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Nobel Prize for Cellular Logistics!

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Earlier this month (October 7, 2013) *"the Nobel Assembly at Karolinska Institutet 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"* (www.nobelprize.org/nobel_prizes/medicine/laureates/2013/press.html and **Fig. 1**). We at *Cellular Logistics* are especially excited about the recognition of Tom Südhoff, as he is an illustrious member of our Editorial Board!

This year's Prize extends the work of previous Nobel Prize winners George Palade, Albert Claude and Christian de Duve, who were the first to describe the trafficking pathways that link the compartments of the endo-exocytic system of eukaryotic cells. (www.nobelprize.org/nobel_prizes/medicine/laureates/1974/). Twenty four years after the prize to the Palade/Claude/de Duve trio, Günter Blobel's contribution to the understanding of the very first step of secretion, the delivery of secretory proteins to the Endoplasmic Reticulum (ER) lumen, was recognized by the 1999 Nobel Prize in Physiology or Medicine (www.nobelprize.org/nobel_prizes/medicine/laureates/1999/). Now, the third prize awarded to the field, further underscores the fundamental importance of cellular logistics - the where, when and how the cell delivers components to the right places in the right amounts and at the right time.

All eukaryotic cells produce thousands of proteins that need to be delivered to specific compartments or exported out of the cell. To move proteins between compartments or to release them to the outside, cells use vesicles. The process of vesicular traffic needs to be tightly controlled so that only the right proteins move to the right organelle and only the right proteins get secreted, and only at the right time. But how is that achieved at the molecular level? While previous work had described the phenomenon of vesicle-mediated traffic, the molecules involved in this phenomenon were completely unknown; these have now been in large part identified and characterized thanks to the work of this year's three Nobel awardees.

One of the key aspects of this year's award is the complementarity of the approaches that were used by the three awardees to unravel the molecular basis of vesicular traffic. The paradigm-shifting contribution of Rothman, now a professor at Yale, was the development of an assay in which vesicle fusion was reconstituted in a test tube. The power of cell-free assays had been demonstrated for other processes, such as DNA replication, protein synthesis and protein translocation into the ER. But, the cell-free recapitulation of a phenomenon as complex as transport between compartments had not been tried before. Rothman's feat allowed the use of biochemical approaches to identify the molecules that mediate vesicle formation and fusion, and led to the discovery of a protein complex that lets vesicles fuse with the correct membranes. These molecules, called SNAREs, work in a "lock and key" mechanism in which the vesicles and target compartments carry specific SNARE molecules: only certain, complementary, pairs of SNAREs can "fit" and allow the vesicles to fuse.[1-3] With the cell-free vesicular transport system, Rothman's lab also discovered additional molecules that drive the fusion cycle and that provide additional level of recognition between the vesicle and the compartment. Rothman's assay has become an indispensable tool for those investigating vesicular traffic, and, since its inception, many laboratories have used it to identify, and elucidate the role of additional proteins required for vesicle generation and/or fusion.

While Rothman was doing biochemistry, Schekman, a cell biology professor at the University of California, Berkeley, used a yeast genetic screen to identify genes responsible for controlling vesicle traffic within the secretory pathway. This, too, was a completely new and courageous approach, especially if one considers that virtually nothing was known about secretion in yeast cells at the time when Schekman began his studies. So, while Rothman was identifying proteins that mediate a single step of transport, Schekman's screen identified genes that mediate multiple steps of transport, all the way from the ER to the cell surface. The Schekman screen was the paradigm for subsequent genetic screens in yeast and other model organisms that emerged over the intervening > 30 years since the publication of his seminal papers.[4,5]

Very satisfyingly, some of the molecules identified in Schekman's genetic screens coincided with those discovered in Rothman's biochemical assays. And, importantly, it was the combination of the two approaches that led to a detailed molecular description of vesicular trafficking. Moreover, the overlap between the biochemical and genetic studies underscored the amazing conservation of the vesicular transport machinery through evolution from yeast to humans, and between the multiple steps of intra-cellular trafficking.

This conservation was used by Südhof, a professor at Stanford, to investigate vesicular traffic in neurons. His lab discovered how release of neurotransmitters is regulated in the brain. His contribution is unique in that it for the first time identified the molecular mechanism that controls vesicle fusion in time.

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Figure 1. Winners of the 2013 Nobel Prize in Medicine or Physiology.

While the majority of trafficking occurs constitutively and is not regulated by specific triggers, in many tissues vesicle fusion occurs only after a specific stimulus. Südhof figured out that in neurons there are specific proteins called synaptotagmins that respond to levels of calcium ions, and facilitate fusion after a stimulatory action potential.[6] Südhof 's discovery for the first time explained how temporal precision is achieved to release vesicles on command. Subsequent studies by Südhof 's lab showed that the same mechanism works in non-neuronal tissues, for example for release of hormones in non-neuronal cells.

As the award of the Nobel Prize indicates, the importance of cellular logistics is paramount: the correct trafficking of proteins is absolutely essential in development and normal physiology. Defects in traffic machinery components have been shown to cause numerous human diseases, including congenital disorder of glycosylation caused by defects in the COG tethering complex; craniofacial disorder (CLSD) caused by defects in a vesicle coating component Sec23a; defects in neural tube closure caused by mutations in another coat component Sec24b.

The clear link of trafficking machinery to human disease raises an important question about the role of basic research in elucidating the human condition. This latest Nobel Prize comes at a precarious time for basic sciences yet it clearly underscores the need for basic research into the workings of the cell. The current scientific climate, with its ever-increasing focus on translational research, often marginalizes basic research. Somehow, the meaning of the word translate is lost in the rush to promote clinically relevant science at the loss of inquiry into basic cellular processes. Yet, it should be obvious that "translational" science implies that there is something to translate from, and basic science is that foundation. Lets hope that the award of the 2013 Nobel Prize to three remarkable "basic scientists" promotes the recognition of the amazing importance of basic research in general and of Cellular Logistics in particular!

If you wish to listen to a podcast of a conversation on the importance of the Nobel Prize to our field and the importance of vesicles (in lay terms suitable for your grandmother) go to http://themixuab.blogspot.com/

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