SUPPORTING INFORMATION

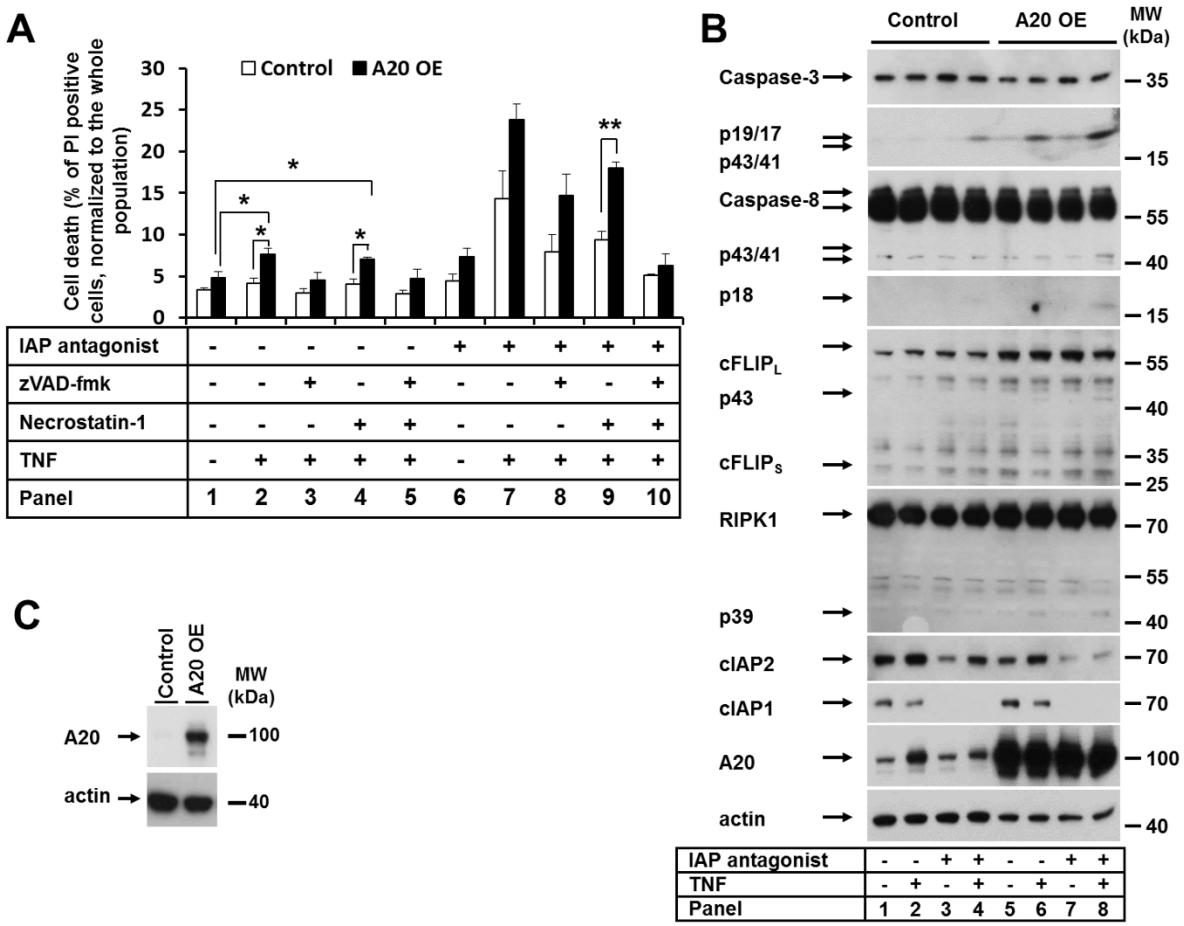

Fig. S1. An increase in A20 expression results in reduced viability of HaCaT cells in response to TNF, in the presence and absence of IAP antagonist. (**A, B**) HaCaT cells were transduced with A20 LV and A20 expression was induced by 4-HT. (**A**) The cells were stimulated as indicated and cell death analyzed by PI staining and FACS analysis. Average values of three independent experiments (±SEMs) are shown, * p<0,05, **p<0,01. (**B**) A20 transduced HaCaT cells were treated as indicated and proteins of interest were analyzed by WB. (**C**) Murine keratinocytes were transduced with RV vector containing murine A20 and cellular lysates were analyzed by WB.

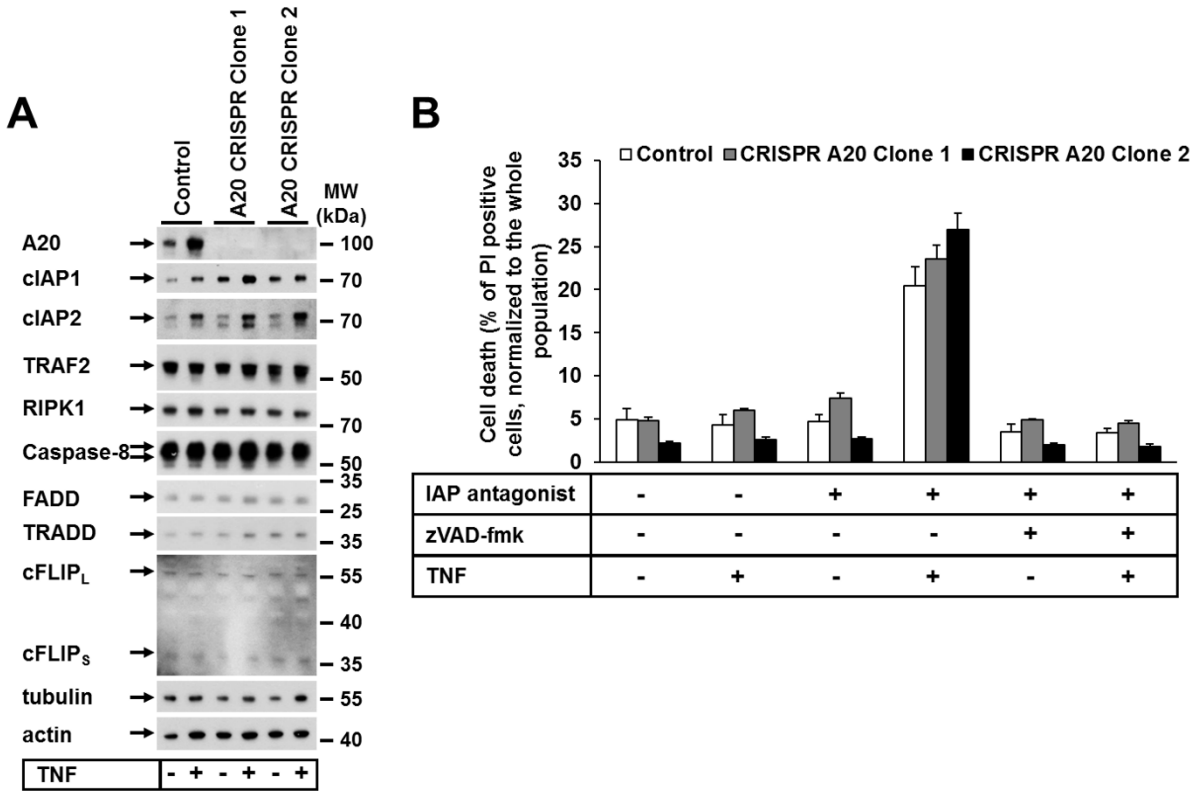

Fig. S2. Loss of A20 in HeLa cells does not alter cell death sensitivity. (**A**) Protein expression in control and A20 CRISPR HeLa clones were analyzed by WB. (**B**) Selected A20 CRISPR HeLa clones were treated as shown and cell death was analyzed by PI staining and FACS analysis. Mean values (±SEMs) of 3 independent experiments are shown. The WBs shown are representative of 2 independent experiments.

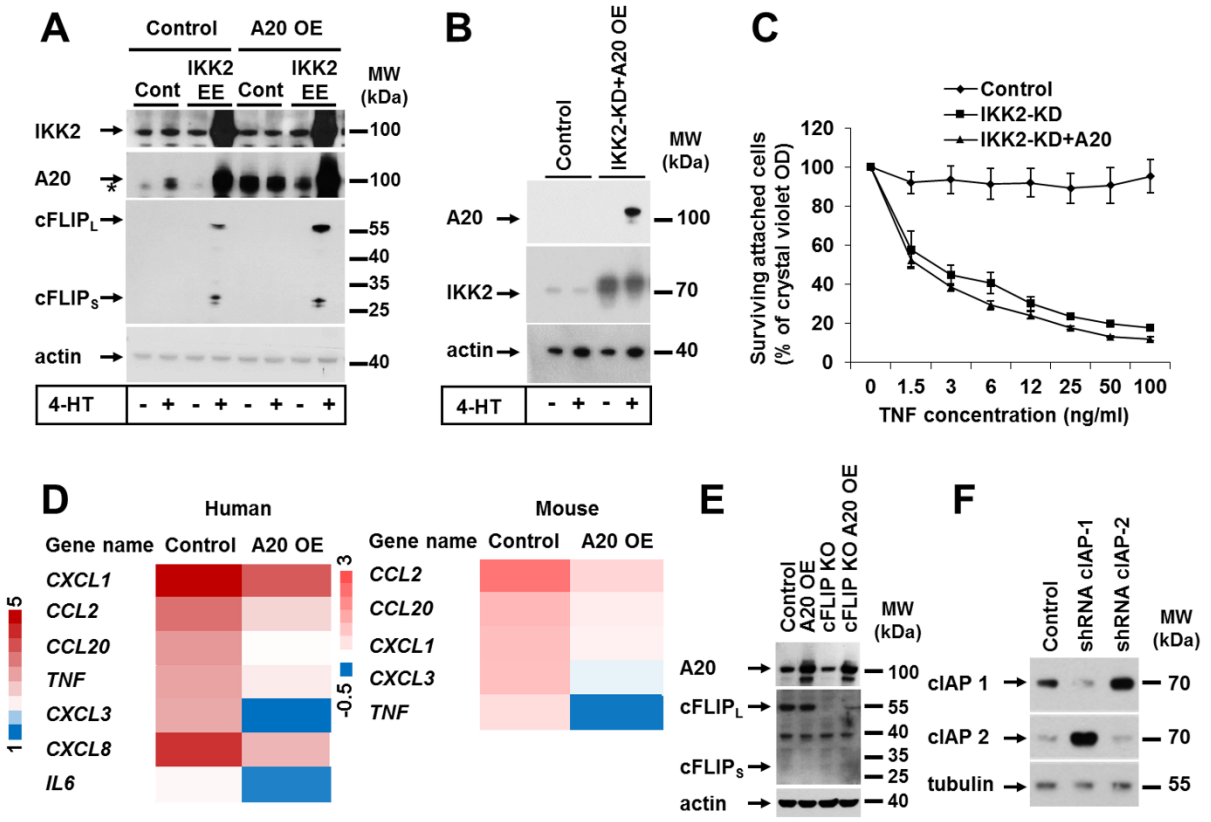

Fig. S3. TNF-induced cell death in keratinocytes with elevated A20 expression is linked with the regulation of canonical NF-κB signaling. (**A**) HaCaT cells were sequentially transduced with LV containing IKK2 EE (inducible expression) and RV containing A20 (stable expression). IKK2 EE expression was induced by 4-HT and the proteins of interest were analyzed by WB. (**B**) HaCaT cells were sequentially transduced with RV containing IKK2 KD (stable expression) and LV containing 4-HT- A20 (inducible expression). A20 expression was induced with 4-HT and cell lysates were analyzed by WB. (**C**). Cells from (B) were treated with the indicated concentrations of HF-TNF for 18 hours. Cell viability was analyzed by crystal violet assay. Values from 3 independent experiments (±SEMs) are shown. (**D**) Heat maps of NF-κB target genes altered upon TNF stimulation of human (n=2), and mouse (n=2) keratinocytes with elevated A20 expression. GEO accession number GSE128249. (**E**) Murine A20 or control vector were expressed in spontaneously immortalized keratinocytes isolated from cFLIP$^{fl/fl}$ animals. The cFLIP locus was deleted via LV expression of Cre recombinase. Cell lysates were analyzed by WB. (**F**) Compensatory regulation of cIAP1 and cIAP2 expression. HaCaT cells were transduced with LV containing shRNA for cIAP1 and cIAP2, and their expression status was investigated by WB.