PRESS RELEASE

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NUS Medicine study: Inability of cells to recycle fats can spell disease

Singapore, 12 February, 2025 — Accumulation of fat molecules is detrimental to the cell. Researchers from the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), have made a breakthrough in understanding how our cells manage to stay healthy by recycling important fat molecules. Their study, published in the journal *Proceedings of the National Academy of Sciences (PNAS)*, reveals how a protein called Spinster homolog 1 (Spns1) helps transport fats out of cell compartments known as lysosomes.

Led by Associate Professor Nguyen Nam Long, from the Department of Biochemistry and Immunology Translational Research Programme (TRP) at NUS Medicine, the team found that Spns1 is like a cellular gatekeeper which can help to move a type of fat molecule called lysophospholipids to the lysosome, the cell's "recycling centre". These fat molecules are then reused for cell functions. Spns1is crucial in maintaining cellular health by ensuring fat recycling is efficient and that harmful fat build-up is prevented.

Fats and other cellular materials reach the lysosome through three main pathways: *endocytosis*, *phagocytosis*, and *autophagy*. In endocytosis, the cell takes in materials from outside by wrapping them within vesicles, which carry them to the lysosome for breakdown. In phagocytosis, immune cells such as macrophages act like the body's cleanup crew, swallowing up large particles like damaged cells or germs and sending them to lysosomes. Lastly, in autophagy, the cell cleans up its own damaged parts, such as old mitochondria, by wrapping them in a membrane bubble called an autophagosome. This bubble then merges with the lysosome, where the contents are broken down and recycled to keep the cell healthy.

Once fats are broken down in the lysosome, they serve several important roles in the cell. One is membrane repair and maintenance. The broken-down fat components, such as *phospholipids* and *sphingolipids*, are reused to rebuild and maintain the cell's protective membranes. Fats also help with energy production, as some of them are processed to provide fuel for the cell's activities. Additionally, certain fats, like sphingosine-1-phosphate (S1P), play a crucial role in cellular communication. These signalling molecules help cells coordinate important processes, such as growth, movement, and survival, ensuring that the body functions smoothly.

In a previous study, the NUS Medicine team has shown that if Spns1 does not work properly, it leads to a buildup of lipid waste inside cells, causing diseases known as lysosomal storage diseases (LSD) in humans. LSDs are a group of over 50 rare genetic disorders caused by problems in the lysosome's recycling process. Diseases like Gaucher disease, Tay-Sachs disease, Niemann-Pick disease, and Pompe disease result from waste buildup in cells, leading

to serious health issues. Dysfunctions of the lysosomal recycling pathway are also found in Parkinson's and Alzheimer's diseases.

In collaboration with Professor Xiaochun Li's group from the University of Texas Southwestern Medical Center (UTSW), the team used a technology called cryoelectron microscopy (cryo-EM) and the functional readouts to take images of Spns1's interactions with a specific type of fat called *lysophosphatidylcholine* (LPC), one of the recycled lysophospholipids in the lysosome. This gave them a better understanding of how Spns1 works and how it senses changes in the cell's environment to perform its job.

"Lysosomal storage disorders are a group of rare genetic diseases that occur when the lysosome fails to recycle important molecules. Our research shows that Spns1 plays a key role in preventing these diseases by ensuring that fats are properly transported out of the lysosome," said A/Prof Nguyen**. "**We now understand more about how our cells recycle these fat molecules at atomic level, and this could help us develop new treatments for diseases where Spns1 fails to work as intended."

The team also ran experiments to confirm that the protein is essential for moving fats out of lysosomes and that certain parts of Spns1 are crucial for its function. The study revealed the following key findings:

- Spns1 acts like a gate, opening and closing to let fats out of the lysosome.
- It relies on specific signals from the cell's environment to know when to open and close.
- Mutations in Spns1 can cause problems with fat transport, leading to the buildup of waste inside cells and human diseases.

"We're excited about the potential of this research to make a real difference for patients with these rare diseases," said Ms Ha Thi Thuy Hoa, co-first author of the paper, from the Department of Biochemistry and Immunology TRP at NUS Medicine. "While this study captured Spns1 in the state where it opens toward the lysosome to pick up fats, we are now working to understand the opposite state, where it opens from the lysosome toward the rest of the cell. This will help us fully understand how Spns1 completes its transport cycle."

The researchers are also exploring potential small molecules that could modulate SPNS1 activity, with the aim of developing targeted drugs for lysosomal storage diseases.

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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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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 2025 by subject and the Quacquarelli Symonds (QS) World University Rankings by subject 2024).

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