

Crystal structure of the Munc18c/Syntaxin4-N-peptide: implications for the role of SM proteins in membrane trafficking

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Sec1p/Munc18 (SM) proteins bind to SNARE (Soluble NSF-attachment protein receptors) proteins and play an essential but poorly understood role in membrane fusion. Divergent modes of regulation have been proposed for different SM proteins indicating that they can either promote or inhibit SNARE assembly. This is in part due to discrete modes of binding that have been described for various SM/SNARE complexes. One mode suggests that SM proteins bind only to Syntaxins preventing SNARE assembly whereas in another they facilitate SNARE assembly and bind to SNARE complexes. The mammalian cell surface SM protein Munc18c binds to an N-peptide in Syntaxin4 and this is compatible with its interaction with SNARE complexes.

We determined the crystal structure of Munc18c in complex with the Syntaxin N-peptide. This structure shows remarkable similarity with a yeast complex indicating that the mode of binding, which can accommodate SNARE complexes, is highly conserved throughout evolution. Modelling reveals that the N-peptide binding mode is present in most but not all yeast and mammalian SM/Syntaxin pairs suggesting that it has co-evolved to fulfill a specific regulatory function. The likely regulatory function will be discussed.