

# Structure reveals how cells 'sugar-coat' proteins

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Biologists at the U.S. Department of Energy's Brookhaven National Laboratory, Stony Brook University, and the University of Wurzburg, Germany, have deciphered the structure of a large protein complex responsible for adding sugar molecules to newly formed proteins - a process essential to many proteins' functions.

The structure offers insight into the molecular "sugar-coating" mechanism, and may help scientists better understand a variety of diseases that result when the process goes awry. The research will appear in the March 12, 2008, issue of the journal *Structure*.

"Proteins perform their functions by interacting at their surfaces with other molecules. So you can imagine that adding or removing sugar molecules will change the protein's surface structure, and therefore its function," said Huilin Li, a biologist at Brookhaven Lab who holds a joint appointment at Stony Brook and is co-corresponding author on the *Structure* paper. "Messing up this process can lead to the production of malformed proteins that are unable to do their jobs," he added.

The results can be devastating. Failure of glycosylation, as the "sugar-coating" process is known, can lead to a variety of genetic disorders characterized by neurological problems including seizures and stroke-like episodes, feeding disorders, and possibly even some forms of muscular dystrophy.

"We studied one enzyme involved in glycosylation, the one that

recognizes the protein sequence and adds the sugar chains to the protein as it is being synthesized by the cell," said William J. Lennarz of Stony Brook University, a coauthor on the paper. "The challenge is that the enzyme, known as oligosaccharide transferase (OT), is large by protein standards, has eight intricately linked components, and sits embedded in a membrane within the cell's protein-manufacturing machinery."

"Membrane proteins, particularly large ones, are very difficult to study structurally," added Li.

So the scientists turned to a technique called cryo-electron microscopy (cryo-EM), which shows great promise in deciphering large membrane protein structures.

"We imaged the purified OT complex by cryo-EM and obtained a first snapshot of the complex by computer reconstruction of the micrographs," said Li, a cryo-EM expert.

In cryo-EM, he explained, samples are frozen in vitreous ice and maintained at cryogenic temperatures ( $-274^{\circ}$  Fahrenheit) using liquid nitrogen while the samples are photographed in the high vacuum of an electron microscope. The sophisticated cryo-EM machine resides in Brookhaven Lab's biology department. Li and his collaborators also measured the mass of the OT complex at Brookhaven's Scanning Transmission Electron Microscope (STEM) facility.

The structure deciphered by the group helps to explain many biochemical phenomena observed about the enzyme complex over the past two decades. It also offers hints as to how the enzyme performs its various jobs, from recognizing the sugar molecules to be added to the protein, scanning the protein as it is formed to identify the sites where sugars should be attached, and transferring the sugar molecules to the protein at the right positions.

"OT physically associates with the protein translocation channel which moves a protein across a membrane and the cell's protein synthesis machinery, forming an efficient three-machine assembly line for protein translation, translocation, and glycosylation," Li said.

The researchers say further research is needed to illuminate the molecular mechanisms of disorders of glycosylation involving oligosaccharide transferase. For example, they would like to do structural studies of the enzyme at higher resolution in complex with substrates or in association with the cell's protein translocation and protein synthesis machinery. A new facility Brookhaven Lab hopes to begin construction on next year, known as the National Synchrotron Light Source II, would greatly increase the precision of this work.

Source: Brookhaven National Laboratory

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