Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

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The Nobel Assembly at Karolinska Institutet has today decided to award

The 2013 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

SUMMARY

The 2013 Nobel Prize honours three scientists who have solved the mystery of how the cell organizes its transport system. Each cell is a factory that produces and exports molecules. For instance, insulin is manufactured and released into the blood and chemical signals called neurotransmitters are sent from one nerve cell to another. These molecules are transported around the cell in small packages called vesicles. The three Nobel Laureates have discovered the molecular principles that govern how this cargo is delivered to the right place at the right time in the cell.

Randy Schekman discovered a set of genes that were required for vesicle traffic. James Rothman unravelled protein machinery that allows vesicles to fuse with their targets to permit transfer of cargo. Thomas Südhof revealed how signals instruct vesicles to release their cargo with precision.

Through their discoveries, Rothman, Schekman and Südhof have revealed the exquisitely precise control system for the transport and delivery of cellular cargo. Disturbances in this system have deleterious effects and contribute to conditions such as neurological diseases, diabetes, and immunological disorders.

How cargo is transported in the cell

In a large and busy port, systems are required to ensure that the correct cargo is shipped to the correct destination at the right time. The cell, with its different compartments called organelles, faces a similar problem: cells produce molecules such as hormones, neurotransmitters, cytokines and enzymes that have to be delivered to other places inside the cell, or exported out of the cell, at exactly the right moment. Timing and location are everything. Miniature bubble-like vesicles, surrounded by membranes, shuttle the cargo between organelles or fuse with the outer membrane of the cell and release their cargo to the outside. This is of major importance, as it triggers nerve activation in the case of transmitter substances, or controls metabolism in the case of hormones. How do these vesicles know where and when to deliver their cargo?

Traffic congestion reveals genetic controllers

Randy Schekman was fascinated by how the cell organizes its transport system and in the 1970s decided to study its genetic basis by using yeast as a model system. In a genetic screen, he identified yeast cells with defective transport machinery, giving rise to a situation resembling a poorly planned public transport system. Vesicles piled up in certain parts of the cell. He found that the cause of this congestion was genetic and went on to identify the mutated genes. Schekman identified three classes of genes that control different facets of the cell´s transport system, thereby providing new insights into the tightly regulated machinery that mediates vesicle transport in the cell.

Docking with precision

James Rothman was also intrigued by the nature of the cell´s transport system. When studying vesicle transport in mammalian cells in the 1980s and 1990s, Rothman discovered that a protein complex enables vesicles to dock and fuse with their target membranes. In the fusion process, proteins on the vesicles and target membranes bind to each other like the two sides of a zipper. The fact that there are many such proteins and that they bind only in specific combinations ensures that cargo is delivered to a precise location. The same principle operates inside the cell and when a vesicle binds to the cell´s outer membrane to release its contents.

It turned out that some of the genes Schekman had discovered in yeast coded for proteins corresponding to those Rothman identified in mammals, revealing an ancient evolutionary origin of the transport system. Collectively, they mapped critical components of the cell´s transport machinery.

Timing is everything

Thomas Südhof was interested in how nerve cells communicate with one another in the brain. The signalling molecules, neurotransmitters, are released from vesicles that fuse with the outer membrane of nerve cells by using the machinery discovered by Rothman and Schekman. But these vesicles are only allowed to release their contents when the nerve cell signals to its neighbours. How is this release controlled in such a precise manner? Calcium ions were known to be involved in this process and in the 1990s, Südhof searched for calcium sensitive proteins in nerve cells. He identified molecular machinery that responds to an influx of calcium ions and directs neighbour proteins rapidly to bind vesicles to the outer membrane of the nerve cell. The zipper opens up and signal substances are released. Südhof´s discovery explained how temporal precision is achieved and how vesicles´ contents can be released on command.

Vesicle transport gives insight into disease processes

The three Nobel Laureates have discovered a fundamental process in cell physiology. These discoveries have had a major impact on our understanding of how cargo is delivered with timing and precision within and outside the cell. Vesicle transport and fusion operate, with the same general principles, in organisms as different as yeast and man. The system is critical for a variety of physiological processes in which vesicle fusion must be controlled, ranging from signalling in the brain to release of hormones and immune cytokines. Defective vesicle transport occurs in a variety of diseases including a number of neurological and immunological disorders, as well as in diabetes. Without this wonderfully precise organization, the cell would lapse into chaos.

James E. Rothman was born 1950 in Haverhill, Massachusetts, USA. He received his PhD from Harvard Medical School in 1976, was a postdoctoral fellow at Massachusetts Institute of Technology, and moved in 1978 to Stanford University in California, where he started his research on the vesicles of the cell. Rothman has also worked at Princeton University, Memorial Sloan-Kettering Cancer Institute and Columbia University. In 2008, he joined the faculty of Yale University in New Haven, Connecticut, USA, where he is currently Professor and Chairman in the Department of Cell Biology.

Randy W. Schekman was born 1948 in St Paul, Minnesota, USA, studied at the University of California in Los Angeles and at Stanford University, where he obtained his PhD in 1974 under the supervision of Arthur Kornberg (Nobel Prize 1959) and in the same department that Rothman joined a few years later. In 1976, Schekman joined the faculty of the University of California at Berkeley, where he is currently Professor in the Department of Molecular and Cell biology. Schekman is also an investigator of Howard Hughes Medical Institute.

Thomas C. Südhof was born in 1955 in Göttingen, Germany. He studied at the Georg-August-Universität in Göttingen, where he received an MD in 1982 and a Doctorate in neurochemistry the same year. In 1983, he moved to the University of Texas Southwestern Medical Center in Dallas, Texas, USA, as a postdoctoral fellow with Michael Brown and Joseph Goldstein (who shared the 1985 Nobel Prize in Physiology or Medicine). Südhof became an investigator of Howard Hughes Medical Institute in 1991 and was appointed Professor of Molecular and Cellular Physiology at Stanford University in 2008.

Key publications:

Novick P, Schekman R: Secretion and cell-surface growth are blocked in a temperature-sensitive mutant of Saccharomyces cerevisiae. Proc Natl Acad Sci USA 1979; 76:1858-1862.

Balch WE, Dunphy WG, Braell WA, Rothman JE: Reconstitution of the transport of protein between successive compartments of the Golgi measured by the coupled incorporation of N-acetylglucosamine. Cell 1984; 39:405-416.

Kaiser CA, Schekman R: Distinct sets of SEC genes govern transport vesicle formation and fusion early in the secretory pathway. Cell 1990; 61:723-733.

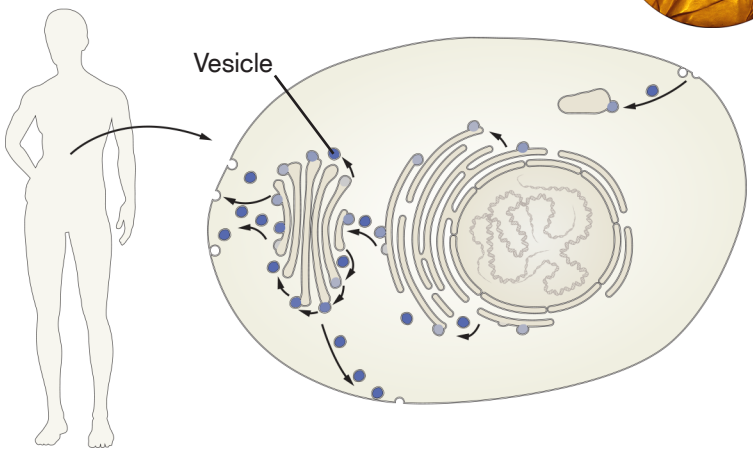
Perin MS, Fried VA, Mignery GA, Jahn R, Südhof TC: Phospholipid binding by a synaptic vesicle protein homologous to the regulatory region of protein kinase C. Nature 1990; 345:260-263.

Sollner T, Whiteheart W, Brunner M, Erdjument-Bromage H, Geromanos S, Tempst P, Rothman JE: SNAP receptor implicated in vesicle targeting and fusion. Nature 1993; 362:318-324.

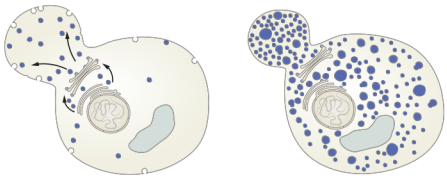
Hata Y, Slaughter CA, Südhof TC: Synaptic vesicle fusion complex contains unc-18 homologue bound to syntaxin. Nature 1993; 366:347-351.

The Nobel Prize in Physiology or Medicine 2013

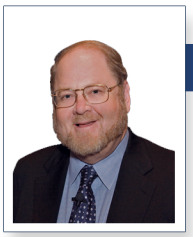
Proper functioning of the cells in the body depends on getting the right molecules to the right place at the right time. Some molecules, such as insulin, need to be exported out of the cell, whereas others are needed at specific sites inside the cell. Molecules produced in the cell were known to be packaged into vesicles (pictured in blue), but how these vesicles correctly deliver their cargo was a mystery.



Randy W. Schekman

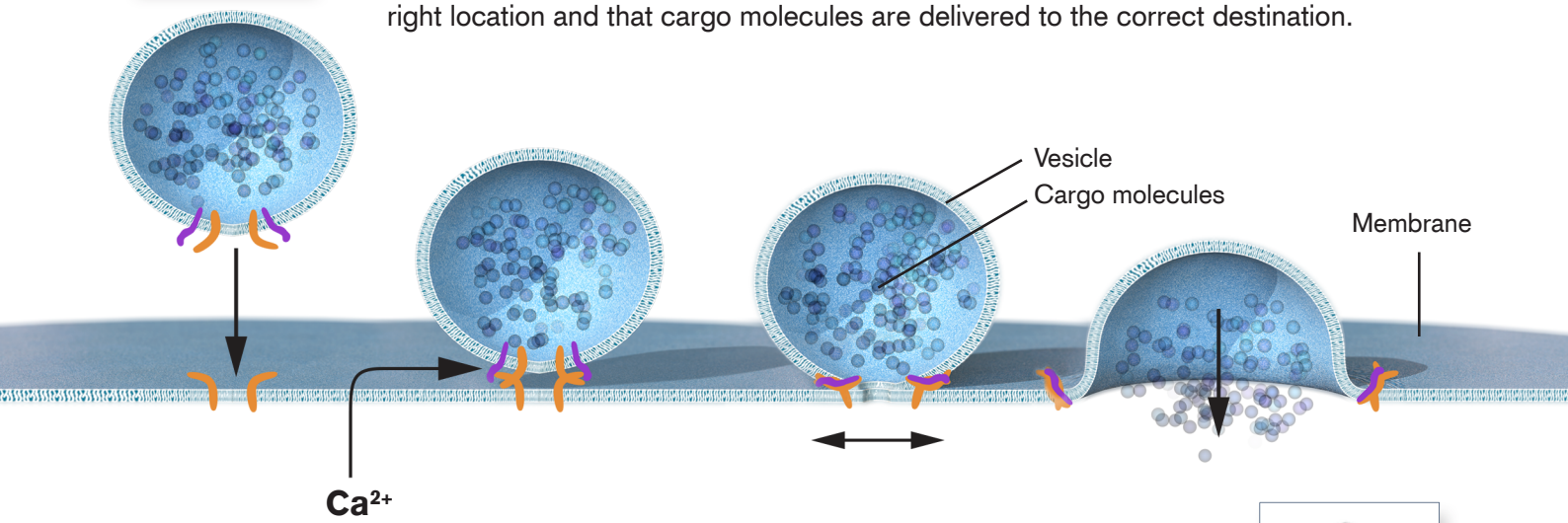


Randy W. Schekman discovered genes encoding proteins that are key regulators of vesicle traffic. Comparing normal (left) with genetically mutated yeast cells (right) in which vesicle traffic was disturbed, he identified genes that control transport to different compartments and to the cell surface.

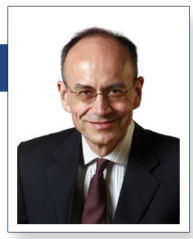


James E. Rothman

James E. Rothman discovered that a protein complex (pictured in orange) enables vesicles to fuse with their target membranes. Proteins on the vesicle bind to specific complementary proteins on the target membrane, ensuring that the vesicle fuses at the right location and that cargo molecules are delivered to the correct destination.



Thomas C. Südhof



Thomas C. Südhof studied how signals are transmitted from one nerve cell to another in the brain, and how calcium controls this process. He identified molecular machinery (pictured in purple) that senses calcium ions (Ca^{2+}) and triggers vesicle fusion, thereby explaining how temporal precision is achieved and how signaling substances can be released from the vesicles on command.

Illustration and layout: Mattias Karlén