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VESICLE TRAFFIC IN THE CELLS - THE 2013 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

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Ključne reči
Nobelova nagrada za fiziologiju ili medicinu; transportni sistem; eksport

Abstract

Nobel Prize in Physiology or Medicine was awarded in 2013 for discoveries of machinery regulating vesicle traffic in eukaryotic cells. This process is critical for the secretion of enzymes, hormones, neurotransmitters, and other products that need to be exported outside of the cell. Understanding of vesicle traffic system will help us in treatment of defects in this process that lead to a number of diseases.

This year, the Nobel Assembly at Karolinska Institute decided to award the Nobel Prize in Physiology or Medicine jointly to James E. Rothman, Randy W. Schekman and Thomas C. Südhof for their discoveries of machinery regulating vesicle traffic, a major transport system in our cells [1]. Molecules that are synthesized in the cell, such as enzymes, hormones or neurotransmitters, need to be transported from one cellular compartment to the other, or exported outside of the cell. These molecules travel surrounded by small portions of membrane, in structures called vesicles, which bud off from one organelle and fuse with another or with the outer membrane, thus delivering their cargo to a specific destination and with precise timing. The three Nobel Laureates discovered which genes are required for vesicle traffic, which proteins form complexes that allow vesicle fusion and how signals instruct synchronous release of vesicle cargo.

James E. Rothman was born in 1950 in Haverhill, Massachusetts, USA. He received his PhD from Harvard Medical School in 1976, and moved to Massachusetts Institute of Technology where he was a postdoctoral fellow. Rothman has also worked at Stanford University in California, Princeton University, Memorial Sloan-Kettering Cancer Institute and Columbia University. He is currently Professor and Chairman in the Department of Cell Biology, Yale University in New Haven, Connecticut, USA [1].

Intracellular traffic of proteins is mediated by transport vesicles that bud off from the membrane of the „donor” compartment, taking away the selected set of proteins. These vesicles deliver their cargo very accurately by fusing selectively with the “acceptor” membrane. Rothman and his colleagues studied the transport of proteins between successive compartments of the Golgi apparatus using a mutant that is missing the Golgi enzyme N-acetylglucosamine (GlcNAc) transferase I and is thus defective in a step of glycosylation [2]. In a cell-free system, they measured the transport of the vesicular stomatitis virus-encoded glycoprotein between successive compartments of the Golgi via the coupled incorporation of GlcNAc.

In his later work, Rothman described a fundamental principle of all vesicular fusion events, from the constitutive secretory and endocytotic pathways (such as the fusion of a vesicle from endoplasmic reticulum with Golgi) to specialized and highly regulated forms of exocytosis (such as the secretion of neurotransmitters and insulin). Together with his colleagues, Rothman identified N-ethylmaleamide-sensitive fusion protein (NSF) and the soluble NSF attachment proteins (SNAPs) as universal components of vesicle fusion apparatus common to both constitutive and regulated fusion. They isolated synaptic SNAP receptors (SNAREs) which appeared to be distributed in a compartmentally specific fashion, with one set attached to the transport vesicles (v-SNAREs) and another set attached to target membranes (t-SNAREs). Rothman proposed a model in which each transport vesicle contains v-SNAREs originating from a donor membrane, and each target membrane contains t-SNAREs, and a fusion would initiate only upon binding of complementary v-SNARE and t-SNARE pairs. According to this model, vesicle-to-target specificity would be assured by unique distribution of v-SNAREs and t-SNAREs among different vesicles and target compartments [3].

Randy W. Schekman was born in 1948 in St Paul, Minnesota, USA. He obtained his PhD from Stanford University in 1974 under the supervision of Arthur Kornberg (Nobel Prize 1959) and in the same department that Rothman joined a few years later [1]. Schekman is currently Professor in the Department of Molecular and Cell Biology, University of California at Berkeley, and an investigator of Howard Hughes Medical Institute.

Schekman and his colleagues developed a genetic approach to study secretion and surface growth in Saccharomyces cerevisiae.

Using a temperature-sensitive mutant strain (sec 1) they observed a reversible block in secretory pathway and accumulation of intracellular membrane-bound vesicles at the restrictive temperature. Upon returning to permissive temperature, the secretion was re-established and that allowed identification of a vesicular intermediate in secretion and cell-surface growth. Schekman proposed that membrane components of the accumulated vesicles are precursors of the plasmalemma and the vesicle soluble components are precursors of the secreted proteins[4]. Later on, Schekman characterized different sec mutations that play a role in either the formation or fusion of a vesicle intermediate in transport from the endoplasmic reticulum to the Golgi apparatus [5]. Some of these genes coded for proteins that were yeast homologs of the proteins Rothman identified in mammals, suggesting an ancient evolutionary origin of the vesicle transport system.

Thomas C. Südhof was born in 1955 in Göttingen, Germany. He received an MD and a Doctorate in neurochemistry in 1982 from Georg-August University in Göttingen, and moved to the University of Texas Southwestern Medical Center in Dallas, Texas, USA, where he was a postdoctoral fellow with Michael Brown and Joseph Goldstein (who shared the 1985 Nobel Prize in Physiology of Medicine). Südhof became an investigator of Howard Hughes Medical Institute in 1991 and Professor of Molecular and Cellular Physiology at Stanford University in 2008 [1].

Neurotransmitters are stored in synaptic vesicles which are released at synapses by fusion with the outer membrane of a neuron using the machinery discovered by Rothman and Schekman. Contrary to constitutive exocytosis, neurotransmitter release needs to occur synchronously and very rapidly and Südhof was interested to find out how. He discovered that cytoplasmic domain of p65, which is a protein specific for synaptic vesicles, contains a sequence homologous to the regulatory region of protein kinase C (PKC). The cytoplasmic domain of p65 binds acidic phospholipids and calmodulin which suggested that it may have a role in mediating membrane interactions during synaptic vesicle exocytosis [6].

Later on, Südhof identified a protein bound to syntaxin, one of the key components of the synaptic vesicle fusion machinery [7]. This protein was named Munc-18, as it is a mammalian homologue of the Caenorhabditis elegans unc-18 which is known to be important for neurotransmission. Südhof proposed a model of the interactions of proteins of the synaptic vesicle fusion complex in which Munc-18 plays a central role because of its stable interaction with syntaxin.

Together, the three Nobel Laureates have described a fundamental process in cell biology. We now understand how vesicles deliver their cargo between cellular compartments and outside of the cell. Tight regulation of vesicle fusion is critical for the secretion of neurotransmitters, insulin, or cytokines. Defect in this process may lead to a number of diseases including neurological and immunological disorders and diabetes.

Sažetak

Nobelova nagrada za fiziologiju ili medicinu dodeljena je 2013. godine za istraživanja koja se odnose na regulaciju transportnog sistema u eukariotskim ćelijama. Ovaj proces je bitan za sekreciju enzima, hormona, neurotransmitera i drugih produkata koji se eksportuju iz ćelije. Poznavanje mehanizma transportnog sistema pomoći će nam da tretiramo njegove greške koje dovode do nastanka brojnih oboljenja.

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