HIGHLIGHTS

MEMBRANE FUSION

Fine-tuning

Membrane fusion is initiated by cognate SNARE proteins (soluble *N*-ethylmaleimide-sensitive fusion protein (NSF) attachment protein receptors) — that is, by specific t-SNAREs on the target membrane (there are three on intracellular membranes) and by a specific v-SNARE on the vesicle membrane. SNARE-mediated fusion is highly specific, but this specificity has only been tested using four SNAREs at a time between two bilayers. As every compartment in the secretory pathway can contain many SNAREs in a single bilayer, Rothman and colleagues decided to study the effect of a fifth SNARE on four cognate SNAREs and, in *The Journal of Cell Biology*, they report the identification of a new functional class of SNAREs — inhibitory (i)-SNAREs.

The authors focused their study on two functionally distinct t-SNARE complexes from the yeast Golgi. Sed5–Bos1–Sec22 (t_{cis}) binds to the v-SNARE Bet1 (v_{cis}), and the concentration of these four SNARE proteins increases towards the *cis*-Golgi. The other t-SNARE complex Sed5–Gos1–Ykt6 (t_{trans}) binds to the v-SNARE Sft1 (v_{trans}) and, although the concentration of v_{trans} increases towards the *cis*-Golgi, t_{trans} probably has a more even distribution.

Rothman and co-workers studied the effect on v_{cis}–t_{cis} and v_{trans}–t_{trans} fusion of including increasing concentrations of a fifth non-cognate SNARE in the t-SNARE-containing liposomes. They found that the v_{cis}–t_{cis} fusion reaction was strongly inhibited by Gos1 and Sft1, and that the v_{trans}–t_{trans} reaction was inhibited by Bet1, Bos1 and Sec22. This work therefore establishes the existence of i-SNAREs, and highlights an interesting pattern — *cis*-Golgi SNAREs inhibit the fusion that is triggered by *trans*-Golgi SNAREs and vice versa.

So, how do i-SNAREs inhibit fusion? An i-SNARE could either replace a cognate SNARE protein of the t-SNARE complex to form a non-functional tetrameric complex (competitive inhibition), or could bind to the cognate SNARE complex to form a non-functional oligomeric complex (non-competitive inhibition). To distinguish between these possibilities, the authors studied whether high concentrations of one of the cognate t-SNAREs could compete to suppress the effects of an i-SNARE. Their results showed that, in the case of v_{cis}–t_{cis} fusion, the i-SNARE (Gos1 or Sft1) replaces Bos1 to form a non-functional tetrameric complex (competitive inhibition). However, in the case of v_{trans}–t_{trans} fusion, the mechanism of i-SNARE inhibition could not be established.

Finally, Rothman and colleagues studied what effect i-SNAREs might have on the specificity of membrane fusion in the Golgi, and used a liposome-fusion assay to recreate the unique SNARE composition that is found in each of the sequential compartments of the Golgi. They showed, for example, that the fusion of v_{cis} with the *trans*-Golgi is ~3% of that with the *cis*-Golgi when i-SNAREs are present, but increases to 40% when both Gos1 and Sft1 are absent. Combining the distributions of i-SNAREs with those of v- and t-SNAREs therefore fine-tunes the specificity of membrane fusion.

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References and links

ORIGINAL RESEARCH PAPER Varlamov, O. *et al.* i-SNARE: inhibitory SNAREs that fine-tune the specificity of membrane fusion. *J. Cell Biol.* **164**, 79–88 (2004)

FURTHER READING Chen, Y. A. & Scheller, R. H. SNARE-mediated membrane fusion. *Nature Rev. Mol. Cell Biol.* **2**, 98–106 (2001)

WEB SITE
James Rothman's laboratory:
http://www.mskcc.org/mskcc/html/10879.cfm