Novel roles of KDEL receptor at the cell surface of mammalian and yeast cells

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Several microbial A/B toxins including cholera toxin and the yeast viral K28 toxin contain a KDEL-like motif at their cell binding subunit which ensures retrograde toxin transport through the secretory pathway. A key step in the invasion process is the initial binding of each toxin to distinct plasma membrane (PM) receptors that are parasitized by the toxins and utilized for cell entry. Recently, we could demonstrate that eukaryotic KDEL receptors (KDELRs) are not only present in membranes of the secretory pathway but also in the PM where they are capable to bind and internalize KDEL-bearing cargo proteins. By analyzing A/B toxin binding and internalization in conjunction with confocal and TIRF microscopy we could identify the KDEL receptor Erd2p as plasma membrane receptor of the viral K28 killer toxin in yeast [1]. Since human KDELR homologs were shown to be fully functional in yeast and capable to restore toxin sensitivity in a Δ*erd2* knock-out, KDELR-mediated toxin uptake from the cell surface is likely to occur also during A/B toxin invasion of mammalian cells. In this respect, we could already show that the addition of an ER-retention motif to a fluorescent variant of ricin toxin A chain is *in vivo* recognized by PM-localized KDELRs as KDEL-cargo and subsequently internalized from the cell surface. In a combined experimental and theoretical approach we showed that cargo binding induces a dose-dependent cellular response that results in receptor cluster formation at and subsequent internalization from the PM, associated and counteracted by anterograde and microtubule-assisted receptor transport to preferred docking sites [2].

[1] B. Becker, M.R. Shaebani et al., Sci. Rep. (2016).

[2] B. Becker, A. Blum et al., Sci. Rep. (2016).