Molecular mechanisms of essential omega-3 fatty acid human carrier

The Major-Facilitator Superfamily transporter MFSD2A has two important functions in the human body: it is the main uptake route of essential omega-3 fatty acids into the brain, and the cellular receptor of membrane fusogenic protein syncytin-2 that mediates cell fusion during placenta development. Researchers have determined the first 3D structure of human MFSD2A-SYNC2 complex revealing key aspects of MFSD2A function and pharmacological mechanisms. The results have been published in *Nature Structural & Molecular Biology*.

The Central Nervous System (CNS) requires uptake of essential omega-3 fatty acids in the form of lysophospholipids for normal development and cognitive function, and this is achieved by Major-facilitator superfamily transporter MFSD2A. This carrier is enriched at the brain-blood barrier (BBB), a specialized and selective cellular barrier that controls the exchange of trophic factors with the blood and protects the brain from pathogenic invasion. Notably, MFSD2A-mediated lipid uptake is key to maintain low rates of solute transport across the BBB, via repression of vesicle trafficking across the endothelium, known as transcytosis. Due to this, MFSD2A has emerged as a potential point of pharmacological intervention to aid therapeutic drug delivery into the CNS. However, the MFSD2A transport mechanism remains incompletely understood, and selective MFSD2A inhibitors that aid controlling BBB permeability have not been reported.

MFSD2A plays a second important function in human physiology, as the receptor of retrovirus-derived envelope protein syncytin 2 (SYNC2), and MFSD2A-SYNC2 complexes mediate cell-cell fusion and formation of the maternal-fetal interface in placenta. Interestingly, SYNC2 shares membrane fusogenic mechanism with human extant retroviruses, like CoV-2 and HIV. In fact, SYNC2 is codified by an ancient viral gene that was integrated in the simian genome >40 million years ago. Therefore, humans use a receptor-mediated fusion machinery from an ancient virus for placenta development, but its receptor-recognition mechanisms remain unknown.

This work represents the first structure determination of a human endogenous retroviral protein (SYNC2) in complex with its cellular receptor (MFSD2A), revealing a receptor recognition mechanism that has been preserved within our cells for millions of years.

Moreover, MFSD2A structure enables direct mapping of mutations that cause microencephaly and intellectual disabilities in humans, and shows the carrier in an important and elusive intermediate state of its transport cycle. A comparison of that conformational state with reported structures of mfsd2a vertebrate orthologs unravels a unique molecular mechanism for omega-3 fatty acid uptake into the brain. This so-called “rock-and-swing” mechanism enables occlusion and translocation of the bulky lipid substrate within the transporter’s core, and likely represents a conserved lipid transport mechanism throughout all kingdoms of live.

Further structural analysis of MFSD2A-SYNC2 complex suggests that SYNC2 binding could preclude important conformational changes of MFSD2A transport cycle. Based on this structural observation, the researchers engineered a soluble SYNC2-fragment that completely inhibit MFSD2A lipid transport. This engineered fragment constitutes a first-in-class molecule with the pharmacological potential to transiently increase BBB transcytosis, and aid delivering therapeutic macromolecules (e.g. antibodies) into the CNS.

To go further:

Structural insights into lysophospholipid brain uptake mechanism and its inhibition by syncytin 2
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