

# Functional analysis of KDEL receptors at the mammalian cell surface

Andrea Blum and Manfred J. Schmitt

*Molecular and Cell Biology, Department of Biosciences and Center of Human and Molecular Biology (ZHMB), Saarland University, D-66123 Saarbrücken, Germany*

Besides having a central function in the retrieval of soluble ER-resident proteins, KDEL receptors (KDELRs) also play important roles in cell signalling and in maintaining Golgi homeostasis [1]. We and others have recently shown that a fraction of KDELRs is also present in the plasma membrane (PM) and capable to bind KDEL cargo such as neuroprotective MANF (mesencephalic astrocyte-derived neurotrophic factor) and KDEL-bearing A/B toxins [2-4]. Under conditions of thapsigargin-induced ER stress, MANF is secreted and KDELR copy number in the PM is increased, pointing towards a cargo-dependent response in subcellular KDELR distribution. In support of a KDELR function at the cell surface, KDELRs were shown to contain endocytotic motifs which are likely involved in the endocytic removal and receptor down-regulation from the plasma membrane. To analyze cell surface function of KDELRs in more detail, we here focus on KDELR signalling, especially in response to cell surface binding of MANF. In a combined approach of RNAseq and proteomic analyses it should be possible to identify MANF-dependent changes in nuclear gene expression. To proof KDELR-dependency of these changes, a CRISPR/Cas9-mediated KDEL1 knock-out in neuroblastoma cells will be performed. Results from these experiments should enable us to propose a model for KDELR signalling from the mammalian cell surface.

[1] J. Cancino et al., *Dev. Cell* 30, 280-94 (2014).

[2] M.J. Henderson et al., *J. Biol. Chem.* 288: 4209-25 (2013).

[3] B. Becker, M.R. Shaebani et al., *Sci. Rep.*, in revision (2016).

[4] B. Becker, E. Gießelmann, A. Blum et al., *Sci. Rep.*, under review.