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COMPLEX MEMBRANE PROTEINS
IN CELLULAR DEVELOPMENT AND DISEASE

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Dissecting host cell intoxification by microbial and plant A/B toxins (Manfred Schmitt)

Microbial and plant proteins of the A/B toxin family such as Cholera and Shiga toxin, Ricin and the yeast viral K28 toxin penetrate eukaryotic target cells by receptor-endocytosis and retrograde transport through the secretory pathway before entering the cytosol to kill their host. Until now, several of these A/B toxins are still a major threat in infectious diseases not only causing diarrhoea but also severe haemolytic uraemic syndrome; the most prominent example for such a scenario is the most recent outbreak of enterohaemorrhagic *Escherichia coli* (EHEC) infections in Germany. Frequently, the disease progresses into dysentery and haemorrhagic colitis which may further develop into life-threatening systemic extra-intestinal complications such as acute renal failure and central nervous system complications that can result in death. As most of the cellular processes and components involved in A/B toxin cell entry and trafficking are still poorly understood, our group is studying two A/B toxin family members of medically relevant protein toxins: (1) the yeast K28 virus toxin and (2) the plant toxin Ricin. In both cases special emphasis is given on two central aspects of host cell intoxification: (i) A/B toxin uptake via ubiquitin-mediated receptor endocytosis and subsequent sorting into the endocytic pathway, and (ii) toxin retrotranslocation from the endoplasmic reticulum into the cytosol as prerequisite for cell killing (Fig. 1). Since A/B toxins somehow use different strategies to enter and penetrate eukaryotic cells, detailed analysis of A/B toxin uptake and intracellular membrane passage will possibly reveal non-canonical endocytic entry routes and extend our current knowledge of endocytosis and intracellular trafficking of medically relevant A/B toxins.

Within the IRTG, our project will focus on two interrelated processes of host cell intoxification, namely endocytic toxin uptake & trafficking, and toxin retrotranslocation from the ER into the cytosol. In addition to related existing projects which investigate toxin uptake via receptor-monoubiquitylation, our IRTG project will focus on the mechanism of receptor clustering at the level of the plasma membrane and analyze cellular components that are responsible for subsequent receptor/toxin sorting into the endocytic pathway of yeast and mammalian cells. Additional attention will be given to the molecular mechanism of ubiquitin/ERAD-independent toxin retrotranslocation from the ER into the host cell cytosol.