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Laboratory of Cell Signaling and Apoptosis

Death receptors, apoptosis, Daxx

Research topics

The laboratory deals with characterization and regulation of the signalling pathways triggered by pro-apoptotic TRAIL receptors (DR4 and DR5), by the Death Receptor 6 (DR6), or affected by apoptosis- and transcription-regulating adapter protein Daxx. In TRAIL-related projects we discovered a novel DR4-interacting protein ARAP1 that in a cell-specific manner affects DR4 membrane localization and we characterized Wnt1-transformed Rat2 fibroblast-mediated suppression of TRAIL-induced apoptosis of human pre-B leukaemia cells. At present we focus on the analysis of oncogenic transformation-induced sensitization of human cells to TRAIL-triggered apoptosis and on examination of TRAIL-induced signalling in tumour-initiating cells. In respect to DR6 signalling we dissected the role of DR6 glycosylation in DR6 membrane localization and currently we characterize molecular and functional properties of DR6(ICP)-interacting proteins. Novel interaction partners of Daxx (e.g. Brg1) were discovered by Y2H screening. These interactions apparently play important roles in regulation of transcription and apoptosis. Daxx associates with Brg1-Swi/Snf complex and is required for transactivation of several Brg1-dependent genes.

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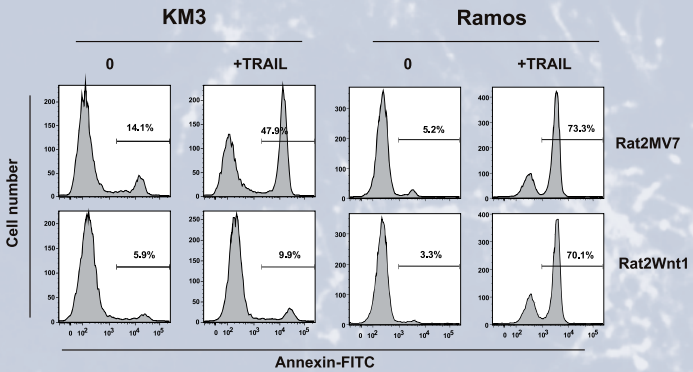
AS CR (AV0Z50520514), Ministry of Education, Youth and Sports (Center of Molecular and Cellular Immunology, 1M0506); EC FP6 STREP project (Oncodeath, LSHG-CT-2006-037278); GA AS CR (Nanomed, KAN200520703)

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;6:2591-9.
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. Neuzil J, Stantic M, Zobalova R, Chladova J, Wang X, Prochazka L, Dong L, Andera L, Ralph SJ. Tumour-initiating cells vs. cancer ‚stem' cells and CD133: what's in the name? **Biochem Biophys Res Commun.** 2007;355:855-9.
4. Tomasetti M, Andera L, Alleva R, Borghi B, Neuzil J, Procopio A. α-tocopheryl succinate induces DR4 and DR5 expression by a p53-dependent route: implication for sensitisation of resistant cancer cells to TRAIL apoptosis. **FEBS Lett.** 2006;580:1925-31.



Rat2Wnt1 fibroblasts inhibit TRAIL-induced apoptosis of pre-B KM3 leukaemia cells but not of more differentiated Ramos Burkitt lymphoma.

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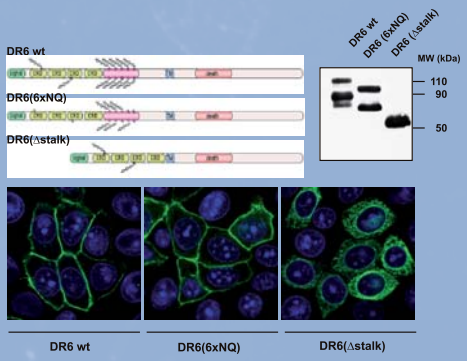
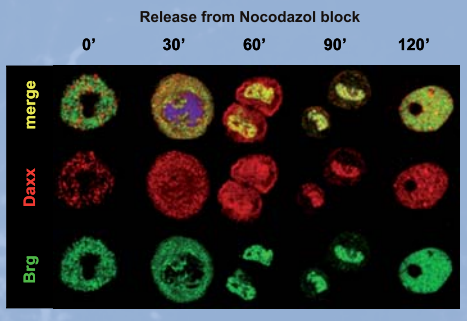
Leonard Nevařil / Diploma Student
Jaromír Novák / Diploma Student
Tomáš Zikmund / Diploma Student



DR6 glycosylation mutants differ in their subcellular localization in transfected MDCK cells.



Daxx co-localizes with Brg1 in post-mitotic HeLa cells.