Mso1p regulates membrane fusion in association with Sec1p, Sso1p, Sso2p and membrane lipids.

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Membrane fusion is a fundamental process that is critical for maintenance of integrity and survival of all eukaryotic organisms. In living cells, flow of proteins and lipids to the cell surface requires execution of several specific membrane fusion events. Exocytosis, the final transport step during protein secretion at the plasma membrane is indispensable for the immune response, hormone signaling and neuronal synaptic transmission in higher eukaryotes. Exocytosis has been highly conserved in evolution. It consists of three tightly spatially and temporarily regulated consecutive steps; docking, SNARE complex assembly and membrane fusion. Previous studies have shown that during neurotransmission, the adaptor proteins of the Mint/X11 family act as scaffolds that bring components of signalling and exocytosis machinery together. The neuronal Mint proteins are involved in regulation of the beta-amyloid precursor proteins that are implicated in development of Alzheimer's disease. In addition, Mint proteins contain a phosphotyrosine-binding (PTB) that binds phosphoinositides. We have previously identified Mso1p as the putative yeast homologue of Mint proteins. Mso1p is needed for membrane fusion in the yeast Saccharomyces cerevisiae and it shares weak sequence homology with the PTB domain of Mints. Our preliminary results show that Mso1p is a PI(4,5)P2-binding protein. These results support the possibility that Mso1p is the functional Mint homologue. In addition, detailed understanding of Mso1p function has the potential to reveal an evolutionarly conserved layer of regulation in membrane fusion. The present study aims at detailed structural and biochemical characterization of Mso1 and its role in membrane fusion regulation. The three dimensional structure of Mint PTB domain is known. In order to confirm the functional similarity of Mso1p with Mint proteins we propose to determine the structure of Mso1p. Furthermore, we will characterize in detail the PIP2 lipid binding domain of Mso1 and verify its role for Mso1 function in membrane fusion both in vitro and in vivo. In addition, the proposed research aims at discovering Mso1-interacting proteins that can reveal novel molecular interactions this protein and provide an original link between membrane fusion and other cellular processes.