IN THE NEWS

Realizing the potential

In theory, embryonic stem (ES) cells can generate any cell type in the body, but harnessing this potential is proving to be far from easy. Nevertheless, some promising results recently emerged from the University of Wisconsin, USA, where Su-Chun Zhang and colleagues generated functioning motor neurons from human ES cells.

The researchers exposed their cells to "a carefully timed cocktail of proteins" (*Reuters*, USA, 30 January 2005), including retinoic acid and sonic hedgehog, as well as various neurotrophic factors. Zhang said, "you need to teach [the cells] to change step by step, where each step has different conditions and a strict window of time" (*Reuters*). The resultant motor neurons showed electrical activity and formed functional synapses with their neighbours.

This protocol could have valuable applications in the field of neural repair: "the feat, which took more than two years of trial and error, is seen as an important step in the dream of creating spinal nerve cells in the laboratory to replace cells damaged by spinal cord injuries or by diseases such as amyotrophic lateral sclerosis" (*China View*, 1 February 2005). However, "the more immediate impact … will likely be to provide a supply of motor nerve cells that can be used to test new drugs intended to treat various nerve ailments" (*China View*).

Unfortunately, as several reports point out, translating this research into therapy is not just a matter of having the necessary technology. ES-cell derivation is still a highly contentious issue, particularly in the USA, where "the administration of President Bush does not support the use of embryonic stem cells except in limited circumstances using cells already in existence as of 2001. Federal funds may not be used to take new stem cells from human embryos" (*Reuters*).

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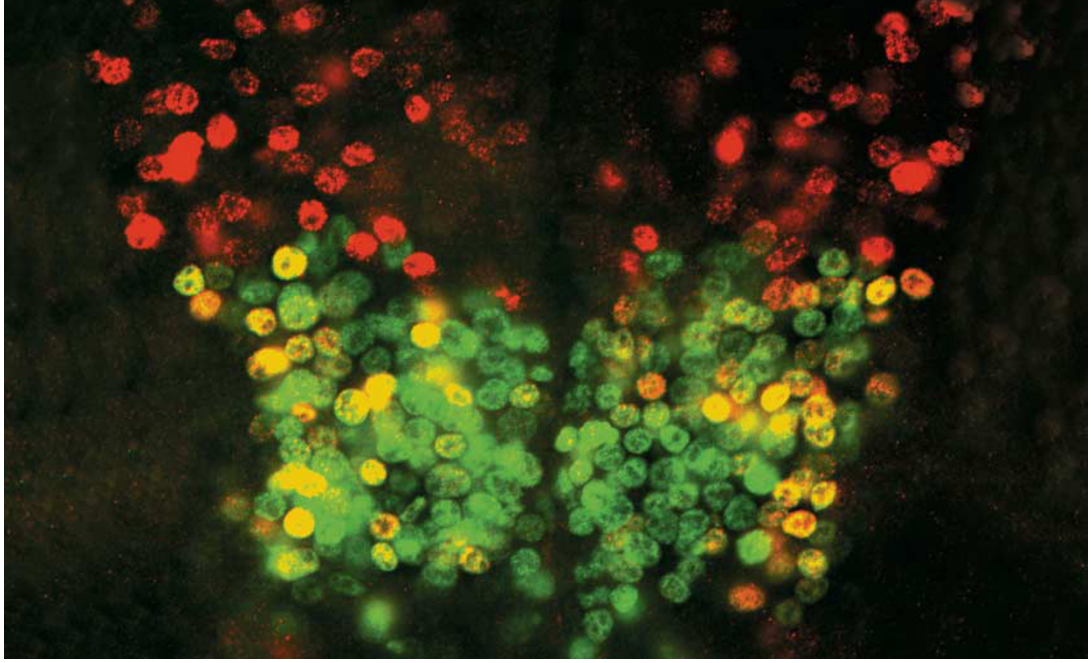

Immunolabelling of OLIG2 (green) stains the nuclei of pMN cells in the ventral neural tube of an embryonic day 3.5 chick embryo. NGN2 (red) is detected in the nuclei of many cells in the neural tube, but is heterogenously expressed by pMN cells (yellow double labelling). The relative balance in OLIG2 and NGN2 levels is believed to be an important determinant for directing pMN cells to produce motor neurons (high NGN2) or oligodendrocytes (low NGN2). Image courtesy of S. Pfaff, Salk Institute, La Jolla, California, USA.

CELL FATE

Striking the right balance

It is well known that the pMN progenitor domain of the embryonic ventral spinal cord gives rise first to motor neurons and later to oligodendrocytes, but how this dual role is accomplished is poorly understood. In a recent report in *Genes and Development*, Lee and colleagues shed new light on the molecular mechanisms that control the fate of progenitor cells in this region.

The basic helix–loop–helix (bHLH) transcription factors OLIG2 and neurogenin 2 (NGN2) are co-expressed in pMN cells that are not yet committed to an oligodendrocyte or motor neuron fate. Subsequently, OLIG2 is downregulated in cells that differentiate as motor neurons, whereas NGN2 is downregulated in cells that become oligodendrocytes. Previous findings have indicated that OLIG2 initially renders cells competent to enter the motor neuron lineage, by inducing the expression of factors such as NGN2 and LHX2. However, Lee *et al.* show that the continued expression of OLIG2 inhibits the post-mitotic development of motor neurons.

The authors showed that constitutive expression of OLIG2 throughout the dorsoventral axis of the neural tube in chick embryos caused a profound reduction in the generation of motor neurons. They also found that OLIG2 could prevent NGN2 from inducing neuronal differentiation in mouse teratocarcinoma cells. These findings prompted the authors to investigate how the activities of NGN2 and OLIG2 might be balanced to coordinate the generation of motor neurons and oligodendrocytes in the pMN domain.

One important clue came from the observation that in the wild-type chick neural tube, there was considerable heterogeneity between individual pMN cells with regard to NGN2 and OLIG2 expression levels. The relative levels of the two factors in any given cell were crucial for determining that cell's fate — cells that expressed relatively high levels of NGN2 differentiated as motor neurons, whereas cells that expressed relatively high levels of OLIG2 remained in a multipotent progenitor state.

To investigate the molecular basis of the antagonistic actions of OLIG2 and NGN2, Lee *et al.* investigated their effects on the expression of *Hb9*, a gene that is involved in motor neuron differentiation. They found that OLIG2 and NGN2 both bind to E-box regulatory elements in the *Hb9* motor neuron-specific enhancer. NGN2, in a complex with the bHLH factor E47, activates *Hb9* expression, whereas OLIG2 functions as a repressor. OLIG2 seems to prevent NGN2 from activating *Hb9* in two ways — by binding to NGN2 itself and sequestering it away from the gene, and by competing to bind to the E-box elements.

So, by maintaining OLIG2 and NGN2 at heterogeneous levels among cells of the pMN domain, the embryo can allow one population of cells to differentiate as motor neurons, while keeping a multipotent progenitor population in reserve for the later generation of oligodendrocytes. The question of how this heterogeneity is established and maintained will no doubt provide an important challenge for future investigations.

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References and links

ORIGINAL RESEARCH PAPER Lee, K.-Y. *et al.* Olig2 and Ngn2 function in opposition to modulate gene expression in motor neuron progenitor cells. *Genes Dev.* **19**, 282–294 (2005)

FURTHER READING Bertrand, N. *et al.* Proneural genes and the specification of neural cell types. *Nature Rev. Neurosci.* **3**, 517–530 (2002) | Rowitch, D. H. Glial specification in the vertebrate neural tube. *Nature Rev. Neurosci.* **5**, 409–419 (2004)