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Laboratory of Cell Signalling and Apoptosis

Death receptors, apoptosis, Daxx

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Research topics

The major focus of our group is aimed at the molecular and functional characterization and regulation of signalling pathways unlashed by the activated death receptors from the TNFR superfamily, namely by pro-apoptotic TRAIL receptors (DR4 and DR5), by the Death Receptor 6 (DR6), or affected by apoptosis- and transcription-regulatory adapter protein Daxx.

TRAIL is considered a novel anti-tumour agent, and thus in-depth knowledge of the regulation of TRAIL-induced signalling is undoubtedly important. Our recently published studies document involvement of DR4-interacting adapter protein ARAP1 in the efficacy of DR4 presentation at the cytoplasmic membrane and Wnt1-expressing Rat2 fibroblast-mediated suppression of TRAIL-induced apoptosis of pre-B leukaemia cells. The current major project deals with the elucidation of the role of activated oncogenes in sensitizing colorectal cancer cells to TRAIL-induced apoptosis. We also evaluate TRAIL-induced signalling in tumour-initiating cells and examine the role of endocytosis in TRAIL receptor signalling and trafficking. DR6 can participate in the regulation of T- and B-cell activation. We have discovered that posttranslational modifications regulate the cellular localization of this highly glycosylated and palmitoylated receptor and we currently characterize potential functions of proteins interacting with its intracellular part. Daxx is an essential adapter protein that is involved in stress- and Fas/CD95-triggered apoptosis and also participates in the regulation of transcription. Using Y2H screening we uncovered several new Daxx-interacting proteins such as Brg1 or SAP30 and we currently characterize functional consequences of their interaction with Daxx.

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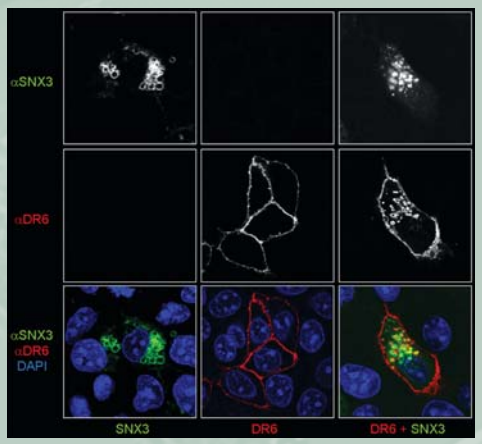
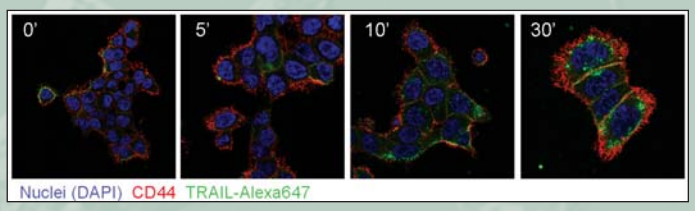
Selected recent papers

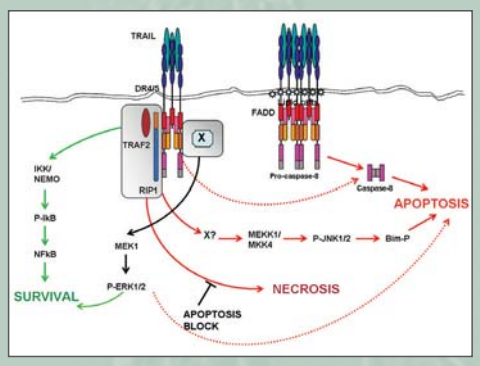
1. Psahoulia FH, Drosopoulos KG, Doubravska L, Andera L, Pintzas A. Quercetin enhances TRAIL-mediated apoptosis in colon cancer cells by inducing the accumulation of death receptors in lipid rafts. **Mol Cancer Ther.** 2007;6:2591-2599.
2. Oikonomou E, Kothonidis K, Zografos G, Nasioulas G, Andera L, Pintzas A. Newly established tumourigenic primary human colon cancer cell lines are sensitive to TRAIL-induced apoptosis in vitro and in vivo. **Br J Cancer.** 2007;97:73-84.
3. Doubravska L, Simova S, Cermak L, Valenta T, Korinek V, Andera L. Wnt-expressing rat embryonic fibroblasts suppress Apo2L/TRAIL-induced apoptosis of human leukemia cells. **Apoptosis.** 2008;13:573-587.
4. Simova S, Klima M, Cermak L, Sourkova V, Andera L. Arf and Rho GAP adapter protein ARAP1 participates in the mobilization of TRAIL-R1/DR4 to the plasma membrane. **Apoptosis.** 2008;13:423-436.



Transfected DR6(ICP)-interacting protein SNX3 pulls DR6 from the cytoplasmic membrane into vesicle-like structures.



Kinetics of Alexa 647-labelled TRAIL endocytosis in HCT116 colon carcinoma cells



TRAIL-induced signalling pathways