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Scientists uncover the role of spindle matrix proteins in NSC reactivation

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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).

More information: Song Li et al, An intrinsic mechanism controls reactivation of neural stem cells by spindle matrix proteins, *Nature Communications* (2017). DOI: 10.1038/s41467-017-00172-9

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