Spiral constriction -- how dynamin mediates cellular nutrient uptake

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Dr. Katja Falber and Professor Oliver Daumke, structural biologists at the Max Delbruck Center for Molecular Medicine (MDC) Berlin-Buch, together with researchers from Freie Universität (FU) Berlin, have determined the molecular structure of dynamin, a 'wire-puller' that mediates nutrient uptake into the cell. Since pathogens such as HIV can also enter the body's cells in this way, understanding the underlying molecular mechanisms can potentially open up new approaches for medical applications.

Many nutrients pass from the blood through cell membrane channels into the body cells. However, appropriate channels do not exist for all nutrients. For example, iron binds outside the cell to a large transport molecule and is imported by other means, via endocytosis, into the cell. The cargo-containing transport molecules bind to the cell membrane, which invaginates inward. The iron molecules along with their transporters are taken up in a small membrane bubble (vesicle) into the cell and released there.

An important 'wire-puller' of endocytosis is the protein molecule dynamin. And that in the most literal sense of the word: If a vesicle forms, the dynamin molecules self-assemble and form a spiral around the neck of the vesicle. Dynamin functions like a small motor: It uses the energy of the cell's GTP to pull the spiral together, constricting the neck of the vesicle so that it detaches from the cell membrane.

The molecular details of this 'pull' mechanism around the vesicle neck

were previously unknown. In their present study, MDC structural biologists Professor Daumke and Dr. Fälber, together with the endocytosis researcher Professor Volker Haucke and the bioinformatician Dr. Frank Noé of FU Berlin, provide fundamental insights into this process. Using X-ray diffraction analysis, they succeeded in building a structural model of dynamin. For this study it was necessary to produce protein crystals of dynamin. To achieve this, the researchers utilized the insights gained in their previous study about a dynamin-related protein. From the X-ray diffraction pattern of these crystals the researchers were then able to derive a detailed picture of dynamin. "Now that we have an idea of how the dynamin molecule is structured, we can understand at the atomic level how the molecular motor dynamin functions," said Professor Daumke.

In addition to nutrient uptake, endocytosis is also essential for the transmission of signals between neighboring nerve cells and for the immune system. In this way, for example, macrophages engulf pathogens and make them harmless. Professor Daumke: "However, pathogens like HIV and influenza viruses utilize endocytosis to enter our body cells and to spread there. That is why it is important to gain an even more detailed understanding of the molecular 'pull' mechanism of dynamin during endocytosis. Then we can find potential approaches for medical applications – especially for patients with muscle and nerve disorders associated with mutations in the dynamin gene." In future research projects funded by the German Research Foundation within the framework of the Collaborative Research Centers (SFB740 and SFB958), the MDC researchers intend to take an even closer look at dynamin. They want to find out what structural changes dynamin accomplishes when the cell's energy carrier GTP binds to the protein and the 'pull' mechanism is set in motion at the vesicle neck.

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