PRESS RELEASE

NUS researchers link neurodegenerative disease protein to defective cholesterol metabolism

The findings suggest drugs that modulate cholesterol metabolism might be a novel therapeutic strategy to treat multiple neurodegenerative diseases.

Singapore, 5 August 2021 — Researchers from the NUS Yong Loo Lin School of Medicine have discovered that brain cells cannot maintain the cholesterol-rich myelin sheath that protects and insulates neurons without a protein called TDP-43. The study, published today in the *Journal of Cell Biology* (JCB), suggests that restoring cholesterol levels through drug intervention could be a novel therapeutic approach for diseases associated with TDP-43.

The TDP-43 protein is linked to multiple neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). TDP-43 plays many vital roles within cells but, under certain circumstances, it can clump together to form toxic aggregates that damage cells and prevent TDP-43 from performing its normal functions. TDP-43 aggregates are found in the brains of most ALS patients and about 45% of FTD patients, and these toxic clumps are also linked to several other neurodegenerative disorders, including some cases of Alzheimer's disease. The aggregates form not only in neurons, but also in other brain cell types such as oligodendrocytes. These cells protect neurons and speed up the transmission of nerve impulses by wrapping neurons in a fatty substance called myelin.

Assistant Professor Ling Shuo-Chien from NUS Medicine's Department of Physiology and his colleagues have previously shown that oligodendrocytes need TDP-43 to survive and wrap neurons in myelin. "Specifically, we found that mice with oligodendrocytes lacking TDP-43 develop progressive neurological phenotypes leading to early lethality. These phenotypes were accompanied by the death of oligodendrocytes and progressive loss of myelin," he said. In this new study, it was found that a reason oligodendrocytes are dysfunctional in the absence of TDP-43 is that they are unable to synthesize or take up the cholesterol they need to sustain myelin production.

Cholesterol is a major component of myelin, with 25 per cent of the body's total cholesterol being found in the central nervous system. Oligodendrocytes are known to synthesise large amounts of cholesterol for themselves, but they can also acquire it from other brain cells called astrocytes. The research team determined that, in the absence of TDP-43, oligodendrocytes lack many of the enzymes required to synthesise cholesterol. They also have reduced levels of the low density lipoprotein receptor that can take in cholesterol from outside the cell. Supplementing these TDP-43-deficient cells with cholesterol restored their ability to maintain the myelin sheath.

Similar defects in cholesterol metabolism may occur in patients, where the formation of aggregates might prevent low-density lipoprotein (LDLR) from performing its normal functions due to co-aggregating with TDP-43. The research team analysed brain samples from FTD

patients, and found that their oligodendrocytes produced lower amounts of two key enzymes required for cholesterol synthesis, while the low density lipoprotein receptor was incorporated into TDP-43 aggregates.

"Our results indicate that simultaneous disruption of cholesterol synthesis and uptake is likely one of the causes of the demyelination phenotype observed in models with TDP-43-deficient oligodendrocytes, and suggest that defects in cholesterol metabolism may contribute to ALS and FTD, as well as other neurodegenerative diseases characterised by TDP-43 aggregates," said Asst Prof Ling.

From these findings, it is possible that drugs which modulate cholesterol metabolism might be a novel therapeutic strategy to treat these diseases. This is especially so if cholesterol dysmetabolism is proven to directly cause neurodegeneration.

About the National University of Singapore (NUS)

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 17 faculties 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 our NUS Overseas Colleges programme in more than 15 cities 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, 30 university-level research institutes, research centres of excellence and corporate labs 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 Asia's leading medical school and ranks among the best in the world (Times Higher Education World University Rankings 2020 by subject and the Quacquarelli Symonds (QS) World University Rankings by Subject 2020).

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