E D I T O R I A L / U V O D N I K

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Ever since pioneering electron microscopic studies revealed the internal morphology of cells, cell biologists have been fascinated by the complex intracellular membrane structure and organization, particularly the endoplasmic reticulum (ER) and the Golgi complex. The ER is the site where the newly made membrane and secretory proteins has been sythetized and they then pass through the Golgi complex, where they undergo many posttranslational modifications, including carbohydrate modifications. Protein transport between ER, Golgi apparatus to cell surface is based on budding of small vesicles and subsequent fusing of these vesicles with target organelle. This complex intracellular transport process, termed vesicle trafficking, is highly organized and critical for diverse processes as cell growth, endocytosis, hormone release, and neurotransmission [1].

The 2013 Nobel Prize honors three scientists, James E. Rothman, Thomas C. Südhof and Randy W. Schekman, who have elucidated the precise molecular mechanisms of vesicle trafficking, a major transport system in our cells [2]. Randy Schekman identified three classes of genes that were required for vesicle traffic [3, 4]. James Rothman discovered that a protein complex enables vesicles to dock and fuse with their target membranes [5, 6]. Thomas Südhof identified molecular machinery that responds to an influx of calcium ions and directs calcium-sensitive proteins in nerve cells to rapidly bind vesicles and release their cargo to the outer membrane of the nerve cell, with temporal precision and on command [7, 8].

Vesicle trafficking is regulated by specific protein complexes. The first group is coat protein complexes, which induce forming a vesicle out of a donor membrane, clathrin or coat protein complex I and II (COPI and COPII) [9, 10]. The second group of proteins are vesicle and target-specific identifiers to dock the vesicle, membrane proteins SNARES (the abbreviation for SNAp REceptors). The third group of proteins are the proteins that help fuse the docked vesicle, NSF (for N-ethylmaleimide Sensitive Factor) and SNAP proteins (for Soluble NSF Attachment Protein) [1, 11].

Secretory proteins travel from the ER to the Golgi apparatus in transport vesicles coated with the protein complexes [1]. Clathrin-coated vesicles mediate transport from the Golgi apparatus and from the plasma membrane or lysosomes. COPII-coated vesicles bud from the ER, and COPI coated vesicles bud from Golgi cisternae. Initially, the cargo molecules bind to specific receptors, which triggers interaction with coat proteins. Coat proteins spontaneously polymerize into a cage-like structure that surrounds the vesicle. Formation of coat structure initiates the "budding" of the membrane. During the COPII budding process, cargo proteins and v-SNAREs are concentrated in designated regions of the ER [8–11]. Docking and fusion of vesicles to the target membrane is regulated by SNARE proteins [1].

SNAREs are receptor protein superfamilies that target and dock specific vesicles to the correct compartment. SNARE proteins have a central role in providing specificity and in catalyzing the fusion of vesicles with the target membrane. They are either vesicle (v-SNARE) or target (t-SNARE) membrane specific proteins. According to the SNARE hypothesis, the road map of vesicular transport is determined by the pattern of localization of SNAREs among compartments. Current evidence suggests that SNARE complex formation promotes membrane fusion by simple mechanical force. The paired v-SNARES, from transport vesicles and t-SNARES, from target membranes, wrap around each other, firmly interact and form stable SNARE complex, which lock the two membranes together. Water molecules are displaced from the interface of the vesicle and target membrane, thus phospholipid membranes could adhere and fuse [6, 7, 11]. Following specific vesicle docking, NSF and SNAP help fuse the docked vesicle by assembling to initiate fusion, with the hydrolysis of ATP, ensuring that the vesicle fuses at the right location and that cargo molecules are delivered to the correct destination [7, 8].

SNAREs have been best characterized in nerve cells, where they mediate the docking and fusion of synaptic vesicles at the nerve terminal plasma membrane. Neurotransmitters are released by synaptic vesicle exocytosis at the active zone of a presynaptic nerve terminal. [12, 13]. Upon arrival of an action potential the neurotransmitter is released from presyn-

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aptic terminals within a few hundred microseconds, and is Ca^{2+}-regulated [12, 13]. Action potential opens Ca^{2+}-channels, and transiently increases the local Ca^{2+}-concentration at the presynaptic active zone. Ca^{2+} then triggers neurotransmitter release by activating synaptotagmin Ca^{2+}-sensors, and induce mechanical activation of the membrane fusion machinery [13]. The SNARE complexes at neuron terminals are the as select targets for various neurotoxins causing botulism and tetanus. These toxins are highly specific proteases that cleave SNARE proteins in the nerve terminals, thus blocking the release of a neurotransmitter [1].

Through their discoveries, the three Nobel Laureates Rothman, Schekman and Südhof, have revealed one of the most fundamental processes in cell physiology. These exquisite discoveries identify how vesicles, carrying cellular molecular cargo, are precisely delivered, in a timely manner. This mechanism is critical for a variety of physiological processes in which vesicle fusion must be controlled, from neurotransmission to release of hormones and cytokines. Disorders in vesicle transport have damaging effects and could contribute to neurological diseases, diabetes, and immunological disorders.

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