Weria Pezeshkian, Haifei Gao, Senthil Arumugam, Ulrike Becken, Patricia Bassereau, Jean-Claude Florent, John Hjort Ipsen, Ludger Johannes, Julian C Shillcock (2017 Jan 24)

**Mechanism of Shiga Toxin Clustering on Membranes**


**Summary**

The bacterial Shiga toxin interacts with its cellular receptor, the glycosphingolipid globotriaosylceramide (Gb3 or CD77), as a first step to entering target cells. Previous studies have shown that toxin molecules cluster on the plasma membrane, despite the apparent lack of direct interactions between them. The precise mechanism by which this clustering occurs remains poorly defined. Here, we used vesicle and cell systems and computer simulations to show that line tension due to curvature, height, or compositional mismatch, and lipid or solvent depletion cannot drive the clustering of Shiga toxin molecules. By contrast, in coarse-grained computer simulations, a correlation was found between clustering and toxin nanoparticle-driven suppression of membrane fluctuations, and experimentally we observed that clustering required the toxin molecules to be tightly bound to the membrane surface. The most likely interpretation of these findings is that a membrane fluctuation-induced force generates an effective attraction between toxin molecules. Such force would be of similar strength to the electrostatic force at separations around 1 nm, remain strong at distances up to the size of toxin molecules (several nanometers), and persist even beyond. This force is predicted to operate between manufactured nanoparticles providing they are sufficiently rigid and tightly bound to the plasma membrane, thereby suggesting a route for the targeting of nanoparticles to cells for biomedical applications.

Ludger Johannes, Christian Wunder, Massiullah Shafaq-Zadah (2016 Dec 17)

**Glycolipids and Lectins in Endocytic Uptake Processes.**

*Journal of molecular biology* : [DOI: S0022-2836(16)30453-3]

**Summary**

A host of endocytic processes has been described at the plasma membrane of eukaryotic cells. Their categorization has most commonly referenced cytosolic machinery, of which the clathrin coat has occupied a preponderant position. In what concerns intra-membrane constituents, the focus of interest has been on phosphatidylinositol lipids and their capacity to orchestrate endocytic events on the cytosolic leaflet of the membrane. The contribution of extracellular determinants to the construction of endocytic pits has received much less attention, despite the fact that (glyco)sphingolipids are exoplasmic leaflet fabric of membrane domains, termed rafts, whose contributions to predominantly clathrin-independent internalization processes is well recognized. Furthermore, sugar modifications on extracellular domains of proteins, and sugar-binding proteins, termed lectins, have also been linked to the uptake of endocytic cargo at the plasma membrane. In this review, we first...
summarize these contributions by extracellular determinants to the endocytic process. We thus propose a molecular hypothesis – termed the GL-Lect hypothesis – on how GlycoLipids and Lectins drive the formation of compositional nanoenvironments from which the endocytic uptake of glycosylated cargo proteins is operated via clathrin-independent carriers. Finally, we position this hypothesis within the global context of endocytic pathway proposals that have emerged in recent years.

Weria Pezeshkian, Haifei Gao, Senthil Arumugam, Ulrike Becken, Patricia Bassereau, Jean-Claude Florent, John Hjort Ipsen, Ludger Johannes, Julian C Shillcock (2016 Dec 13)
**Mechanism of Shiga Toxin Clustering on Membranes.**
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**Summary**

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**Spatiotemporal control of interferon-induced JAK/STAT signalling and gene transcription by the retromer complex.**
*Nature communications* : 13476 : [DOI : 10.1038/ncomms13476]

**Summary**

Type-I interferons (IFNs) play a key role in the immune defences against viral and bacterial infections, and in cancer immunosurveillance. We have established that clathrin-dependent endocytosis of the type-I interferon (IFN-α/β) receptor (IFNAR) is required for JAK/STAT
signalling. Here we show that the internalized IFNAR1 and IFNAR2 subunits of the IFNAR complex are differentially sorted by the retromer at the early endosome. Binding of the retromer VPS35 subunit to IFNAR2 results in IFNAR2 recycling to the plasma membrane, whereas IFNAR1 is sorted to the lysosome for degradation. Depletion of VPS35 leads to abnormally prolonged residency and association of the IFNAR subunits at the early endosome, resulting in increased activation of STAT1- and IFN-dependent gene transcription. These experimental data establish the retromer complex as a key spatiotemporal regulator of IFNAR endosomal sorting and a new factor in type-I IFN-induced JAK/STAT signalling and gene transcription.