PRESS RELEASE

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Insights into functions of micronutrient transporters may pave way for new treatments for neurological diseases

28 May 2024, Singapore – The nutrients in our bodies help to provide daily energy and power the maintenance of cellular structure and function. But how do nutrients get distributed throughout the body in a specific manner?

Led by Associate Professor Nguyen Nam Long, scientists from the Immunology Translational Research Programme at the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine) have discovered that Mfsd7c or FLVCR2 and Mfsd7b or FLVCR1 are the transporters for micronutrient choline and ethanolamine. Human cells have a very limited capacity to synthesise these essential nutrients, which need to be derived from foods.

The team gained molecular insights into how these two transporters deliver essential nutrients within the cells in the body. In particular, the researchers were able to uncover the atomic structures of these transporters and how its atomic structures contribute to the making of this elite nutrient transport system, and possibly, laying the foundation as a drug target and future therapeutic development for neurological diseases.

Working in collaboration with counterparts from the Max Planck Institute of Biophysics at Frankfurt, Germany, the NUS researchers shed light on the atomic architecture of these two transporters. The team expressed and purified these human proteins from mammalian cells to determine the atomic structures of these two protein transporters.

Cryo Electron Microscopy (Cryo-EM), an advanced imaging technique that helps to illuminate the three-dimensional structure of molecules at near-atomic resolution, was used to capture different angles of the architecture of these proteins during the transportation of micronutrient choline and ethanolamine. The team was then able to use molecular dynamics simulations to build working models for these transporters, which resembled their operations when transporting these micronutrients in real life.

At the molecular level, the research team observed that due to slight atomic structures, protein FLVCR1 prefers to deliver ethanolamine, which is an essential molecule that human cells must acquire from foods, while protein FLVCR2 has a higher affinity for transporting choline. Choline is also critical for building cell membranes and the synthesis of the neurotransmitter acetylcholine and can be found in foods such as egg yolks, beef, chicken breast, fish and dairy products. Proteins FLVCR1 and FLVCR2 assist the cells to receive or secrete choline or ethanolamine, according to demand. Previous research done by the NUS Medicine team had

already identified the transporter role played by FLVCR2/MFSD7c to export choline from the brain via the blood brain barrier.

From the original intention of investigating how the mutations of proteins FLVCR1 and FLVCR2 causes different diseases, the research has now taken a different turn, prompting the team to take this knowledge a step further to understand how proteins FLVCR1 and FLVCR2 operate to transport these micronutrients through the cell membranes for absorption into the body. Protein FLVCR2/MFSD7c has also been identified as a drug target for the treatment of Alzheimer's disease because blocking its function at the blood-brain barrier can increase the level of choline for making more acetylcholine, a neurotransmitter that is reduced in patients with Alzheimer's disease. Understanding the intricacies of how nutrients are transported lays the foundation for drug development where small molecules or biologics can be designed to target the FLVCR2/MFSD7c function easily.

The study's Principal Investigator Associate Professor Nguyen Nam Long, who is also from the School's Department of Biochemistry says, "Our work shows the key roles that FLVCR2/MFSD7c and FLVCR1/MFSD7b have in transporting choline and ethanolamine throughout our body. On one hand, this work provides the new knowledge for understanding of how our cells distribute these essential nutrients after ingesting from foods, it also provides foundation for new therapeutic approaches, such as how to design and develop new therapeutics and drugs to target protein FLVCR/MFSD7c more easily to treat diseases, particularly improving brain function for senior citizens and those with Alzheimer's disease. We are currently taking advantage of this knowledge for drug development for FLVCR/MFSD7c."

Titled 'Molecular mechanism of choline and ethanolamine transport in humans', the study was published in Nature on 22 May 2024.

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For media enquiries, please contact:

Amanda YAP
Assistant Manager, Communications
Yong Loo Lin School of Medicine
Email: medajyjy@nus.edu.sg

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Our multidisciplinary and real-world approach to education, research and entrepreneurship enables us to work closely with industry, governments and academia to address crucial and complex issues relevant to Asia and the world. Researchers in our faculties, research centres of excellence, corporate labs and more than 30 university-level research institutes focus on

themes that include energy; environmental and urban sustainability; treatment and prevention of diseases; active ageing; advanced materials; risk management and resilience of financial systems; Asian studies; and Smart Nation capabilities such as artificial intelligence, data science, operations research and cybersecurity.

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About the NUS Yong Loo Lin School of Medicine (NUS Medicine)

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Through a dynamic and future-oriented five-year curriculum that is inter-disciplinary and inter-professional in nature, our students undergo a holistic learning experience that exposes them to multiple facets of healthcare and prepares them to become visionary leaders and compassionate doctors and nurses of tomorrow. Since the School's founding in 1905, more than 12,000 graduates have passed through our doors.

In our pursuit of health for all, our strategic research programmes focus on innovative, cutting-edge biomedical research with collaborators around the world to deliver high impact solutions to benefit human lives.

The School is the oldest institution of higher learning in the National University of Singapore and a founding institutional member of the National University Health System. It is one of the leading medical schools in Asia and ranks among the best in the world (Times Higher Education World University Rankings 2024 by subject and the Quacquarelli Symonds (QS) World University Rankings by subject 2024).

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