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NEURODEVELOPMENT

Nascent neurons need nature and nurture

How genetic and environmental factors contribute to the generation of various subtypes of inhibitory neurons called interneurons in the brain is unclear. A study in mice provides new insight into this process.

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The mature brain contains an enormous variety of locally projecting inhibitory neurons known as interneurons. How the brain's precise complement of interneurons is generated during development is a subject of lively debate. At its heart, this question is one of nature versus nurture. Young interneurons are 'born' in a region called the subpallium and undergo a long migration to reach their final positions in the brain's cortex — but it remains unclear how much of an interneuron's mature fate is bestowed by its genetic identity, which is established when the cell stops proliferating, and how much is acquired through nurture during migration. Writing in *Nature Neuroscience*, Lim *et al.*[1] investigate how migration influences cellular identity.

There is evidence to support roles for both nature and nurture in defining the identities of the different classes, types and subtypes of interneuron in the mature brain. Intrinsic gene-expression programs are thought to begin to define interneuron identities in the embryo, and to unfold over a lengthy period of time[2–4]. The expression of certain genes remains conserved in specific types of interneuron from their birth through to adulthood[4], whereas others affect interneuron maturation more transiently during early embryonic development[5]. Such intrinsic processes are thought to cooperate with the interneuron's environment to establish neuronal circuits and brain connectivity in the adult[6]. For example, after arrival in the cortex, neuronal activity affects several aspects of interneuronal development[7–9].

The authors studied the migration pathways of two types of interneuron — one characterized in the adult by expression of the protein somatostatin, the other by expression of the protein parvalbumin. Both types are born in the same general region of the subpallium. Interneurons from this region reach the embryonic cortex predominantly by two migration routes[10]: one that takes them through the marginal zone above the cortex; and one that transits below the cortex, through the subventricular zone.

Does the route taken by an immature interneuron have an effect on the identity of the mature cell it will become? To find out, Lim *et al.* specifically labelled somatostatin- or parvalbumin-expressing interneuron precursors in the marginal zone with a fluorescent protein, and observed the cells' development. The authors found that both populations tend to develop complex projections at the end of their migration through the marginal zone. These projections, called translaminar axons, cross different layers of the cortex. This finding led the researchers to propose that migration through the marginal zone influences the growth and branching of axons through some general mechanism.

To examine this idea, Lim and colleagues performed time-lapse imaging experiments in brain slices grown in culture. Consistent with their hypothesis, interneurons 'abseiled' down into the cortex after travelling through the marginal zone. During this process, most of these cells anchored their nascent axon in the marginal zone like a trailing rope (Fig. 1). Thus, migration route and axonal development seem to be linked for these cells.

Next, the authors investigated the consequences of deleting genes that are expressed in somatostatin-interneuron precursors that migrate through the marginal zone, but not in those that pass through the subventricular zone. The group found that deletion of one such gene, *Mafb*, in these cells results in about a 20% decrease in the fraction of somatostatin-interneuron precursors migrating through the marginal zone. Moreover, those neurons that failed to migrate through the marginal zone lacked their characteristic translaminar projections. Finally, Lim *et al.* isolated migrating interneurons from both routes and transplanted them back to the beginning of the migration path in a cultured brain slice. Slightly more than 60% of the cells from the marginal zone entered the same migration path again, hinting that intrinsic differences between neurons influence which cells take which path.

Taking their results together, Lim and colleagues conclude that, early in development, genetic factors determine what type of interneuron a cell will become, and direct the cell down the appropriate migratory path. However, there is also evidence from the current work for environmental effects on interneuron development.

First, the effects of migration route on axonal branching seem to be largely independent of genetic priming, because somatostatin- and parvalbumin-interneuron precursors

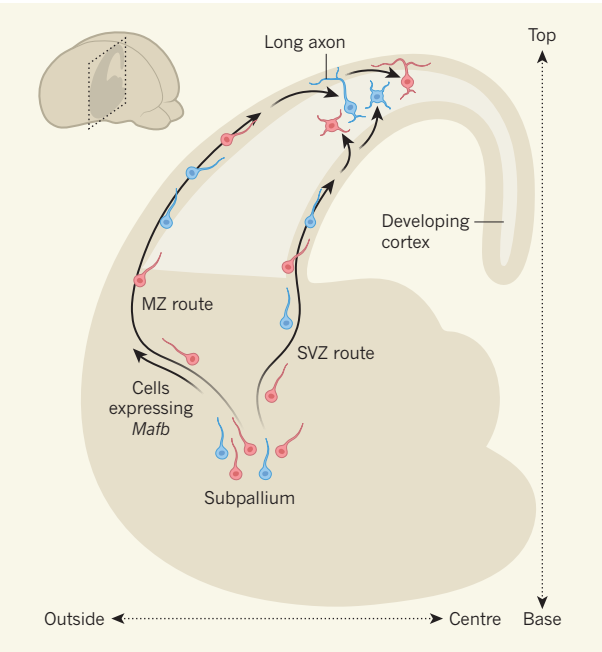

Figure 1 | Intrinsic and environmental cues govern the development of interneurons. Cells called interneurons become progressively more diverse as they mature. Interneurons generated in the subpallium of the mouse brain can be divided into a group that will become mature cells expressing the protein somatostatin (red), and another that will express the protein parvalbumin (blue). Neurons from each group migrate to the cortex through one of two routes: along the marginal zone (MZ) above the developing cortex or along the subventricular zone (SVZ) below it. Lim *et al.*[1] report that an intrinsic cue — expression of the gene *Mafb* — leads cells to migrate through the MZ, and to develop long axonal projections when they move into the cortex, whereas cells that migrate through the SVZ develop short local axons. However, the migration route taken and development of projections also depends on environmental cues, often involving neuronal activity (not shown). The orientation of the brain is indicated in the inset, and by dotted arrows.

are similarly affected. Second, although *Mafb*-deficient cells that fail to migrate through the marginal zone lack their translaminar projections, they do retain other properties characteristic of cells that follow the marginal-zone route. Third, almost 40% of interneurons transplanted into brain slices from the marginal zone picked a different migratory route the second time round. It is therefore likely that stochastic processes are a major part of the distribution of interneurons between migration paths. A balance between predetermined and environmentally specified aspects of interneuron development seems to be emerging.

One explanation for how such a balance might work involves the expression of genes such as *Mafb* in newly born interneurons acting as a virtual 'look-up table'. In this scenario, the expression of intrinsic signals might bias the response of developing neurons to subsequent environmental cues. As such, the combination of early gene expression coupled with later environmental cues might jointly determine the cells' final identity and connectivity.

Determining the influences of environmental cues on particular interneuron populations requires the ability to selectively target those populations. The identification this year[4,11] of genes expressed early in development that are specific to particular interneuron populations promises to provide a way to probe the contributions of early intrinsic and later environmental cues in particular interneuron subclasses. Certainly, the present paper provides strong evidence for how the two aspects of development are linked. ■

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