Mechanisms of Shiga toxin-mediated toxicity and microvesicle release

Enterohemorrhagic *Escherichia coli* (EHEC) is a non-invasive bacterium that colonizes the human intestine. From the intestine it releases its main virulence factor, Shiga toxin. Shiga toxin is a member of the AB5-toxin family, consisting of an enzymatically active A-subunit and a receptor binding pentameric B-subunit. The Shiga toxin B-subunit binds the glycolipid receptor globotriaosylceramide (Gb3/CD77), leading to internalization of the toxin. Following internalization, Shiga toxin is transported to the Golgi apparatus and the endoplasmatic reticulum.

Shiga toxin receptor binding induces calcium influx. Shiga toxin stimulation of cells also leads to shedding of microvesicles. An initial observation leading to this thesis was that elevated levels of blood cell-derived microvesicles circulate in EHEC-infected patients and these may contain Shiga toxin. The toxin is thus taken up by target organ cells in the kidney leading to renal failure. The mechanism by which toxin is taken up and microvesicles are released will be the focus of these studies in order to ultimately develop a treatment that prevents the shedding of toxin-positive microvesicles.