Abstract
The raft hypothesis has had a major impact by placing lipids at the center stage of membrane biology research. It has caused intense debate on the structure and mechanisms by which functionally relevant raft assemblies are generated. Our recent studies have uncovered a novel mechanism by which nanodomain construction by glycosphingolipid-binding polyoma viruses (e.g. SV40) or protein toxins (e.g. Shiga toxin) induces membrane curvature changes and drives the formation of endocytic plasma membrane invaginations, leading to the clathrin-independent uptake of these pathogens or pathogenic factors into cells (Römer et al., 2007, Nature 450, 670-675; Ewers et al., 2010, NCB 12, 11-18). These internalization pathways are characterized by the fact that the scission step does not strictly require the activity of the GTPase dynamin. In another study, we could indeed show that actin polymerization on endocytic tubule membranes triggers membrane reorganization, nanodomain formation and dynamin-independent scission (Römer et al., 2010, Cell 140, 540-553). We could also provide evidence that at least in the case of the bacterial Shiga toxin, endocytic tubules are enriched in sphingolipid species that are not the direct toxin receptors (Safouane et al., ahead of press, Traffic). This lipid sorting mechanism is dominant over curvature-mediated lipid sorting, and to be efficient, theoretical arguments suggest that these tubule membranes must be poised near a lipid demixing point at physiological temperature. The possibility that specific lipids, including the ‘raft-type’ lipids may generate membrane areas close to phase separation and may undergo induced domain formation opens exciting perspectives on how lipid repartitioning can be exploited for membrane mechanics. We are now analyzing how cortical actin dynamics contributes to nanoclustering, and we are identifying protein machinery that is recruited to induced invaginations for their targeting to endosomes. We are also studying cellular proteins that like the above-mentioned toxins induce tubular plasma membrane invaginations, thereby regulating the cell surface dynamics of various markers with critical roles in key cellular processes such as cell migration and T-cell signaling.