Why stem cells don't just want to make neurons

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Research being presented today at the UK National Stem Cell Network annual science conference provides another piece in the puzzle of why it can be so hard to produce large numbers of the same type of cell in the lab – a process that is vital for scaling up stem cell production for therapeutic use. This knowledge will help researchers to develop strategies for obtaining the desired cell type for use in either research or medicine.

The work will be presented by Dr Robert Kelsh from the University of Bath and was funded in part by the Biotechnology and Biological Sciences Research Council (BBSRC). It shows for the first time that a gene called Sox10 coordinates a vital part of healthy development: once a stem cell has committed to becoming a neuron it sends out a signal telling surrounding cells to become something else – a characteristic that certainly hinders making pure samples of these cells for therapies.

Dr Kelsh said "We've known for a while that Sox10 is important for healthy development – in fact mutations in Sox10 cause some rare human diseases – but this is the first time it has been shown to help achieve the balance of neurons and glia, the cells that support neurons."

Mutations in Sox10 are associated with Waardenburg syndrome – a rare inherited condition causing deafness and reduced hair, skin and eye pigment – and Hirschsprung's disease, which occurs as a result of incomplete development of nerves in the large intestine and leads to severe digestive problems.

Dr Kelsh continued "Often when you produce stem cells in the lab, you want them to take on a particular set of characteristics – say, those of a nerve cell. But it can be really difficult to get 100% of cells that are the same – there are often a significant minority of cells with other characteristics. We think this might be because inside an animal it is crucial that stem cells generate the right numbers of the right types of cells and in the right locations, and there are mechanisms that ensure this is the case.

"Encouraging a cell down one route in the lab may well trigger activation of these balancing mechanisms, and thus act to limit the proportion of cells that go down this route. For this reason, understanding the mechanisms generating this balance is crucial."

Previously, research suggested that some types of stem cells – especially those that give rise to nerve cells in the body (not the brain or spinal cord) and the cells that produce skin pigments - start in the embryo with the potential to become any cell type until they reach their final location in the body. At this point a cell specialises to become whatever cell type is needed. But in recent years researchers have been accumulating evidence that there are a succession of changes that occur before or during the time the cells are moving towards their destination – they are actually making a series of incremental specialisations.

Dr Kelsh and his team have used Zebrafish to study one of these intermediate stages in a developing organism and not just in a petri dish. They have discovered that a gene called Sox10 helps to coordinate the discussion between neighbouring stem cells to ensure that a balance is struck, and all cell-types are represented in the right proportions. Inside the Zebrafish this helps in the regulation of healthy development by ensuring that neurons are formed alongside appropriate numbers of their support cells that allow them to function properly.

This work gives clues to understanding why getting pure cell populations is so difficult in cultures, but also perhaps the therapeutically-reassuring news that given the right stem cells in the right environment, natural mechanisms for ensuring the balance of cell-types in the organ may aid regeneration of a functional organ desired.

Professor Douglas Kell, Chief Executive, BBSRC said "Cells are complex systems with wiring diagrams that are still unknown and often highly nonlinear. They have evolved to achieve goals that may differ from those of the biotechnologist. Changes to one part of the system often lead to unanticipated consequences. And to understand tem requires the methods of systems biology. Stem cell biology is therefore both fascinating and complex. This research highlights just how critical it is to appreciate the subtleties of stem cell developmental biology. The potential to harness these cells in medical applications is exciting, but without a detailed understanding of the biological processes that drive them to become one cell type or another, and how they may choose to differentiate, we will never realise this potential."

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