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Singapore scientists uncover how neural stem cells are activated intrinsically by spindle matrix proteins

Opens new avenues for research that could potentially lead to therapies for microcephaly, Alzheimer's disease

SINGAPORE, 2 August 2017 – A multicentre research team led by Duke-NUS Medical School (Duke-NUS)'s Neuroscience and Behavioural Disorders Programme has uncovered that spindle matrix proteins can play an intrinsic role in regulating neural stem cell (NSC) reactivation and proliferation. This discovery is an early important step towards opening up avenues for further research that could lead to potential stem cell-based therapies for neurodevelopmental and neurodegenerative disorders such as microcephaly and Alzheimer's disease.

Only a small fraction of adult NSCs in mammalian brains is proliferative and most of NSCs are in a non-dividing state, also known as quiescence. The balance between NSC proliferation and quiescence is essential for brain development and emerging evidence suggest that its imbalance is linked to neurodevelopmental disorders, such as microcephaly. On the other side, the population of quiescent NSCs in the brain increases with ageing, which is associated with declining brain function. Understanding how endogenous NSCs can be activated has huge potential in regenerative medicine. However, it is poorly understood how NSCs switch between proliferation and quiescence *in vivo*.

The study, published in *Nature Communications,* is a first of its kind conducted on fruit flies (*Drosophila melanogaster)* that demonstrates a critical role of the spindle matrix complex containing chromator (Chro) functioning as an essential nuclear factor for controlling gene expression during NSC reactivation. The study suggests that Chro plays an important role in maintaining the balance between NSC proliferation and quiescence, as it is not only critical for NSC reactivation (exit from quiescence), but also essential for preventing re-entry into inactivation.

"In this study, we have uncovered that spindle matrix proteins play a novel role in regulating reactivation of neural stem cells. It may be in its early stage, but this should help to open up avenues for further research and the development of potent therapies for neurodevelopmental disorders in the future," said lead author Hongyan Wang, an Associate Professor and Deputy Director of Duke-NUS' Neuroscience and Behavioural Disorders Programme.

The team employed state-of-art genomic technique for transcriptome analysis *in vivo* and identified binding-sites of Chro in NSCs. The main findings from these experiments suggest that Chro is a master nuclear factor that reactivates NSCs through regulating gene expression of key transcription factors that either promote or repress the proliferation of NSCs. The study also suggests that Chro functions downstream of Insulin/PI3k pathway, which is known to promote NSC reactivation and mutations of which are found in microcephalic patients.

"Our study demonstrates that some of the players such as transcription factors *Grainy Head and Prospero* act downstream of Chro and identifies the likely pathway by which NSCs are activated," added Professor Wing-Kin Sung, who is from the National University of Singapore (NUS) School of Computing and a Senior Group Leader at A*STAR's Genome Institute of Singapore (GIS).

In addition to Hongyan Wang and Wing-Kin Sung, other co-authors of this publication include Song Li (first author), Shenli Zhang, Angie Lay Keng Tan, Su Ting Tay and Chwee Tat Koe from Duke-NUS, Patrick Tan from Duke-NUS, National Cancer Centre Singapore, NUS and GIS, and Yingjie Zhang from Duke-NUS and NUS.

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About Duke-NUS Medical School

The Duke-NUS Medical School (Duke-NUS, 杜克 — 新加坡国立大学医学院) was established in 2005 as a strategic collaboration between the Duke University School of Medicine, located in North Carolina, USA, and the National University of Singapore (NUS). Duke-NUS offers a graduate-entry, 4-year MD (Doctor of Medicine) training programme based on the unique Duke model of education, with one year dedicated to independent study and research projects of a basic science or clinical nature. Duke-NUS also offers MD/PhD and PhD programmes. Duke-NUS has five Signature Research Programmes: Cancer and Stem Cell Biology, Neuroscience and Behavioural Disorders, Emerging Infectious Diseases, Cardiovascular and Metabolic Disorders, and Health Services and Systems Research.

Duke-NUS and SingHealth have established a strategic partnership in academic medicine that will guide and promote the future of medicine, tapping on and combining the collective strengths of SingHealth's clinical expertise and Duke-NUS' biomedical sciences research and medical education capabilities.

For more information, please visit www.duke-nus.edu.sg

About A*STAR's Genome Institute of Singapore (GIS)

The Genome Institute of Singapore (GIS) is an institute of the Agency for Science, Technology and Research (A*STAR). It has a global vision that seeks to use genomic sciences to achieve extraordinary improvements in human health and public prosperity. Established in 2000 as a centre for genomic discovery, the GIS will pursue the integration of technology, genetics and biology towards academic, economic and societal impact.

The key research areas at the GIS include Human Genetics, Infectious Diseases, Cancer Therapeutics and Stratified Oncology, Stem Cell and Regenerative Biology, Cancer Stem Cell Biology, Computational and Systems Biology, and Translational Research.

The genomics infrastructure at the GIS is utilised to train new scientific talent, to function as a bridge for academic and industrial research, and to explore scientific questions of high impact.

For more information about GIS, please visit www.gis.a-star.edu.sg

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

The Agency for Science, Technology and Research (A*STAR) is Singapore's lead public sector agency that spearheads economic oriented research to advance scientific discovery and develop innovative technology. Through open innovation, we collaborate with our partners in both the public and private sectors to benefit society.

As a Science and Technology Organisation, A*STAR bridges the gap between academia and industry. Our research creates economic growth and jobs for Singapore, and enhances lives by contributing to societal benefits such as improving outcomes in healthcare, urban living, and sustainability.

We play a key role in nurturing and developing a diversity of talent and leaders in our Agency and Research Institutes, the wider research community and industry. A*STAR oversees 18 biomedical

sciences and physical sciences and engineering research entities primarily located in Biopolis and Fusionopolis.

For more information on A*STAR, please visit www.a-star.edu.sg

About National University of Singapore (NUS)

A leading global university centred in Asia, the National University of Singapore (NUS) is Singapore's flagship university, which offers a global approach to education and research, with a focus on Asian perspectives and expertise.

NUS has 17 faculties and schools across three campuses. Its transformative education includes a broad-based curriculum underscored by multi-disciplinary courses and cross-faculty enrichment. Over 38,000 students from 100 countries enrich the community with their diverse social and cultural perspectives. NUS also strives to create a supportive and innovative environment to promote creative enterprise within its community.

NUS takes an integrated and multi-disciplinary approach to research, working with partners from industry, government and academia, to address crucial and complex issues relevant to Asia and the world. Researchers in NUS' Schools and Faculties, 30 university-level research institutes and centres, and Research Centres of Excellence cover a wide range of themes including: energy, environmental and urban sustainability; treatment and prevention of diseases common among Asians; active ageing; advanced materials; risk management and resilience of financial systems. The University's latest research focus is to use data sciences, optimisation research and cybersecurity to support Singapore's Smart Nation initiative.

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

About National Cancer Centre Singapore

National Cancer Centre Singapore (NCCS) provides a holistic and multi-disciplinary approach to cancer treatment and patient care. We treat almost 70 per cent of the public sector oncology cases, and they are benefiting from the sub-specialisation of our clinical oncologists. NCCS is also accredited by the US-based Joint Commission International for its quality patient care and safety. To deliver among the best in cancer treatment and care, our clinicians work closely with our scientists who conduct robust cutting-edge clinical and translational research programmes which are internationally recognised. NCCS strives to be a global leading cancer centre, and shares its expertise and knowledge by offering training to local and overseas medical professionals. www.nccs.com.sg