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Combined treatment with small molecules targeting c-FLIP and Mcl-1 promotes apoptosis and necroptosis in pancreatic cancer cells

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There are three isoforms of c-FLIP reported to be recruited to the death inducing signaling complex (DISC): long (c-FLIPL), short (c-FLIPS) and raji (c-FLIPR). While c-FLIPS and c-FLIPR have an anti-apoptotic role, c-FLIPL can act in both anti- and pro-apoptotic manner depending on its concentration. We designed a small molecule called FLIPinB which interacts with c-FLIPL to stabilize the active center of caspase-8 within the caspase-8/c-FLIPL heterodimer and increases caspase-8 activity. We concentrated on pancreatic cancer cells, SUIT-020, which are resistant towards single treatments. To further enhance the pro-apoptotic effects of FLIPinB we carried out combinatorial treatments with the Mcl-1 inhibitor S63845 and gemcitabine. Our previous studies showed that moderate concentrations of gemcitabine have only small effects on SUIT-020 cells. Here we show that combinatorial treatment with CD95L/TRAIL, gemcitabine, FLIPinB and S63845 leads to an increased loss of cell viability. Moreover, this increased cell viability loss was accompanied by enhanced caspase activity. Further, we have shown that this combinatorial treatment might induce both apoptotic and necroptotic pathways via an increase in the amounts of complex IIa and complex IIb after combined treatment. Taken together, our study suggests new approaches for the development of novel cancer therapies targeting apoptosis.