, R. et al., J. Biol. Chem., 279:46415-46423, 2004)

Figure

In the case of FasL-Fas system, contrary to TNF-α-TNFR system, signaling pathway of apoptosis and transcription factor activation separates downstream of caspase-8 and enzymatic activity of caspase-8 is required for both pathways. Current our goal is identification of targets (substrates) of caspase-8, which are important for FasL-induced NF-κB and/or AP-1 activation.