

PRESS RELEASE

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Little-known protein choline transporter in brain may be key therapeutic target for ageing and Alzheimer's disease

6 May 2024, Singapore – In a groundbreaking study published in *Cell Research*, researchers from the Yong Loo Lin School of Medicine at the National University of Singapore (NUS Medicine) have unveiled unexpected findings that could pave the way for novel therapeutic interventions in Alzheimer's disease and other neurological disorders.

While tracking the changes of metabolite quantity levels, researchers from the Immunology Translational Research Programme at NUS Medicine, led by Associate Professor Nguyen Nam Long, focused on unravelling the normal biological role of the protein Mfsd7c, mutations of which are linked to Fowler syndrome, a debilitating neurological disorder. Through meticulous experimentation utilising pre-clinical models and comprehensive metabolomics analyses, the researchers discovered novel functions of the orphan transporter called Mfsd7c as a facilitative transporter of choline at the blood-brain barrier (BBB).

Contrary to conventional wisdom that the brain imports free choline from the bloodstream, the study revealed that Mfsd7c is essential for exporting excessive choline out of the brain. This unexpected finding challenges the previously established theories of choline metabolism in the brain and opens new avenues for understanding neurological diseases.

To discover this new biology, the team injected a compound called lysophosphatidylcholine (LPC) into the pre-clinical models. The LPC enters the brain and releases choline that allow researchers to trace the source of choline from the blood. They found that the labelled choline, derived from blood LPC, accumulated in the brain of pre-clinical models where the Mfsd7c protein was inhibited. The brain lipid profile was unchanged throughout. This finding indicated that the excessive amount of choline from LPC has been exported out of the brain via the Mfsd7c protein at the blood-brain barrier.

The human brain contains approximately two-thirds of its weight in lipids. Lipids that contain choline is key for brain development and function. Choline is especially needed by the brain and nervous system to regulate memory, moods and muscle control as well. "It is widely known that the brain imports free form of choline from the blood. Strikingly, our study revealed that the Mfsd7c protein is required for exporting excessive choline out of the brain; and that LPC is a major carrier of choline to the brain. In a nutshell, the study demonstrates that the brain does not ingest free choline like other organs such as the liver, it takes choline which is associated with the circulating lipids," explained Assoc Prof Nguyen.

"The potential implications of our discovery are profound, particularly in the context of Alzheimer's disease and other age-related cognitive disorders. By targeting Mfsd7c, we may have a new avenue for developing therapeutic compounds to enhance brain function," added Associate Professor Nguyen.

Interestingly, the study also demonstrated that targeting the Mfsd7c protein in pre-clinical models increases brain choline and acetylcholine levels. Targeting the Mfsd7c protein would also provide a much-needed boost in choline and acetylcholine levels in senior citizens and patients with Alzheimer's disease who have shown declined levels of acetylcholine in the brain. Choline is the precursor for the synthesis of acetylcholine which plays an important role in regaining memory, learning and muscle control which could provide further insights into creating newer therapeutics for patients with Alzheimer's disease.

"Our study results have revealed an unexpected finding for choline source in the brain. It not only provides a foundation for future work to reveal the disease mechanisms of Fowler syndrome, but also lays the foundation for treatment of neurological diseases," added Assoc Prof Nguyen, who is also Principal Investigator of this study.

Choline is a micro-nutrient that is critical for building cells, and can be obtained by eating choline-rich foods such as egg yolks, beef, chicken breast, fish, broccoli and dairy products. For adults, the daily dietary intake of 400-500mg of choline is recommended because human cells cannot synthesise sufficient levels of choline for its own usage. For pregnant women, choline deficiency will lead to a high risk of childbirth defects. Persistent choline deficiency also leads to fatty livers, a condition that could bring about liver cancers if untreated.

The research team is now focused on leveraging their discovery to develop drugs targeting Mfsd7c in the brain, with the ultimate goal of translating their findings into tangible therapeutic interventions for neurological disorders.

This groundbreaking study represents a significant step forward in our understanding of brain metabolism and offers hope for the development of effective treatments for Alzheimer's disease and related conditions.

The study, titled '[*MFSD7c functions as a transporter of choline at the blood-brain barrier*](#)' was published in *Cell Research* on 2 February 2024.

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The National University of Singapore (NUS) is Singapore's flagship university, which offers a global approach to education, research and entrepreneurship, with a focus on Asian perspectives and expertise. We have 16 colleges, faculties and schools across three campuses in Singapore, with more than 40,000 students from 100 countries enriching our

vibrant and diverse campus community. We have also established more than 20 NUS Overseas Colleges entrepreneurial hubs around the world.

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.

For more information on NUS, please visit nus.edu.sg.

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

The NUS Yong Loo Lin School of Medicine is Singapore's first and largest medical school. Our enduring mission centres on nurturing highly competent, values-driven and inspired healthcare professionals to transform the practice of medicine and improve health around the world.

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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