Laboratory of Molecular Immunology

Membrane microdomains, chimeric antigen receptors, myeloid leukaemia, C/EBP transcription factors

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In 2013-2014 our laboratory was dealing with three topics:

1. Membrane rafts and immunoreceptor signalling (principal investigator Václav Hořejší).

For many years a major topic of our laboratory has been signalling molecules present in membrane rafts, namely several transmembrane adaptor proteins discovered previously by us, and their involvement in immunoreceptor signalling. Currently we are working on clarification of the relationship between various types of native membrane microdomains and detergent-resistant membrane fragments (DRMs).

2. Chimeric antigen receptors (CARs) (principal investigator Pavel Otáhal).

CARs are transmembrane constructs expressed in T lymfocytes capable of (a) specific recognition of e.g. tumour antigens and (b) effective signalling resulting in killing of the recognized tumour cell. CARs appear to be promising tools for cancer immunotherapy. We are currently developing new types of such potentially clinically useful CARs.

3. Mechanisms of leukemogenesis (principal investigator Meritxell Alberich-Jorda).

Acute myeloid leukaemia (AML) is a malignant haematopoietic disease that represents over 90% of acute leukaemias in adults. Changes in expression of critical transcription factors have been shown to deregulate haematopoiesis and aberrations in myeloid transcription factors have been observed in AML patients. Our research team is particularly interested in the CCAAT/enhancer binding protein (C/EBP) transcription factor family, which regulates the commitment of haematopoietic stem cells towards the myeloid lineage. Specifically, we investigate the functions of C/EBPγ and C/EBPα transcription factors and their target genes in normal haematopoiesis and malignant transformation in AML. Also, we aim to identify small molecules able to reactivate targets of the C/EBPα, ultimately resulting in therapeutic restoration of granulocytic differentiation in AML.

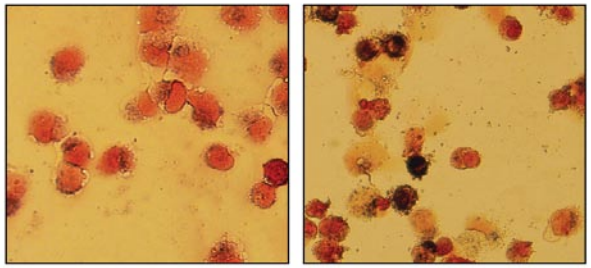

Fig. 1. K562 cells were transfected with constructs encoding transcription factor C/EBPα and oestradiol receptor (ER). Upon β-oestradiol stimulation C/EBPα-ER translocates to the nucleus and induces granulocytic differentiation, as demonstrated by the blue signal upon Nitroblue tetrazolium staining (right). Controls expressing only ER but not C/EBPα do not differentiate (left).

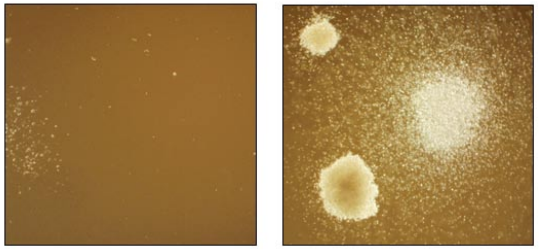

Fig. 2. Expression of dominant-negative transcription factor TCF4 (dnTCF4) in murine bone marrow cells strongly enhances their differentiation into colonies of myeloid and lymphoid cells in vitro (right), as compared to controls (left).

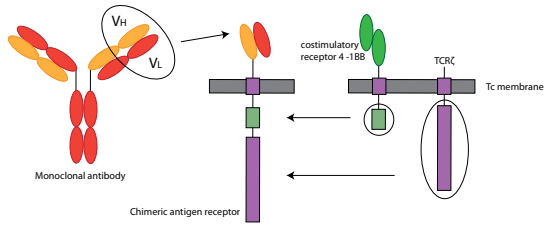

Fig. 3. Schematic view of construction of a chimeric antigen receptor composed of antigen recognition domain (originating from a mAb) and signalling domains taken from 4-1BB (CD137) and TCR ζ .

- GACR, GBP302/12/G101 – Molecular mechanisms of signalling through leukocyte receptors, their role in health and disease, 2012-2018, V. Hořejší, Pe. Dráber, D. Filipp
- MH, NT13462 – Optimization of immunotherapy and flow cytometric minimal residual disease assessment in resistant acute lymphoblastic leukaemia, 2012-2015, P. Otáhal
- MEYS, LK21307 LK-NÁVRAT – C/EBPγ in normal haematopoiesis and acute myeloid leukaemia: identification of molecular mechanisms involved in cell transformation, 2013-2015, M. Alberich-Jorda

1. Horejsi V, Hrdinka M: Membrane microdomains in immunoreceptor signaling. **FEBS Lett 2014** 588(15): 2392-7.
2. Stepanek O, Draber P, Horejsi V: Palmitoylated transmembrane adaptor proteins in leukocyte signaling. **Cell Signal 2014** 26(5): 895-902.
3. Hrdinka M, Hořejší V: PAG – a multipurpose transmembrane adaptor protein. **Oncogene 2013** 33(41): 4881-4892.
4. Liss A, Ooi CH, Zjablovskaja P, Benoukraf T, Radomska HS, Ju C, Wu M, Balaštík M, Delwel R, Brdička T, Tan P, Tenen DG, Alberich-Jorda M: The gene signature in CCAAT-enhancer-binding protein α dysfunctional acute myeloid leukemia predicts responsiveness to histone deacetylase inhibitors. **Haematologica 2014** 99(4):697-705.
5. Zhang H, Alberich-Jorda M, Amabile G, Yang H, Staber PB, Diruscio A, Welner RS, Ebralidze A, Zhang J, Levantini E, Lefebvre V, Valk PJ, Delwel R, Hoogenkamp M, Nerlov C, Cammenga J, Saez B, Scadden DT, Bonifer C, Ye M, Tenen DG: Sox4 is a key oncogenic target in C/EBPα mutant acute myeloid leukemia. **Cancer Cell 2013** 24(5): 575-88.

From the left: Miroslava Kardošová, MSc / PhD Student, Prof. Václav Hořejší, PhD / Head of Laboratory, Meritxell Alberich-Jorda, PhD / Research Fellow, Pavla Angelisová, PhD / Research Fellow, Carlos Lozano Asencio/ Diploma Student, Jana Pokorná / Technician, Polina Zjablovskaja, MSc / PhD Student

Not in the picture: Eva Tvrzníková / Secretary, Pavel Otáhal, MD, PhD / Research Fellow, Barbora Svobodová, MSc / PhD Student, Šimon Borna / Diploma Student