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Review

SNAREs and traffic

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Abstract

SNAREs (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors) are now generally accepted to be the major players in the final stage of the docking and the subsequent fusion of diverse vesicle-mediated transport events. The SNARE-mediated process is conserved evolutionally from yeast to human, as well as mechanistically and structurally across different transport events in eukaryotic cells. In the post-genomic era, a fairly complete list of "all" SNAREs in several organisms (including human) can now be made. This review aims to summarize the key properties and the mechanism of action of SNAREs in mammalian cells.

Keywords: Soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor; Vesicle fusion; Membrane traffic; Synaptic transmission; Exocytosis; Endocytosis

1. Introduction

The highly-organized eukaryotic cell contains many membrane-enclosed intracellular organelles/compartments and it requires precise mechanisms to govern protein transport between different organelles, particularly in the secretory and endocytic pathways. Small shuttling vesicles (such as synaptic vesicles of neurons) or larger transport containers (such as zymogen granules of pancreatic acinar cells) are the major intermediates in anterograde or retrograde translocation of proteins between various compartments in the secretory and endocytic pathways. The basic steps underlying vesicle-mediated transport are vesicle/container formation from a donor compartment, translocation of transport intermediates to a target compartment, tethering of transport intermediates with the target compartment, and, finally, the docking and fusion of vesicles/containers with the target compartment [1].

SNAREs function in the final event of docking of vesicles/containers with the target compartment and catalyze the fusion of the apposing membranes of the transport intermediate and the target compartment [2–4]. Functionally, SNAREs can be classified into v-SNAREs that are associated with the vesicle/container and t-SNAREs that are associated with the target compartment (Table 1). Specific interaction of v-SNARE on the transport intermediate with the cognate t-SNARE on the receiving target compartment underlies the central event of docking and fusion process of vesicle-mediated transport. Our current knowledge is that v-SNARE usually consists of a tail-anchored SNARE having a single SNARE motif, while a t-SNARE consists of either two or three polypeptides [5]. A heterodimeric t-SNARE is usually comprised of a member of the syntaxin (Syn) subfamily, which contributes one SNARE motif as the t-SNARE heavy chain, and a member of the SNAP-25 subfamily, which contributes two SNARE motifs as two t-SNARE light chains. A heterotrimeric t-SNARE is formed by one member of the Syn subfamily (as the heavy chain), one member of the SNARE subfamily related to the N-terminal half of SNAP-25 (as one of the two light chains), and one member of the SNARE subfamily related to the C-terminal half of SNAP-25 (as the other light chain). Interaction between v-SNARE and t-SNARE leads to the formation of the *trans*-SNARE complex (or SNAREpin), in which the

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Table 1
Classification of SNAREs. Functionally, SNAREs can be classified into v-SNAREs associated with the vesicle (or other forms of transport intermediates) and t-SNARE associated with the target compartment

Functionally	v-SNARE	t-SNARE
Sub-classification of t-SNARE	Heavy chain & Light chain	
Structurally according to the central residue of SNARE motif (0 layer)	R-SNARE	Q-SNARE
Sub-classification of Q-SNARE	Qa, Qb & Qc	

A t-SNARE is generally assembled from one heavy chain and two light chains of SNARE domains. The two light chains can come from one or two proteins. Based on the residue in the 0 layer in the four-helical SNARE bundle of the SNARE domain, SNAREs can be structurally divided into Q-SNAREs (those having a Q/Gln residue) and R-SNARE (those having an Arg/R residue). The Q SNAREs can be further subdivided into Qa-, Qb-, and Qc-SNAREs based on amino acid sequence of the SNARE domain.

four SNARE motifs assemble as a twisted parallel four-helical bundle, which catalyzes the apposition and fusion of the vesicle with the target compartment [6–8].

2. The general mode of SNARE action

All newly-made SNAREs are first delivered to their hosting compartment(s) via the secretory and endocytic pathways. The general mode of action of SNAREs in vesicle-mediated transport is highlighted in Fig. 1. First, the v-SNARE is packaged together with other cargo proteins into the budding vesicle so that the resulting transport intermediate is competent to fuse with the target compartment. SNAREs may also play an active role in the formation of the vesicle through direct interaction with coat proteins, as exemplified by the interaction of SNAREs with COPII coat proteins during the formation of vesicles from the endoplasmic reticulum (ER) [9,10]. Interaction of SNAREs with the COPI machinery has also been observed [11]. Similarly, the interaction of Vti1b with epsinR is involved in the formation of shuttling vesicles between the late endosome and trans-Golgi network (TGN) [12]. A role for VAMP2 in rapid endocytosis of synaptic vesicles also suggests that SNAREs function in driving the formation of transport vesicles [13].

Next, during the tethering event mediated by various tethering factors [14,15], vesicles are positioned precisely at the region of the target compartment where the t-SNAREs

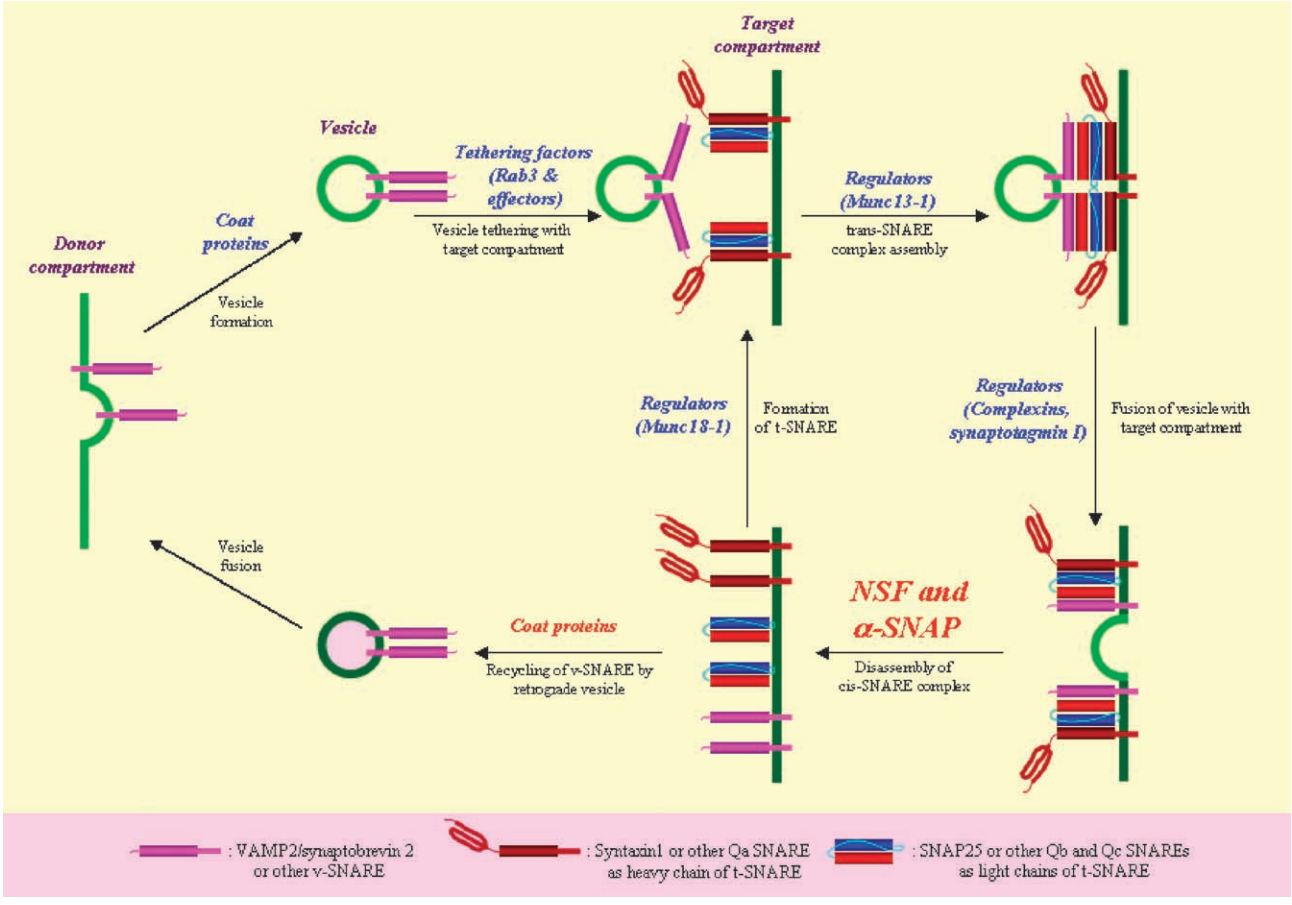

Fig. 1. The general mode of SNARE action using the synaptic SNARE complex as an example.