Mutation of a self-processing site in caspase-8 compromises its apoptotic but not its nonapoptotic functions in bacterial artificial chromosome-transgenic mice

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Caspase-8, the proximal enzyme in the death-induction pathway of the TNF/nerve growth factor receptor family, is activated upon juxtaposition of its molecules within the receptor complexes and is then self-processed. Caspase-8 also contributes to the regulation of cell survival and growth, but little is known about the similarities or the differences between the mechanisms of these nonapoptotic functions and of the enzyme's apoptotic activity. In this study, we report that in bacterial artificial chromosome-transgenic mice, in which the aspartate residue upstream of the initial self-processing site in caspase-8 (D387) was replaced by alanine, induction of cell death by Fas is compromised. However, in contrast to caspase-8-deficient mice, which die in utero at mid-gestation, the mice mutated at D387 were born alive and seemed to develop normally. Moreover, mice with the D387A mutation showed normal in vitro growth responses of T lymphocytes to stimulation of their Ag receptor as well as of B lymphocytes to stimulation by LPS, normal differentiation of bone marrow macrophage precursors in response to M-CSF, and normal generation of myeloid colonies by the bone marrow hematopoietic progenitors, all of which are compromised in cells deficient in caspase-8. These finding indicated that self-processing of activated caspase-8 is differentially involved in the different functions of this enzyme: it is needed for the induction of cell death through the extrinsic cell death pathway but not for nonapoptotic functions of caspase-8.