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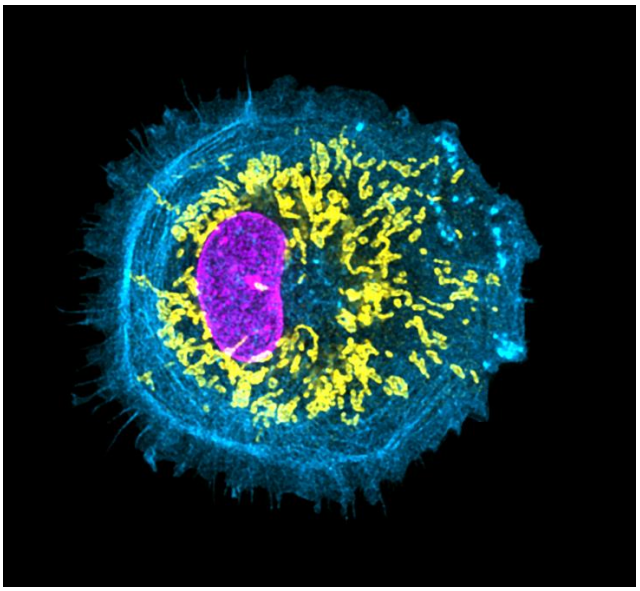
NEW STUDY REVEALS THE CRITICAL ROLE OF MICROGLIA IN HUMAN BRAIN DEVELOPMENT

Scientists have found that microglia play a crucial role in regulating the number of cells that become neurons in the brain, enhancing our understanding of brain development and disorders.



*Super-resolution image of human stem cell-derived Microglia cells with labeled mitochondria (yellow), nucleus (magenta), and actin filaments (cyan). These Microglia cells help in the maturation of neurons in human brain organoid models. Photo credit: A*STAR's SIgN*

SINGAPORE – An international team of scientists has uncovered the vital role of microglia, the immune cells in the brain that acts as its dedicated defense team, in early human brain development. By incorporating microglia into lab-grown brain organoids, scientists were able mimic the complex environment within the developing human brain to understand how microglia influence brain cell growth and development. This research represents a significant leap forward in the development of human brain organoids and has the potential to significantly impact our understanding of brain development and disorders. The study, "iPS-cell-derived microglia promote brain organoid maturation via cholesterol transfer" was published in Nature on 1 November 2023.

To investigate microglia's crucial role in early human brain development, scientists from A*STAR's Singapore Immunology Network (SIgN) led by Professor Florent Ginhoux, utilised

cutting-edge technology to create brain-like structures called organoids, also known as “mini-brains” in the laboratory. These brain organoids closely resemble the development of the human brain. However, previous models were lacking in microglia, a key component of early brain development.

To bridge this gap, A*STAR researchers designed a unique protocol to introduce microglia-like cells generated from the same human stem cells used to create the brain organoids. These introduced cells not only behaved like real microglia but also influenced the development of other brain cells within the organoids.

A*STAR's Institute of Molecular and Cell Biology (IMCB)'s Dr Radoslaw Sobota and his team at the SingMass National Laboratory for Mass Spectrometry applied cutting edge quantitative proteomics approach to uncover changes in protein. Their analysis provided crucial insights into the protein composition of the organoids, further confirming the study’s findings.

What sets this study apart is the discovery of a unique pathway through which microglia interact with other brain cells. The study found that microglia play a crucial role in regulating cholesterol levels in the brain.The microglia-like cells were found to contain lipid droplets containing cholesterol, which were released and taken up by other developing brain cells in the organoids. This cholesterol exchange was shown to significantly enhance the growth and development of these brain cells, especially their progenitors.

Cholesterol, makes up about 25% of the body's total cholesterol content, is abundantly present in the brain and is essential for the structure and function of neurons. Abnormal cholesterol metabolism has been linked to various neurological disorders, including Alzheimer's and Parkinson's Disease.

To investigate the roles of lipids in brain development and disease, researchers from the Department of Biochemistry at the Yong Loo Lin School of Medicine (NUS Medicine), led by Professor Markus Wenk, took on the crucial task of data acquisition, particularly in the field of lipidomics to draw valuable insights into the lipid composition and dynamics within the brain organoids containing microglia.

Using this information, another team from the Department of Microbiology and Immunology at NUS Medicine and led by Associate Professor Veronique Angeli, found that cholesterol affects the growth and development of young brain cells in human brain models. Microglia use a specific protein to release cholesterol, and when this process is blocked, it causes the organoid cells to grow more, leading to larger brain models. “It has always been known that the microglia is key to brain development, however their precise role remains poorly understood. This finding from our team at the Department of Microbiology and Immunology

is particularly impactful because we finally understand how cholesterol is transported. Our next focus will be finding out how we can regulate cholesterol release to optimise brain development and slow down, or prevent, the onset of neurological conditions," added Assoc Prof Veronique, who is also Director of the Immunology Translational Research Programme at NUS Medicine.

Moreover, Dr Olivier Cexus from the University of Surrey and formely at A*STAR, progressively deciphered the complex molecular interactions within the brain organoids using proteomic and lipidomic analysis. This provided valuable insights into the metabolic cross-talks involved in brain development and potential implications for diseases.

Together, these collective efforts were instrumental in deepening our understanding of the roles of microglia and the molecular components within brain organoids and its implications for human health.

Prof Florent Ginhoux, Senior Principal Investigator at A*STAR's SIgN and Senior author of the study said, "Understanding the complex roles of microglia in brain development and function is an active area of research. Our findings not only advance our understanding of human brain development but also have the potential to impact our knowledge of brain disorders. This opens up new possibilities for future research into neurodevelopmental conditions and potential therapies."

Co-author of the study, Professor Jerry Chan, Senior Consultant, Department of Reproductive Medicine, KK Women's and Children's Hospital, and Senior National Medical Research Council Clinician Scientist, added, "There is currently a lack of tools to study how microglia interacts with the developing brain. This has hampered the understanding of microglia-associated diseases that play an important role during the early development of conditions such as autism, schizophrenia, and neurodegenerative diseases such as Alzheimer's and Parkinson's disease.

"The development of these novel microglia-associated brain organoids with same-donor pluripotent stem cells gives us an opportunity to study the complex interactions between microglia and neurons during early brain development. Consequentially, this may enable us to study the role of microglia in the setting of diseases and suggest ways to develop new therapies in time."

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For media queries and clarifications, please contact:

Sharmaine Loh
Manager, Corporate Communications
Agency for Science, Technology and Research (A*STAR)
Tel: +65 9862 1834
Email: Sharmaine_loh@hq.a-star.edu.sg

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

Natasha Meredith
Media Officer
University of Surrey
Email: n.meredith@surrey.ac.uk

About the Agency for Science, Technology and Research (A*STAR)

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About A*STAR's Singapore Immunology Network (SIgN)

The Singapore Immunology Network (SIgN) is a research consortium established in 2006 under the Agency for Science, Technology and Research (A*STAR)'s Biomedical Research Council. The mission of SIgN is to advance human translational immunology research, contribute scientific knowledge and make innovative discoveries in immune-based therapeutics and technologies so as to improve lives and further socio-economic growth. SIgN is home to about 150 researchers comprising of renowned Principal Investigators, post-doctoral fellows and support staff working under the directorship of Professor Lam Kong Peng. SIgN also contributes to nurturing and retaining research talents to help build up the research ecosystem in Singapore.

SIgN research activities are broadly categorized into three main focus areas: Immuno-Oncology, Immune Potential, Regulation & Ageing and Immuno-Pathology. Our research groups are supported by a strong in-house cluster of cutting-edge technology platforms. Through partnership with hospitals and companies, SIgN is also committed to translate research findings into clinical and commercial applications. All in all, SIgN is working towards contributing to an enriching and vibrant research environment in Singapore. For more information about SIgN, please visit www.a-star.edu.sg/sign

About 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 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 Asia's leading medical schools 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 2023).

For more information about NUS Medicine, please visit https://medicine.nus.edu.sg/.

About the University of Surrey

The University of Surrey is a research-intensive university, conducting world-leading research, delivering excellent innovation in teaching and producing highly employable graduates.

Areas of research focus include sustainability, connecting society and technology to equip humanity to live better, more sustainable lives; artificial intelligence, with research steering these new technologies so they remain people-centred in the way they operate, develop and are governed; and pushing the boundaries of our understanding of the ways human and animal health overlap, interact and share common problems and solutions – within a 'One Health, One Medicine' research approach.

The University is consistently independently ranked as high performing. In the most recent Research Excellence Framework (REF2021), the University ranked in the top 20 in the UK for the overall quality of research outputs. It is ranked 9th in the UK and 46th worldwide in the Times Higher Education Impact Rankings 2023, reflecting its dedication to the UN's Sustainable Development Goals. Within the UK, Surrey is 9th in the National Student Survey 2022, 13th in the Complete University Guide 2024, 22nd in The Times and The Sunday Times Good University Guide 2023, and 24th in The Guardian University Guide 2023.

To contact the media team please email mediarelations@surrey.ac.uk.