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Mechanism of Vesicular Transport - The Main Transport System in the Cells of Living Organisms

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Abstract

The functioning of the nervous system is based on the process of communication between nerve cells. This process is carried out in specialized areas - synapses. In most synapses, signal transmission occurs through the release of specialized substances from nerve endings - mediators during exocytosis of synaptic vesicles. The molecular mechanisms of synaptic transmission at chemical synapses occupy a central place in neurophysiology. These mechanisms involve the intracellular transport of substances within cells, which is necessary to maintain homeostasis in nerve cells by responding to physiological signals. Proteins synthesized in the cytosol are distributed to the appropriate organelles according to the sorting sequence of their specific amino acids. This short report analyzes the contribution of famous scientists working in the USA to the discovery of the mechanisms of vesicular transport - the main transport system in the cells of living organisms. For these studies, three American scientists - Randy W. Schekman, born in 1948, in the USA; James E. Rothman, born in 1950, in the USA, and Thomas C. Südhof, born in 1955 in Germany, but worked in the USA were awarded the Nobel Prize (2013).

Keywords: Intracellular transport; Synaptobrevin; SNAP-25; Syntaxin; SNARE; Vesicles.

Short commentary

Intracellular transport is the movement of vesicles and substances within cells. Intracellular transport is necessary to maintain homeostasis within cells by responding to physiological signals. Proteins synthesized in the cytosol are distributed to the appropriate organelles according to the sorting sequence of their specific amino acids. Since intracellular transport is highly dependent on microtubule movement, cytoskeletal components play an important role in the movement of vesicles between organelles and the plasma membrane.

In 2013, three American scientists (Randy W Schekman, born in 1948, in the USA); James E. Rothman, born in 1950, in the USA and Thomas C. Südhof, born in 1955 in Germany, but worked in the USA) were awarded the Nobel Prize in Physiology or Medicine for discovering the mechanisms of vesicular transport - the main transport system in the cells of living organisms (Figures 1-3). The existence of intracellular transport has been known since the beginning of the twentieth century. However, from a molecular point of view, the details of this process began to become clear only after the publication of works by R. Schekman, published in the journal PNAS and Cell [1-3]. In the joint work of J. Rothman and R. Schekman [4,5], it was established that the NSF and SNAP proteins-products of the sec 17 and sec 18 genes-are associated with vesicles, participate in vesicular transport, and contribute to the recognition of vesicle delivery sites. Continuing his work to isolate vesicle-associated proteins, Rothman discovered three more key proteins: synaptobrevin, SNAP-25 and syntaxin. These proteins had previously been found by other scientists in synapses, but their functions remained unknown. Rothman grouped them into the group SNARE (soluble NSF-attachment protein receptors). Synaptobrevin was associated with vesicles, and SNAP-25 and syntaxin were associated with cell membranes. This discovery allowed

J. Rothman to formulate the SNARE hypothesis, a key hypothesis that explains why vesicles fuse with cell membranes exactly where they are needed [5].

According to this model, fusion is regulated by two groups of receptors: t-(target)-SNARE (syntaxins) and v-(vesicle)-SNARE (synaptobrevins), that is, molecules located on the membrane and on vesicles, respectively. Thus, the SNARE hypothesis is a hypothesis about a universal "docking and fusion unit." It is currently believed that SNARE proteins are a collection of integral membrane proteins equipped with a membrane (or sometimes lipid) anchor located at the C-terminal region. The N-terminal domain of these proteins opens into the cytoplasm. There is a large group of SNARE proteins (about 60 proteins in mammalian cells) that carry out the fusion of intracellular transport vesicles with the cell membrane or target organelle (for example, a lysosome). Thus, the main role of SNARE proteins is to mediate the fusion of vesicles with the target membrane [4,5]. What was Thomas Südhof's contribution to solving the problem?.

Figure 1: Randy Wayne Schekman (born December 30, 1948) is an American cell biologist at the University of California, Berkeley, former editor-in-chief of Proceedings of the National Academy of Sciences and former editor of Annual Review of Cell and Developmental Biology.

Figure 2: James Edward Rothman (born November 3, 1950) is an American biochemist. He is the Fergus F. Wallace Professor of Biomedical Sciences at Yale University, the Chairman of the Department of Cell Biology at Yale School of Medicine and the Director of the Nanobiology Institute at the Yale West Campus.

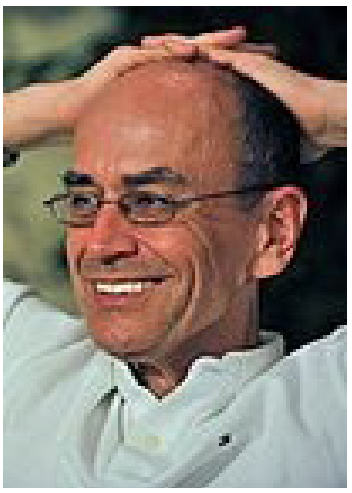

Figure 3: Thomas Christian Südhof (born December 22, 1955), is a German-American biochemist known for his study of synaptic transmission. Currently, he is a professor in the school of medicine in the department of molecular and cellular physiology, and by courtesy in neurology, and in psychiatry and behavioral sciences at Stanford University.

Thomas Südhof is a neurophysiologist by education and experience. He studied how signal transmission occurs at synapses between neurons. He was interested in the process of neurotransmitter release into the synaptic cleft. He knew that neurotransmitter molecules are packaged in vesicles and must be released into the space between the membranes of two neurons at exactly the right time. It turned out that this process depends on fluctuations in the intracellular concentration of Ca2+ ions. Südhof focused his attention on two proteins: complexin and synaptotagmin [4]. By studying mice with impaired function of the genes encoding complexin or synaptotagmin, he determined that these two proteins respond to Ca2+ concentration and are a kind of controllers that prevent the constant uncontrolled formation of vesicles. It turned out that synaptotagmin, on the one hand, is a Ca2+ sensor, and on the other hand, interacts with SNARE proteins and triggers the mechanism of vesicle formation [5]. Südhof also identified the Munc18 protein, a mutation in which consistent with the yeast sec1-1 phenotype described by Schekman. This protein, and the family to which it belongs, are collectively called SM proteins (from Sec/Munc). It turned out that, together with SNARE proteins, they participate in the process of vesicle formation [5,6]. Thus, the work of Schekman, Rothman and Südhof became part of one great achievement, which described the cell transport system involving vesicles [1-7]. Thanks to the work of these scientists, it became clear how bubbles are formed, how they find their delivery site, and how their formation is regulated in precisely a certain place and at a certain time.

Declarations

Conflicts of interest: The authors declare no conflict of interest.

All authors have read and agreed to the published version of the manuscript.

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