Protein-Protein Interactions in Vesicle Membrane Remodeling

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Vesicle transport is responsible for protein trafficking between different organelles and plasma membrane, and is orchestrated by a network of dynamic protein-protein interactions. For vesicle formation, membranes have to be bent at the site of invagination/tabulation. There are several mechanisms to achieve this including clathrin coats, coatamer proteins, BAR domains, ESCRT complexes etc. Rab and Arf family proteins are involved in various stages of vesicle transport by interacting with effectors which are often multi domain proteins whose domains make transient but specific interactions. The small GTPases alternate between GTP- and GDP-bound states. They are activated by guanine nucleotide exchange factors (GEF) which replace their GDP with GTP.

Once activated, the GTP-bound Arf or Rab can interact with a number of effectors for specific functions such as cellular localization, control of vesicle budding or fusion, and membrane remodeling. The effector/small GTPase specificities are achieved in most cases by the surface area including Switches I/II and interswitch antiparallel beta sheet. This will be illustrated using crystallographic examples: (1) Arf1 in complex with the N-terminal GAT domain of GGA, (2) Rab11 in complex with the Rab11-binding domain (RBD) of FIP3/Arfophlin-1, dual effector for Rab11 and Arf5/6, and (3) Rab27a with Exophilin4/Slp2-a, a Rab27 effector responsible for melanosome and secretory granules. In these cases, the interswitch beta sheet align parallel to the helices of the effectors, which will orient the effector helices perpendicular to the membrane to reach other partner proteins in the cell. On the other hand, there are cases where the interswitch beta sheet and effector helices lie orthogonal to each other. One remarkable example is a complex between a GTPase and a BAR domain. The complex structure shows a curved surface ideally shaped for bending the target membrane using both the concave surface of the BAR domain as well as the small GTPase itself.