Caspase-8-and JNK-dependent AP-1 activation is required for Fas ligand-induced IL-8 production

Norihiko Matsumoto, Ryu Imamura, and Takashi Suda

Despite a dogma that apoptosis does not induce inflammation, Fas ligand (FasL), a well-known death factor, possesses pro-inflammatory activity. For example, FasL induces nuclear factor κB (NF-κB) activity and interleukin 8 (IL-8)-production by engagement of Fas in human cells. Here, we found that a dominant negative mutant of c-Jun, a component of the activator protein-1 (AP-1) transcription factor, inhibits FasL-induced AP-1 activity and IL-8 production in HEK293 cells. Selective inhibition of AP-1 did not affect NF-κB activation and vice-versa, indicating that their activations were not sequential events. The FasL-induced AP-1 activation could be inhibited by deleting or introducing the lymphoproliferation (lpr)-type point mutation into the Fas death domain (DD), knocking down the Fas-associated DD protein (FADD), abrogating caspase-8 expression with small interfering RNAs (siRNAs), or using inhibitors for pan-caspase and caspase-8 but not caspase-1 or caspase-3. Furthermore, wild-type, but not a catalytically inactive mutant, of caspase-8 reconstituted the FasL-induced AP-1 activation in caspase-8-deficient cells. Fas ligand induced the phosphorylation of two of the three major mitogen-activated protein kinases (MAPKs): extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) but not p38 MAPK. Unexpectedly, an inhibitor for JNK but not for MAPK/ERK kinase inhibited the FasL-induced AP-1 activation and IL-8 production. These results demonstrate that FasL-induced AP-1 activation is required for optimal IL-8 production, and this process is mediated by FADD, caspase-8, and JNK.

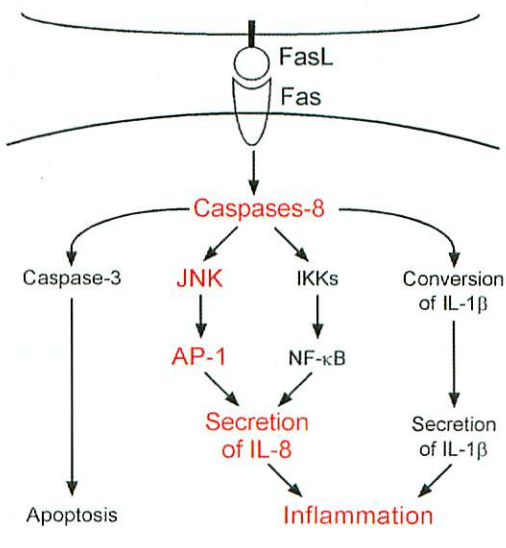

Figure. Fas ligand is well known death factor that induces apoptosis in a caspase-8 dependent manner. We previously demonstrated that stimulation by Fas ligand induces IL-1β secretion in LPS-primed mouse macrophages and IL-8 secretion in human embryonic kidney (HEK)-293 cells. Interestingly, it was found that both of these inflammatory responses are caspase-8 dependent. In this study, we further discovered that activation of Fas by Fas ligand induces AP-1 activation in a caspase-8- and JNK-dependent manner. This AP-1 activation is required for the Fas ligand-induced IL-8 production in HEK293 cells.