Close-up look at brain uptake of omega-3

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New details on the structure and function of a transport protein could help researchers develop drugs for neurological diseases that are better able to cross the blood-brain barrier. The findings were published in the journal *Nature* by researchers at Columbia University Vagelos College of Physicians and Surgeons, Duke-NUS Medical School, Weill Cornell Medicine and colleagues.

Omega-3 fatty acids, like docosahexaenoic acid (DHA), are important for brain and eye development. They are derived mainly from dietary sources and converted by the liver into a lysolipid called lyso-phosphatidyl-choline (LPC) in order to cross from the blood into the brain and retina via the blood-brain and blood-retina barriers, respectively. These barriers are formed by cells lining blood vessels, or endothelial cells, that tightly regulate what enters these two vital organs.

A protein called Major Facilitator Superfamily Domain containing 2A (MFSD2A) is located on the membrane of these endothelial cells, and acts as a molecular gateway that allows DHA to cross these barriers. How MFSD2A mediates uptake of lysolipids carrying omega-3 fatty acids, however, remained a mystery.

"We set out to determine the structure of MFSD2A in order to understand how it transports essential omega-3 fatty acids in the form of LPC to the brain," said Dr. Chua Geok Lin, a senior research fellow with the Cardiovascular and Metabolic Diseases (CVMD) Programme, Duke-NUS, who is a co-author of the study. "This is important because MFSD2A is essential for getting omega-3 fatty acids like DHA across

the blood-brain barrier."

Dr. Rosemary Cater, a Simons Foundation Fellow at Columbia University's Vagelos College of Physicians and Surgeons, and first author of the paper, explained, "If we knew what MFSD2A looked like, we could solve this mystery and use the information to design neurotherapeutics that could hijack this molecular gateway, disguised as omega-3 fatty acid lysolipids—sort of like seeing what a lock looks like in order to design a key that fits."

The collaborative study, led by Dr. Filippo Mancia at Columbia University, Dr. David Silver at Duke-NUS, and Dr. George Khelashvili at Weill Cornell Medicine, leveraged leading experts in the field from across a number of US research institutions—namely Columbia University, Weill Cornell Medicine, the New York Structural Biology Center, University of Chicago and University of Arizona—and Duke-NUS in Singapore.

To study the structure of MFSD2A, the research team used a special type of electron microscopy, which involves cooling samples to cryogenic temperatures and viewing molecules on a sub-nanomolar scale, in combination with novel biochemical assays. This allowed them to uncover atomic-level details of the protein's structure, which were then used to inform computer simulations exploring the mechanism of how it works.

According to Dr. Mancia, associate professor of physiology and cellular biophysics at Columbia University Vagelos College of Physicians and Surgeons, "It's extremely exciting to be able to view a protein's shape at such a resolution. We are talking about measurements of less than a billionth of a metre in size—and this information is critical to understand how it works at a molecular level."

"Using large-scale atomistic ensemble molecular dynamics (MD) simulations, followed by detailed analysis of the MD data with advanced methods of computational biophysics, such as Markov State Modelling, we were able to 'un-freeze' the cryo-EM structure of MFSD2A and study mechanistic details of how this transporter interacts with substrates," explained Dr. Khelashvili, assistant professor of physiology and biophysics at Weill Cornell Medicine. "Combined with the functional data, the computational findings shed light on the molecular mechanisms by which this atypical MFS transporter mediates uptake of single-chain phospholipids into the brain."

"Some years ago, we discovered that human mutations in the gene that codes for MFSD2A lead to microcephaly, a birth defect in which the baby's head is very small," said Dr. Silver, Professor and Deputy Director of Duke-NUS' CVMD Programme. "This underscores the importance of lysolipid transport by MFSD2A."

The study is the latest to add to the growing body of knowledge first initiated by Prof Silver in 2014, when he published on the discovery of MFSD2A and its role in transporting DHA to the brain. In 2017, he co-founded Singapore-based Travecta Therapeutics with the aim of harnessing this knowledge to develop new therapeutic agents that can be selectively delivered across the blood-brain barrier by MFSD2A for treatment of diseases of the central nervous system and eyes. Travecta is currently conducting preclinical studies for several therapeutic targets with the company's lead asset for pain, TVT-004, scheduled to begin clinical trials in the next several months.

A license agreement between Duke-NUS and Travecta was facilitated by Duke-NUS' Centre for Technology and Development, under the School's Office of Innovation and Entrepreneurship, granting the company rights to commercialise the research.

"The blood-brain barrier excludes the uptake of approximately 98 percent of drugs, limiting the treatment of neurological diseases," Prof Silver explained. "The structural information we revealed in our study can be exploited to better design neurotherapeutics that can be transported by MFSD2A."

The authors said further research is needed to uncover more details on how MFSD2A mediates transport of lysolipids across the blood-brain barrier.

More information: Rosemary J. Cater et al, Structural basis of omega-3 fatty acid transport across the blood–brain barrier, *Nature* (2021). DOI: 10.1038/s41586-021-03650-9

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