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Molecular Analysis Shows Complexity Behind Cargo Delivery System of Mammalian Cells

Comparing the human genome to the genomes of other organisms reveals that the cellular system for transporting proteins is much more complex in humans. According to the scientists who made the comparison, their research suggests that the complex physiology of mammals is achieved, in part, through a more finely tuned regulation of the transport system.

The researchers, led by Howard Hughes Medical Institute investigator Richard H. Scheller, published their analysis in the February 15, 2001, issue of the journal *Nature*. The study is part of a collection of papers published by *Nature* that analyzes the completed human genome sequence. Scheller's co-authors include Stanford University School of Medicine colleagues, Jason B. Bock, Hugo T. Matern and Andrew A. Peden.

In their analyses, the researchers compared the genes for components of the transport system found in yeast, the fruitfly *Drosophila*, the roundworm *C. elegans* and humans.

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In an interview about the *Nature* article, Scheller explained that all membrane and secreted proteins are initially synthesized along with lipids in the endoplasmic reticulum, and they must travel through a series of membrane compartments to their final destinations in the cell. "Cells have developed an

extremely remarkable vesicle transport system that enables these proteins to travel through these distinct compartments," Scheller said.

Vesicle transport involves a number of processes, such as the budding of the bubble-like vesicles from a membrane, movement of the vesicle to its proper target compartment, fusion of the vesicle with the compartment membrane and transfer of its cargo. Vesicles take on their cargo by binding to protein-specific protein complexes called coats that associate with a specific compartment, said Scheller. "So, in a sense, the number of these coat complexes gives us a hint about the number and types of vesicles that can be formed."

In their comparative analysis, the scientists found that the number of coat complexes increased only slightly from yeast, flies and worms to humans. But they found that the number of individual subunits of these complexes expanded significantly in humans.

"This indicates that instead of evolving new coat complexes to accommodate increased cargo complexity, mammals have used a modular system where specificity can be achieved through subunit exchange," wrote the researchers.

The scientists also analyzed the genomes to determine the number of transport-related proteins, called Rabs, among the different organisms. Rab proteins play a key role in regulating targeting of the vesicle and docking of the vesicle at the target compartment. In their comparison, the scientists found that the number of Rabs "scaled roughly with the total number of predicted genes."

The scientists also compared the number of SNAREs and Sec1 proteins, which are involved fusing the vesicle with the membrane of its target compartment. "We found two findings of particular interest," said Scheller. "The first was that in the lower organisms such as yeast, there were more SNARE proteins than there are Rab proteins, and in *C. elegans* and *Drosophila*, there are about equal numbers of Rabs and SNAREs. But we also found that in mammals, there are many more Rab proteins than there are SNARE proteins.

"Thus, while the complexity of the basic membrane docking process has increased only slightly as one moves to mammals, the regulatory proteins have increased extremely dramatically. While this is not a huge surprise, it's not necessarily something that I would have predicted," said Scheller.

According to Scheller, the complexity of the mammalian nervous system represents an example of why the increased number of Rab proteins could be significant. "One of the Rab proteins seems to be important in membrane trafficking events that modulate the strength of connections between neurons. We think that's a process important in learning and memory, and obviously learning and memory is not something yeast does."

The genome study also enabled the scientists for the first time to divide the SNARE proteins into four families, each of which contributes a necessary protein that makes up the structure that fuses vesicles with target membranes.

The researchers' comparison revealed an increase in Sec1 genes in mammals. These genes encode proteins that are important as chaperones for molecules involved in vesicle fusion.

The researchers wrote that the evolutionary jump in the number of transport proteins "implies that mammals orchestrate the complexities of multicellular physiology through not only more finely tuned regulation, but also tissue-specific specialization of the core trafficking machinery."

"The genome is now another element of the toolkit of the modern life scientist," said Scheller. "Now that we know about all these proteins, we can use the genes to do the biology to understand how they function in membrane trafficking."