Molecular roles of Myo1c function in lipid raft exocytosis

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Lipid rafts are highly dynamic membrane subdomains enriched in specific protein and lipid components that create specialized ‘organizing’ platforms essential for an array of important cellular functions. The role of lipid rafts in membrane trafficking involves the constant remodelling of the plasma membrane through membrane uptake and balanced exocytosis of intracellular membranes. Our lab has identified the first motor protein, myosin 1c (Myo1c) involved in driving the recycling of lipid-raft enriched membranes from the perinuclear recycling compartment to the cell surface. This newly discovered role for Myo1c in lipid raft exocytosis is crucial for cell spreading, migration and pathogen entry; key cellular processes that require cell surface expansion and plasticity. Here we present a model suggesting Myo1c’s possible molecular functions in lipid raft recycling and discuss its wider implications for important cellular functions.

Our lab however has recently established that the actin-based motor protein myosin1c (Myo1c) promotes endocytic recycling by controlling the generation of lipid raft-enriched tubular recycling carriers extending from the recycling compartment.3 We demonstrated that Myo1c is a lipid raft-associated motor protein that specifically controls recycling of lipid raft-associated cargo to the plasma membrane. Abolishing Myo1c function by RNA interference or overexpressing a dominant-negative mutant induced a collapse of raft-enriched recycling tubules and lipid rafts accumulated in the recycling compartment causing a dramatic loss of raft markers from the cell surface. Conversely, overexpression of exogenous Myo1c increased lipid raft levels at the cell surface. Myo1c selectively regulated lipid raft exocytosis to the plasma membrane, but it was dispensable for recycling of cargo, such as the transferrin receptor, along separate parallel pathways. The dramatic defect in lipid raft recycling following Myo1c knockdown had a severe impact on cell spreading, cell migration and cholesterol-dependent Salmonella entry, demonstrating that Myo1c-mediated raft delivery to the cell surface plays a pivotal role in processes which require the correct targeting of signaling molecules and extra membrane fundamental for plasma membrane expansion and remodeling.3

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We observed that Myo1c is present at the plasma membrane and also on dynamic raft-enriched tubular carriers emanating from the perinuclear recycling
Figure 1. Model outlining the possible molecular roles of Myo1c in lipid raft recycling. (A) Myo1c could mediate cargo sorting at the endocytic recycling compartment (ERC), a process that is crucial for the correct recycling of proteins by distinct pathways. By linking lipid raft membranes and cargo proteins associated with these microdomains to adjacent actin filaments, Myo1c could cluster molecular cargo for subsequent transport to the cell surface. (B) Myo1c might initiate the generation of recycling tubules at the ERC by membrane deformation. By anchoring the membrane to surrounding actin filaments Myo1c motor activity could generate a force to deform the membrane for nascent tubular carriers. Through its ATP-driven powerstroke Myo1c could create the tension that would actively pull on the ERC membrane. Thereby Myo1c might prime the formation of tubule precursors, which may then be elongated toward the plasma membrane by microtubule-associated kinesin motors. (C) Myo1c could also be involved in the final stages of exocytosis, where it might propel cargo transport through the dense cortical actin filament network. It is also plausible that Myo1c together with its binding partner RalA and the exocyst complex mediates the docking and fusion of lipid raft enriched recycling carriers with the plasma membrane. These proposed activities are not mutually exclusive and it is possible that each might contribute to Myo1c function in lipid raft exocytosis.

Cellular Processes Dependent on Myo1c-Mediated Raft Exocytosis

The severe defect in lipid raft targeting to the cell surface in Myo1c depleted cells has a profound impact on cellular processes that require the dynamic remodelling and expansion of the plasma membrane. This defect was found to impair leading edge protrusion, underlying cell spreading, migration and cholesterol-dependent Salmonella invasion. In summary, these novel roles for Myo1c suggest that it may act as a general regulator of stimulated exocytosis by utilizing its ability to link lipid raft microdomains, actin filaments and the RalA-mediated exocytic machinery for cargo delivery. Myo1c does indeed facilitate the transport of diverse raft-associated cargos including GLUT4, aquaporin-2 and Nephi to the cell surface. Moreover, RalA and the exocyst complex are also involved in the translocation of vesicles containing the GLUT4 transporter and
aquaporin-2,12,13,35 suggesting that Myo1c, RaLA and the exocyst complex are part of the core machinery required for raft exocytosis. What are the lipid raft-associated cargoes of Myo1c that might regulate cell spreading, migration and bacterial invasion? The central cytoskeletal regulators Racl and Cdc42 localize to raft microdomains, which are known to modulate small GTPase targeting and activation.16,17 Importantly, defective lipid raft trafficking was observed to mislocalize Racl, which blocked cell spreading, migration and Salmonella-induced macropinocytosis.18,19 In addition, Myo1c may supply membranes to influence cell plasticity, as there is recent evidence that the exocytosis of lipid rafts not only delivers key protein components to the plasma membrane, but also provides the extra membrane required for cell surface expansion.20 This would be consistent with Myo1c-dependent formation of raft-enriched membrane-tubules, which emanate from a previously defined ‘membrane-storage’ compartment.20 Thus the diverse lipid and protein composition of raft microdomains is reflected in the array of pathways in which they participate, indicating a pivotal role for Myo1c in a range of cellular processes.

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