# Sensitizing cancer cells to the FAS ligand through strong activation of the p53 protein may prove to be a spectacular solution in anticancer therapy.

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The p53 protein activates the pro-apoptotic gene *FAS,* which encodes the death receptor for the FAS ligand (FASLG). Cancer cells are resistant to programmed cell death triggered by FASLG.
We have discovered that two substances actinomycin D (ActD) and nutlin-3a (Nut3a) act synergistically in the activation of p53 and stimulation of a subset of p53-target genes. ActD stimulates kinases involved in the activation of p53, while Nut3a prevents the interaction of p53 with its inhibitor, the MDM2 protein. ActD+Nut3a activates the expression of many genes connected with apoptosis, what unexpectedly does not result in extensive programmed cell death.
We hypothesized that proposed drug combination (ActD+Nut3a) sensitizes cancer cells to the pro-apoptotic activity of FASLG.
We exposed various cancer cell lines and normal human fibroblast to ActD+Nut3a for 45h and next we treated cells with recombinant FASLG. We observed apoptosis by flow cytometry and activation status of caspase-3,-6, -8, -9, and -10 by immunoblotting (Western-blot). The cell viability was determined by the MTS assay and cell staining on culture plates. ActD and Nut3a strongly synergized in sensitizing cells to apoptosis triggered by FASLG. This combination killed almost all cells within 5h. The cell death was accompanied by a strong activation of all examined caspases. In engineered p53-deficient cells this pro-apoptotic effect was completely lost. Hence, the observed cell sensitization is entirely dependent on p53.
Therefore, the combination of ActD+Nut3a activates p53 in a way, which overcomes the resistance of cancer cells to apoptosis triggered by FASLG. The implementation of the proposed project opens the path to a completely new therapeutic approach in oncological treatment and provides new information on the effect of strong activation of the p53 protein.
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