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Commentary

Clues to brain function from bakers' yeast

Suzanne R. Pfeffer

Department of Biochemistry, Stanford University School of Medicine, Stanford, CA 94305-5307

In 1979, Novick and Schekman (1) reported a yeast mutant (*sec1*) that was conditionally defective in invertase secretion at 37°C. The cells stopped dividing at that temperature; however, protein and lipid synthesis continued for several hours. Thus, the cells became dense and accumulated numerous small (100 nm) secretory vesicles. This mutant paved the way for Novick and Schekman to identify a larger number of gene products that were essential in yeast secretion; mutations in these proteins blocked vesicular transport between the endoplasmic reticulum (ER) and the Golgi complex and from the Golgi complex to the plasma membrane or vacuole (yeast lysosome).

Yeast contained membrane-bound organelles analogous to mammalian cells and proteins passed between them in a similar vectorial order, but were the systems truly analogous? Hints of molecular analogies came when it was found that a crude yeast cytosol fraction could sustain the transport of proteins between mammalian cell Golgi cisternae in a cell-free system (2). Later, it was shown that a key cytosolic intracellular transport factor termed NSF (*N*-ethylmaleimide-sensitive fusion protein) was the mammalian homolog of the yeast SEC18 gene product (3). This discovery provided strong evidence that vesicular transport events measured in reconstituted systems reflected physiologically relevant aspects of the secretory pathway in living cells (4, 5). In addition, it provided the most concrete evidence that yeast did it just like animal cells.

The homologies are now numerous and include two reports appearing in this journal (6, 7) and elsewhere (8) of the discovery of a mammalian protein related to the *Saccharomyces cerevisiae* SEC1 gene product. Sec1 protein functions in the delivery of yeast secretory vesicles to the plasma membrane (1, 10). As described below, the newly identified Sec1-related protein is expressed specifically in the nervous system and is likely to function in synaptic vesicle release.

A molecular understanding of the transport of proteins between membrane-bound compartments may soon be at hand. Moreover, the process about which we are learning the most is the release of neurotransmitter from nerve terminals (see refs. 11–14 for review). Neurotransmitter release, or exocytosis, begins with a synaptic vesicle docking with its cognate target, the presynaptic plasma membrane. It now appears that proteins termed VAMPs (or synaptobrevins) represent key elements of the vesicle-targeting machinery; these interact with a group of proteins termed syntaxins located on the specific target membrane. Ras-like GTPases of the so-called rab family (Ypt in yeast) may regulate this association (16). Yeast homologs of VAMPs and syntaxins have already been implicated in ER-to-Golgi transport as well as in transport from the Golgi to the plasma membrane and in transport from the Golgi to the vacuole (11).

Another key advance has come from the discovery that two proteins needed for intra-Golgi transport, NSF and the so-called SNAP proteins (soluble NSF membrane attachment proteins), interact with membranes by binding to a complex of VAMP, syntaxin, and another unrelated protein termed SNAP-25 (17). The beauty of this observation is best appreciated when one realizes that NSF and SNAP act at many different steps of the secretory pathway (4, 5). Together, these findings implicate a homologous molecular basis for membrane traffic throughout the secretory pathway that is conserved from yeast cells to mammalian neurons. To simplify the terminology in this field, Rothman and coworkers (17) have proposed that the vesicle-targeting proteins (VAMP family members) be termed v-SNAREs and that the target membrane-identifying proteins be termed t-SNAREs; t-SNARE–v-SNARE interactions would result in specific vesicle transfers.

Now for Sec1. The sequence of the yeast Sec1 protein was recently determined (18) and found to be related to two other cytosolic yeast proteins involved in intracellular transport, Slp1 and Sly1 (19). Slp1 is needed for transport from the Golgi to the vacuole (20); Sly1 functions in ER-to-Golgi transport (21). Thus, Sec1 is a member of a family of proteins required for transport vesicle targeting and/or fusion. Genetic evidence suggests that Sec1 family members interact with ras-like GTPases of the Sec4/Ypt (rab) type; there is some indication for an interaction between Sec1 and Sec4 and stronger evidence for an interaction between Sly1 and Ypt1 (21, 22).

How does all of this relate to the brain? Aalto *et al.* (23) recently reported genetic evidence that Sec1 interacts with two other yeast proteins, Sso1 and Sso2. Sure enough, Sso1 and Sso2 are related to the syntaxin family of proteins (15), which participate in mammalian neurotransmitter release. Satisfyingly, the neuronal Sec1 relative interacts with mammalian syntaxin (6–8), analogous to Sec1–Sso1/Sso2 interaction in yeast (23).

Hata *et al.* (8) have termed the mammalian Sec1 protein Munc-18 based on a much higher degree of homology (59%; ref. 24) with the unc-18 gene product of *Caenorhabditis elegans*. Indeed, the homology with Sec1 is less significant, with 27% identity (6, 7). *Unc-18* mutations lead to paralysis and an accumulation of neurotransmitter, strongly suggesting that the n-Sec1 (Munc-18) protein functions in neurotransmitter release *in vivo*. Nevertheless, the nomenclature in this field is becoming impossible for the noncognoscenti. Given the nervous system-specific expression of the protein, it seems most straightforward to refer to it as n-Sec1 (6).

How might Sec1 act? Sec1 has been shown to form a stoichiometric complex with a syntaxin (6–8) and to be required for neurotransmission in *C. elegans*. It is reasonable to propose that Sec1 family members participate in regulating the availability of t-SNAREs for v-SNARE interaction. Rab (or Ypt) GTPases present on transport vesicles may add another layer of regulation to this docking process by interaction with Sec1 or one of its relatives. The reconstitution of these interactions using purified components (cf. ref. 9) will surely reveal the details of Sec1 function.

Thus, the story is slowly coming together. Syntaxin-like (t-SNARE) proteins seem to define vesicle targets; VAMP or synaptobrevin-related v-SNARE proteins reside on transport vesicles and direct them to the appropriate t-SNARE. Ras-like GTPases, NSF and SNAPs (Sec17 and -18), and proteins like n-Sec1 are likely to regulate this association. But the end of the story is not as close as it seems; the functions of numerous other Sec proteins (and their homologs for other transport steps) have yet to be determined.

Nevertheless, the molecular basis for vesicle trafficking and neurotransmitter release will soon be at hand. Perhaps to everyone's surprise, yeast cells continue to provide valuable clues to brain function.

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