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VENT cells – a load of hot air?

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Recent work on chick embryo development challenges the view that the nervous system of the gut is solely derived from one source of cells, the neural crest cells. This research could overthrow some dogmas of developmental biology and could have important implications in pharmacology and gene therapy.

Evidence against the dogma

The enteric nervous system (ENS) is a large nervous system that is independent of the CNS and that is thought to be derived from neural crest cells – cells that, during early embryonic development, migrate to the gut from the dorsal region of the neural tube. Neural crest cells give rise to a variety of cell types, including neurons and glia of the peripheral nervous system and skeletal elements in the head.

It has been classically assumed that these dorsally emigrating neural crest cells are the only cell population that leaves the neural tube, with the exception of some Schwann cells that migrate along ventral pathways. However, research by Gurkirpal Sohal and colleagues at the Medical College of Georgia (http://www.mcg.edu) puts a question mark on this concept. Working with chick embryos, the researchers demonstrated that, after the neural crest cells have left the neural tube, cells also emigrate from the lateral and ventral neural tube. In a series of research papers, they showed that these ventrally emigrating neural tube (VENT) cells are multipotent and can give rise to hepatocytes, smooth muscle cells, cartilage – in other words, virtually any cell type [1–3]. In their latest paper, they demonstrated that VENT cells can also differentiate into cells of the ENS (Fig. 1), interstitial cells of Cajal (pacemaker cells that are responsible for the motility to the gut) and epithelial cells that line the gut [4].

Controversies

To some scientists, these findings do not come entirely unexpected. 'The belief that the ENS is derived from the neural crest mainly comes from experiments using grafts that typically take the whole neural tube,' Marianne Bronner-Fraser at the California Institute of Technology (http://www.caltech.edu) points out. 'They did not really differentiate between the dorsal and ventral neural tube. So in a way, [these new findings] are not surprising, it is just that people did not look at this particular cell population.'

Bronner-Fraser finds Sohal's work convincing because his group has come to the same conclusion using two different cell-labelling methods: in their first experiments, they dyed cells on the luminal side of the ventral tube by applying filter paper impregnated with the fluorescent lineage tracer DiI (1,1-dioctadecyl-3,3,3',3'-tetramethylindocarbo cyanine percholate). Later, they injected a retrovirus carrying the *lacZ* reporter gene into the lumen of the neural tube and followed the fate of the VENT cells by staining for β-galactosidase.

However, Sohal's work has earned harsh criticism from scientists in the field. Many are concerned that during injection of the virus, viral particles might have leaked from the lumen of the neural tube, resulting in the labelling of other cell lineages. Using a GFP expression vector, Abigail Tucker at King's College London (http://www.kcl.ac.uk) failed to find evidence for VENT cells [5]. 'I particularly wanted to see them,' she says. 'I thought they sounded very interesting.' Tucker used a fluorescent label to see immediately what she had labelled, and observed that 'you have mislabelling out of the neural tube in 30% of your cases'.

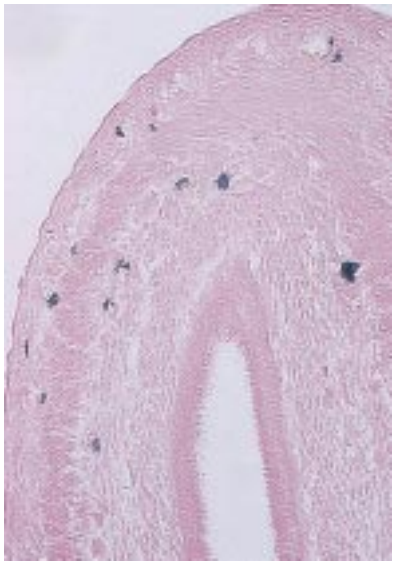

Figure 1. Cross-section through the gut of a chick embryo showing ventrally emigrating neural tube (VENT) cells giving rise to the enteric nervous system (blue cells). Figure kindly provided by Gurkipal Sohal (Medical College of Georgia; http://www.mcg.edu). Amplification ×40.

Tucker believes that the experiments with DiI are also flawed because, with this approach, the neural crest is disrupted. Recent evidence suggests that cells do not migrate from the ventral neural tube unless the neural crest is damaged [6]. 'This paper really was the end of VENT cells,' concludes Tucker.

Going against the party line

Sohal is not taken back by criticism. 'Any time you have a new idea in

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science, it is very difficult to go forward,' he remarks. 'This is a fundamental discovery, and people find it hard to believe that such a discovery could not have been made much earlier.'

Indeed, his findings could have a major impact on the way we look at where cells come from and how embryos develop. 'We would have to go back and look at the contribution of VENT cells to every tissue of the body,' says Sohal.

Eventually, this research could shed light on the pathogenesis of congenital disorders, for example, ailments of the gastrointestinal tract. Take Hirschsprung's disease, a disorder that affects one in 5000 babies and that is characterized by the absence of the ENS in the hindgut. Don Newgreen at the University of Melbourne, Australia (http://www.unimelb.edu.au), suggests that, if there really are two pathways to arrive at the same cell type, and if the VENT cells really are a cell source that is of functional importance, it might be possible to use them to replace defective or absent ENS cells. Also, 'comparisons [between the two routes to ENS development] will help greatly in identifying the common pathways we could focus on and control, pharmacologically or by cell or gene therapy,' adds Newgreen. According to Sohal, cells originating from heterogeneous sources might also express different receptors and could thus require treatment with different drugs.

But these are all hypothetical applications. The immediate challenge for Sohal and colleagues is to isolate the VENT cells. 'Once we have a specific marker for these cells, and once we have identified genes that are uniquely expressed in these cells, more people will be convinced,' believes Sohal.

References

1 Ali, A.A. *et al.* (1999) Ventrally emigrating neural tube cells differentiate into vascular smooth muscle cells. *Gen. Pharmacol.* 33, 401–405

2 Sohal, G.S. *et al.* (1999) Ventrally emigrating neural tube cells contribute to the formation of Meckel's and quadrate cartilage. *Dev. Dyn.* 216, 37–44

3 Sohal, G.S. *et al.* 1999. Ventral neural tube cells differentiate into hepatocytes in the chick embryo. *Cell. Mol. Life Sci.* 55, 128–130

4 Sohal, G.S. *et al.* (2002) A second source of precursor cells for the developing enteric nervous system and interstitial cells of Cajal. *Int. J. Dev. Neurosci.* 20, 619–626

5 Yaneza, M. *et al.* (2002) No evidence for ventrally migrating neural tube cells from the mid- and hindbrain. *Dev. Dyn.* 223, 163–167

6 Vermeren, M. *et al.* (2003) Integrity of developing spinal motor columns is regulated by neural crest derivatives at motor exit points. *Neuron* 37, 403–415

Anticancer drug shows promise against lupus

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A drug that is currently in Phase II clinical trials for use as an anti-tumour agent has been found to reduce the expression of cytokines that contribute to immunopathogenesis in lupus patients. Furthermore, a structurally related compound significantly reduced the clinical symptoms of lupus in a mouse model, including urine protein excretion, enlarged spleen and kidney disease. Scientists are optimistic that the anti-tumour drug could enter clinical trials for lupus within two years.

Histone deacetylase inhibitors

The two drugs, suberonylanilide hydroxamic acid (SAHA) and trichostatin A (TSA), belong to a class of compounds that alter the acetylation of histones [1,2]. Specifically, they act by inhibiting histone deacetylase and thus increase histone acetylation. Histones regulate the packaging of genes into chromatin; the acetylation and deacetylation of histones result in changes to the chromatin structure that ultimately affect gene expression.

TSA is a naturally occurring compound produced by *Streptomyces*. It was identified in 1974 and was subsequently found to inhibit histone deacetylase, said Nilamadhab Mishra, Instructor in Internal Medicine at Wake Forest University School of Medicine (http://www.wfubmc.edu/school/).

SAHA, a second-generation histone deacetylase inhibitor based on the structure of TSA, has entered Phase II clinical trials in cancer patients. Aton Pharma (http://www.atonpharma.com/) the sponsor of these trials, report that it has excellent oral bioavailability and long duration of action, and can inhibit histone deacetylase at well-tolerated doses.

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