Medical Xpress

New ways to mass produce human neurons for studying neuropsychiatric disorders

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Scientists from Singapore have streamlined the process of using human stem cells to mass produce GABAergic neurons (GNs) in the laboratory. This new protocol provides scientists with a robust source of GNs to study many psychiatric and neurological disorders such as autism, schizophrenia, and epilepsy, which are thought to develop at least in part due to GN dysfunction.

GNs are inhibitory neurons that reduce neuronal activation, and make up roughly 20 per cent of the human brain. They work alongside excitatory neurons (ENs) to ensure balanced neural activity for normal brain function. The coordinated interplay between GNs and ENs orchestrate specific activation patterns in the brain, which are responsible for our behaviour, emotions, and higher reasoning. Functional impairment of GNs results in imbalanced neural activity, thereby contributing to the symptoms observed in many psychiatric disorders.

The availability of high quality, functional human GN populations would facilitate the development of good models for studying psychiatric disorders, as well as for screening drug effects on specific populations of neurons. Scientists worldwide have been hard at work trying to generate a consistent supply of GNs in the laboratory, but have been faced with many challenges. Protocols involving multiple complex stages, poor yield, and requiring a long time to generate mature and functional GNs are just some of the limitations encountered.

Many of these limitations have now been overcome by the development of a rapid and robust protocol to generate GNs from human pluripotent stem cells (hPSCs) in a single step. With the addition of a specific combination of factors, hPSCs turn into mature and functional GNs in a mere six—eight weeks. This is about two—three times faster than the 10 - 30 weeks required for previous protocols. In addition, this new protocol is highly efficient, with GNs making up more than 80 per cent of the final neuron population.

To develop this protocol, the team from Duke-NUS Medical School (Duke-NUS), A*STAR's Genome Institute of Singapore (GIS) and the National Neuroscience Institute (NNI) first identified genetic factors involved in GN development in the brain. The team then tried many different combinations of these factors, and succeeded in confirming that mature and functional human GNs were indeed generated.

"Just like how a balance of Yin and Yang is needed in order to stay healthy, a balance of ENs and GNs is required for normal brain function. We now know a fair bit about ENs because we have good protocols to make them. However, we still know very little of the other player, the GNs, because current protocols do not work well. Yet, when these GNs malfunction our brain goes haywire," commented Dr Alfred Sun, a Research Fellow at NNI and co-first author of the publication alongside Mr Qiang Yuan, an NUS Graduate School PhD student.

"Our quick, efficient and easy way to mass produce GNs for lab use is a game changer for neuroscience and drug discovery. With increased recognition of the essential role of GNs in almost all neurological and psychiatric diseases, we envisage our new method to be widely used to advance research and drug screening," said Dr Shawn Je, Assistant Professor in the Neuroscience and Behavioural Disorders Programme at Duke-NUS, and senior author of the study.

The speed and efficiency of generating GNs with this new protocol provides researchers unprecedented access to the quantities of neurons necessary for studying the role of GNs in disease mechanisms. Drugs and small molecules may now be screened at an unparalleled rate to discover the next blockbuster treatment for autism, schizophrenia, and epilepsy.

Provided by Duke-NUS Medical School

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