Research reveals gene 'language' critical in infant brain development

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In what they're calling a 'biological surprise', a team of expert international geneticists led by a University of Otago researcher have discovered a key piece of information about how the human brain is put together and how such a complex piece of wiring assembles itself in utero.

The finding recently appeared as a feature article in *Nature Genetics*.

This discovery could represent a first step in understanding how neural stem cells could possibly be used to repair damage in the brain of infants and children.

Professor Stephen Robertson, the Cure Kids Professor of Paediatric Genetics at the University of Otago, is leading the team of scientists. He says the significance of the work "lies in finding two key genes and a language that these genes use to conduct brain development in a human". In effect, they have picked up the 'radio signal' of neural stem cells and understood the language as they 'talk' to each other.

The hope is that this discovery will help shed light on how these neural stem cells can be 'nudged' into action to get them to compensate for neurological disorders and to repair the damaged brain of a child, whether it is a genetically determined disability, lack of oxygen at birth or brain damage in infancy from a variety of causes.

In the infant brain, new neurons derived from neural stem cells can pick

up the job of damaged or dead neurons and this offers the opportunity for potential repair. Learning how to control stem cells – speak their language and understand their working machinery – will be core knowledge as scientists work towards harnessing them for therapeutic use.

The therapeutic possibilities could be developed along two lines; the first is based on the observation that infants, in particular, still have considerable reserve stem cells in place that could be 'recruited' (perhaps with a drug), in the context of brain injury or disease. The second line of research, which is a more difficult proposition, will investigate what happens later in childhood when there are fewer of these cells, and how they could potentially be administered from an outside source.

A prominent Munich-based specialist in brain cell biology, Magdalena Götz, is a lead collaborator of the project, and says the finding is "new and significant". She says when she first received an email from Professor Robertson in 2009 it "was immediately clear to us that his work had identified a new set of genes that instruct stem cells in the brain on how to increase in number and take up their correct position in the developing brain. The signals that instruct developing neurons to perform this task are complex and the whole process is still poorly understood. It has been enormously satisfying to find another piece in this jigsaw and put it in place".

Professor Robertson describes the process: "The human brain develops from a single layer of cells that forms very early at the top end of the developing embryo. This layer of cells, called the neuroepithelium, houses a population of stems cells that have two major developmental tasks to perform to orchestrate brain development. The first is that they must renew themselves but retain the capability to turn into any type of brain cell when required. Clearly as the brain develops these two tasks need to be regulated – on one hand the cells need to proliferate, and then

on the other, at appropriately timed points during brain development, they must change into mature brain cells – neurons and the like – to actually make a functioning and integrated brain.

"The signals and triggers to initiate and time these critical decisions in the life of the brain stem cell are sought after keenly. Understanding them will potentially give some handle on how we might be able to harness stem cells and grow them in controlled ways for use therapeutically."

As a clinical geneticist Professor Robertson studies people with very rare brain disorders. This new discovery has come as "a result of studying a newly defined genetic condition that is very rare with the hope that we might be able to identify a key part of the molecular machinery that conducts the stem cell orchestra during the symphony of brain development. In this condition stem cells seem to have lost their capability to regulate their division and maturation into neurons. The result is that in MRI scans we can see bands of neurons buried deep within the brain, instead of forming the outer layer of the brain – the gray matter," he says.

Using very comprehensive and deeply detailed DNA sequencing techniques, graduate student Mary Gray (now Dr Mary Gray) found two genes that underpin this rare syndrome of brain mal-development.

The products of these two genes – proteins called DCHS1 and FAT4 – had been discovered nearly 20 years ago and were known to mediate a linking bridge between cells. As a result of this function these proteins were dubbed adhesion molecules, part of the machinery that not only keeps cells stuck to one another but also a portal of communication between adjacent cells.

In collaboration with two prominent specialists in brain stem cell biology

from Munich, Dr Silvia Cappello and Professor Götz, Professor Robertson and his team sought to study the mechanism of how damage to the genes encoding these adhesion proteins might lead to abnormal stem cell behaviour. Using studies on embryonic mice they were able to first reproduce a very similar disease state by reducing the function of either gene in a controlled fashion.

Their questions then turned to what was the nature of the signal – the language – used by adjacent stems cells to communicate to one another and trigger stem cell production and maturation. Remarkably, Dr Cappello's experimental results were able to point to a well-known signaling pathway which DCHS1 and FAT4 use to regulate stem cells in the developing brain.

This discovery is the result of five years of research; Cure Kids provided the enabling funding to explore their ideas and a subsequent project grant from the Health Research Council of New Zealand allowed the team to bring it to fruition.

Provided by University of Otago