The functional pas de deux of v-SNARE transmembrane domains and lipids in membrane fusion

Madhurima Dhara, Maria Mantero Martinez, Mazen Makke, Yvonne Schwarz, Ralf Mohrmann and Dieter Bruns

Membrane fusion is initiated once the assembled *trans*-SNARE complexes as the core fusion machinery exert the mechanical force necessary on the adjoining phospholipid membranes. Our recent work suggested an active role of SNARE transmembrane domains (TMDs) in promoting membrane merger. Yet the its molecular mechanism remained unclear. Our results demonstrate that naturally occurring v-SNARE TMD isoforms, varying in the number of helix-destabilizing, ß-branched valine or isoleucine residues, differentially regulate fusion pore dynamics. Thus, TMD flexibility represents an unrecognized mechanistic determinant adapted by v-SNARE variants to promote transmitter release. Furthermore, we show that membrane-incorporated lipids like lysophosphatidylcholine or oleic acid affected fusion induction and subsequent pore expansion in a membrane leaflet-specific fashion and in a manner that correlated with their intrinsic curvature preference of highly bent fusion intermediates. Thus, membrane mechanics represent a rate-limiting energy barrier for Ca^{2+}-triggered fusion of chromaffin granules, which proceeds via the formation of a membrane stalk intermediate into a lipidic fusion pore. Collectively, our results suggest that both, support of membrane curvature by v-SNARE TMDs and SNARE force generated membrane bending promote fusion pore formation and progressive expansion.