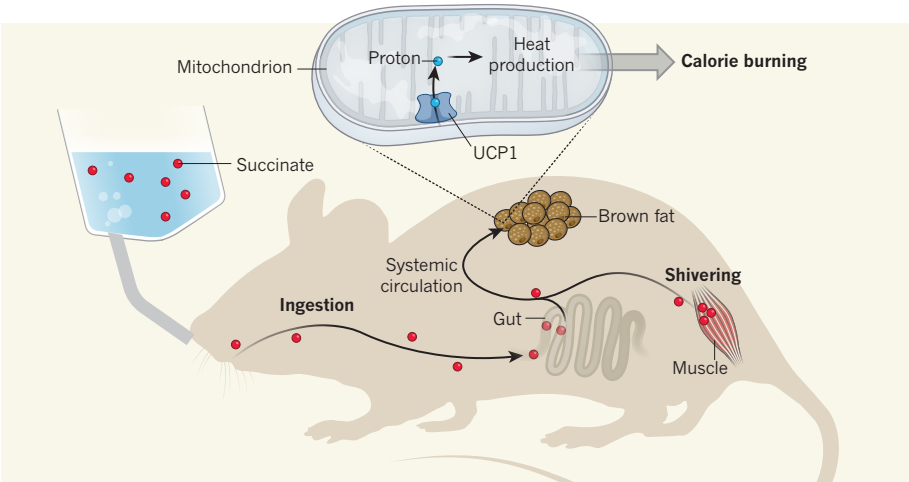

Figure 1 | Circulating succinate molecules mediate calorie burning. Mills *et al.*[1] report a mechanism by which weight gain can be controlled in mice. Succinate added to drinking water is ingested and enters the systemic blood circulation from the gut. Succinate is also released into the circulation by muscle cells during shivering in response to cold. From the circulation, succinate can enter brown-fat cells, which contain many organelles called mitochondria. Here, it triggers the mitochondrial protein UCP1 to leak protons (hydrogen ions; H^+), converting chemical energy into heat and thereby burning calories.

the blood, Mills and colleagues injected mice with succinate tagged by a heavy isotope of carbon. They found that the carbon isotope accumulated preferentially in brown fat. Thus, brown fat seems to be programmed to use circulating succinate as a fuel. Consistent with this, the authors showed that isolated brown-fat cells, but not most other cell types tested, avidly took up and burnt succinate.

Mills *et al.* next showed that acute succinate administration in mice raised the local temperature of brown fat. And, strikingly, administering succinate in drinking water for four weeks prevented obesity in mice on a high-fat diet. These metabolic effects depended on UCP1 — most of the beneficial metabolic effects of succinate were absent in mice genetically engineered to lack this protein. Thus, succinate activates heat production and calorie burning in brown fat (Fig. 1).

How exactly does succinate trigger heat production? In the TCA cycle, succinate is consumed by the enzyme succinate dehydrogenase. The activity of this enzyme produces molecules called reactive oxygen species (ROS), which have been proposed to promote heat generation by brown fat[7]. The authors therefore suggest that succinate accumulation induces calorie burning by increasing the activity of succinate dehydrogenase and so increasing ROS levels. However, it is unclear whether the contribution of circulating succinate to the TCA cycle in brown-fat cells is really sufficient to alter ROS levels and heat generation.

As an alternative explanation, perhaps succinate triggers a yet-to-be-discovered signalling system in brown fat. Or perhaps circulating succinate is sensed in a different part of the body, such as the brain, which then signals to brown fat to activate heat production. Defining the mechanism at work is of more than academic interest — it might prove important in determining the ideal dose and schedule for succinate administration in humans, or for identifying pharmacological alternatives to bulk succinate intake. Finding the molecular players involved will be crucial, the most obvious missing protein being the transporter that carries succinate into brown fat.

Humans, of course, differ from mice in many ways. One of the most obvious is our larger body size, which is associated with a lower ratio of body surface area to mass. As a consequence, we are better at staying warm than are mice, but worse at getting rid of heat. It is probably for these reasons that brown fat makes up a much lower percentage of our body mass[8]. Moreover, we lose brown fat as we age. This could limit the extent to which activation of metabolic processes in brown fat can alter calorie expenditure. Accordingly, methods to induce brown-fat properties in existing white fat might be needed as a complementary approach[5]. It will nevertheless be interesting to see whether succinate can induce substantial calorie burning in humans.

Taking a step back, circulating TCA intermediates have not previously been considered as key factors in metabolism. But several TCA intermediates are present in the circulation at substantial levels, and some of them, such as citrate, flow into and out of the bloodstream to a greater extent than does succinate[9]. The finding that circulating succinate has a well-defined, and perhaps even medically important, metabolic role raises the possibility that circulating TCA intermediates will more generally prove to be vital metabolic players. ■

Sheng Hui *and* **Joshua D. Rabinowitz** *are at the Lewis-Sigler Institute for Integrative Genomics, and in the Department of Chemistry, Princeton University, Princeton, New Jersey 08544, USA.*
e-mails: shui@princeton.edu; joshr@princeton.edu

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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.

CHRISTIAN MAYER & GORD FISHELL

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 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. ■

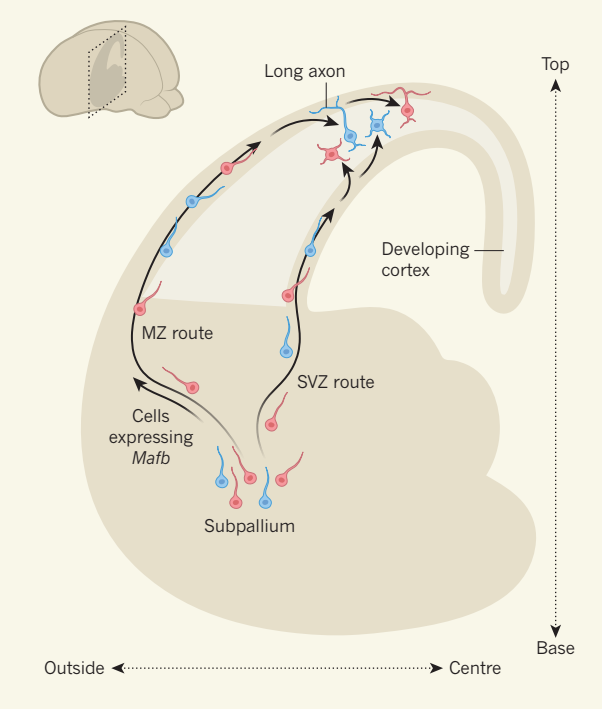

Figure 1 | Intrinsic and environmental cues govern the development of interneurons. Cells called interneurons become progressively more diverse as they mature. Interneurons generated in the subpallium of the mouse brain can be divided into a group that will become mature cells expressing the protein 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.

Christian Mayer *is at the Max Planck Institute of Neurobiology, 82152 Martinsried, Germany.* **Gord Fishell** *is at the Department of Neurobiology, Harvard Medical School, Boston, Massachusetts 02115, USA.*
e-mails: cmayer@neuro.mpg.de; gordon_fishell@hms.harvard.edu

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