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Membrane fusion specificity

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Abstract

Isolated SNARE proteins have been shown to confer only partial specificity on the fusion of artificial liposomes that mimic cellular membranes, modifying the SNARE hypothesis of membrane fusion.

Significance and context

Transport between different intracellular compartments is mediated by the budding of membrane-bounded transport vesicles from the donor compartment and their fusion with the membrane of the acceptor compartment. Proteins of the SNARE (soluble *N*-ethlymaleimide-sensitive fusion protein receptor) family reside in all vesicle membranes (v-SNAREs) and target compartment membranes (t-SNAREs) and have been proposed to pair specifically with each other to ensure that a vesicle will only dock and fuse with the correct target compartment. SNAREs are also thought to provide the driving force for membrane fusion by pulling the two membranes together as a consequence of their pairing. Taking advantage of the complete *Saccharomyces cerevisiae* genome sequence to identify all the potential v-SNAREs, McNew *et al.* use an established liposome fusion system that is thought to mimic intracellular fusions to test these v-SNAREs for fusion with three sets of t-SNAREs. They conclude that v-SNAREs on one liposome almost always mediate fusion only when paired with the correct (cognate) t-SNARE on the acceptor liposome, thus supporting the hypothesis that SNAREs encode the specificity of membrane fusion.

Key results

The domain of each SNARE that mediates fusion is the coiled-coil-forming domain (an β helix). The v-SNARE contributes one coil-forming domain, whereas the t-SNARE group is comprised of two or three proteins that contribute a total of three coils to the SNARE complex, which is a four-helix bundle. McNew *et al*. show that when the vacuolar t-SNAREs (Vam3p/Vam7p/Vti1p) are tested with 11 different SNARE coils, the cognate v-SNARE (Nyv1p) induces a greater level of fusion than the non-cognate SNAREs, indicating specificity. Similarly, with the Golgi t-SNARE trio (Sed5p/Bos1p/Sec22p), the endoplasmic reticulum (ER) to Golgi SNARE Bet1p (the sequence and structure of which indicate it is actually a t- rather than a v-SNARE) is the only 'v'-SNARE to result in fusion. With the plasma membrane t-SNARE couple (Sso1p/Sec9p - Sec9p contributes two coils), the cognate v-SNARE

(Snc1p) also yields greater fusion than other SNAREs. Fusion is not completely specific, however, because the Golgi-to-ER v-SNARE Sec22p also gives a robust fusion signal in this test, as does the vacuolar v-SNARE Nyv1p. This shows that SNAREs are not always faithful determinants of fusion specificity.

Links

Two related papers in the same issue of *Nature* (full text available to subscribers only) show that the distribution of cognate t- and v-SNAREs between the donor and target liposomes (their topology) is also important for fusion. A News and Views article covering these three papers(Scales SJ *et al*., *Nature***407:**144-146) appeared in the same issue of *Nature* and is available to subscribers.

Conclusions

McNew *et al*. conclude that the SNARE proteins by themselves are sufficient to confer specificity to membrane fusion, as proposed in the SNARE hypothesis.

Reporter's comments

While this paper provides evidence that SNAREs in isolation do contribute some specificity to membrane fusion, the main conclusion is a little strong for the data shown. In the case of the ER to Golgi SNARE complex, for example, it is debatable whether or not this is truly cognate. Sec22p, which is used in place of Bet1p as part of the Golgi t-SNARE trio, is actually a v-SNARE and probably functions in the opposite direction of transport to the others. Furthermore, the presence of this v-SNARE on the target membrane probably prevents fusion with other v-SNAREs on the donor membrane simply because cognate SNARE complexes should contain only one v-SNARE; thus many of the SNARE combinations tested for fusion specificity were not valid. There were also many cases where four t-SNAREs did not result in fusion, which, while validating the theory that three t-SNAREs should complex with one v-SNARE, is not a true test of specificity. Given the relative promiscuity of the plasma membrane t-SNAREs (which fused with at least four of the five v-SNAREs), one cannot conclude that SNAREs are absolute determinants of specificity. In addition, many potential combinations of t-SNAREs were not tested, which means we cannot tell if the plasma membrane promiscuity is the exception rather than the rule. The authors do concede, however, that in the cellular context, other proteins may enhance specificity by regulating whether or not the SNAREs can access each other. Specificity is therefore most likely to be regulated not only by SNARE protein complexing, but by other upstream factors as well.

Table of links

Nature

Scales SJ *et al*., *Nature***407:**144-146

References

1. McNew JA, Parlati F, Fukuda R, Johnston RJ, Paz K, Paumet F, Söllner TH, Rothman JE: Compartmental specificity of cellular membrane fusion encoded in SNARE proteins. Nature. 2000, 407: 153-159. 0028-0836