The silencer of death domains (SODD) has been proposed to prevent constitutive signaling of tumor necrosis factor receptor 1 (TNFR1) in the absence of ligand. Besides TNFR1, death receptor 3 (DR3), Hsp70/Hsc70, and Bcl-2 have been characterized as binding partners of SODD. In order to investigate the in vivo role of SODD, we generated mice congenitally deficient in expression of the sodd gene. No spontaneous inflammatory infiltrations were observed in any organ of these mice. Consistent with this finding, in the absence of SODD no alteration in the activation patterns of nuclear factor kappaB (NF-kappaB), stress kinases, or ERK1 or -2 was observed after stimulation with tumor necrosis factor (TNF). Activation of NF-kappaB by DR3 was also unchanged. The extents of DR3- and TNF-induced apoptosis were comparable in gene-deficient and wild-type cells. Protection of cells against heat shock as mediated by the Hsp70 system and against staurosporine-induced apoptosis was independent of SODD. Furthermore, resistance to high-dose lipopolysaccharide (LPS) injections, LPS-D-GalN injections, and infection with listeriae was similar in wild-type and gene-deficient mice. In conclusion, our data do not support the concept of a unique, nonredundant role of SODD for the functions of TNFR1, Hsp70, and DR3.