Laboratory of Cell Signalling and Apoptosis

Death receptors, TRAIL, Daxx, cancer, cell death

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Our group is interested in deciphering the signalling pathways leading to programmed death of cancer cells including cancer stem cells and uncovering mechanisms participating in regulation of these pathways. In our major focus stands TRAIL (TNFα-Related Apoptosis Inducing Ligand), a ligand from the TNFα family capable of inducing apoptosis of a number of transformed cells and not being harmful to the normal ones. TRAIL-induced apoptosis of sensitive cells is triggered by its interaction with TRAIL-R1/DR4 and/or TRAIL-R2/DR5. These receptors contain an α-helical protein-protein interaction domain called the death domain and belong together with Fas/CD95 or TNFR1 to the subfamily of TNFR receptors named "death receptors". We analyse several aspects of TRAIL's biological activities such as the role of endocytosis in TRAIL ligand-receptor(s) Death-Inducing Signalling Complex (DISC) formation and activation, TRAIL signalling in human embryonic stem cells (hESCs) and from them derived somatic progenitors or the effect of overexpressed/activated oncogenes such as c-Myc on TRAIL-induced apoptosis. In our collaborative projects we uncovered two novel drugs sensitizing resistant cancer cells to TRAIL-induced apoptosis and participated in the analysis of multiple aspects of TRAIL-induced signalling in leukaemia and colon carcinoma cells. In our other death receptors-related project we characterize molecular and expression patterns of the Death Receptor 6 (DR6), which can participate in the regulation of T- and B-cell activation. We have discovered that posttranslational modifications of DR6 can affect the cellular localization of this highly glycosylated and palmitoylated receptor, and we currently analyse regulation of DR6 expression in T cells. Part of our group also analyses molecular and functional properties of the for embryonic development essential adapter protein Daxx. Daxx apparently participates in stress- and Fas/CD95-triggered apoptosis, and it is also involved in the regulation of multiple other processes such as transcription or cell cycle. We currently characterize functional consequences of its interaction with several new Daxx-binding proteins such as Brg1 or BAP1 and in collaboration we assess the role of Daxx in DNA damage response.

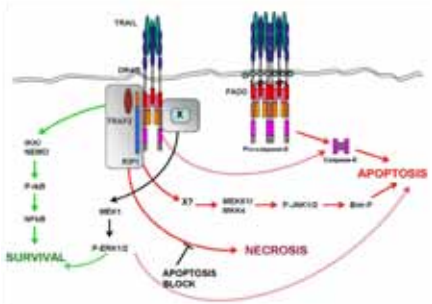

Fig. 1. Signalling pathways triggered by activated TRAIL receptors.

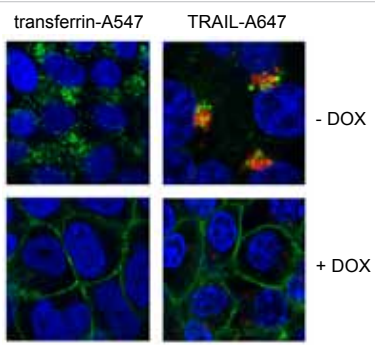

Fig. 2. Endocytosis of the activated TRAIL receptor is blocked by inducible expression of the dominant-negative dynamin-1. In green either Alexa547-labelled transferrin or TRAIL, in red lysosomal marker LAMP-1, +DOX stands for doxycycline-mediated induction of the dominant-negative dynamin-1 expression.

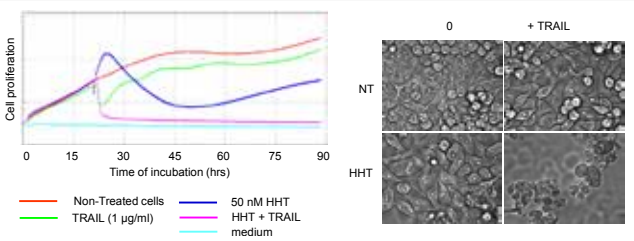

Fig. 3. Natural alkaloid homoharringtonine (HHT) enhances TRAIL-induced growth suppression/apoptosis of TRAIL-resistant colon carcinoma cell line RKO. Real-time cell proliferation assay (xCELLigence, Roche) and phase-contrast photographs.

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- AS CR, KJB500520801 – Dissection of Bid function in TRAIL-induced apoptosis, 2008-2010, M. Koc
- Ministry of Health of the Czech Republic, NS10287 – Experimental therapy of mantle cell lymphoma (MCL), 2009-2011, L. Anděra
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