Making more brain

Adults make new brain cells. But where do those nerve cells come from? New findings suggest that a subpopulation of glia—the brain’s filler material—act as the all-important neuronal precursors. Even more startling, a widespread glial cell type called the astrocyte can be converted into a neuronal precursor by the expression of a single gene.

“These astrocytes are not viewed anymore as a specialized cell type but rather as a precursor cell,” said Magdalena Götz (Max-Planck Institute, Göttingen, Germany). “And once we think we have precursors everywhere, we can think how to manipulate these precursors.”

Precursor activity is most obvious in the developing brain. In the neocortex, for example, it was thought that newly born neurons migrated up the long processes of radial glial cells. But Stephen Noctor and Arnold Kriegstein (Columbia University, New York, NY) used time-lapse movies to show that the radial glia divide to form neurons, which then use the radial glia as migration tracks. According to Noctor, “this is a mechanism that could generate cortical columns.”

In adults the radial glia are converted into astrocytes. Fiona Doetsch and Arturo Alvarez-Buylla (University of California, San Francisco, CA) have suggested that certain adult astrocytes can act as neural stem cells, whereas Jonas Frisén (Medical Nobel Institute, Stockholm, Sweden) believes that the ependymal cells lining the brain ventricle are doing the same job.

Several researchers have noted, however, that Frisén’s technique for labeling ependymal cells may also label the astrocytes, as the latter cells briefly extend processes to the ventricle wall. “That to me is a reasonable explanation of the conflicting results,” said Kriegstein.

However this debate is resolved, the majority of astrocytes are still seen as rather inanimate stuffing. But now Götz has found that the addition of the transcription factor Pax6 to astrocytes reawakens their ability to make neurons. “This is quite remarkable,” said Kriegstein. “Just by adding that one gene you can convert an astrocyte into a neuron generator.”

Götz isn’t about to start throwing Pax6 into the brains of Alzheimer’s patients: for starters this would be difficult given the slow or nonexistent division of astrocytes, and in addition there is concern as other Pax proteins have been associated with tumorigenesis. But Götz is confident of eventual benefits. “This shows for the first time that maybe you could use these normal astrocytes to replace neurons,” she said.

Reference: Noctor, S.C., et al. 2001. Nature. 409:714–720.

The secret to social sniffing

Mice sniff their way through their social universe. The key to that universe is a nine-amino acid peptide called oxytocin, without which mice become socially inept. Now Larry Young (Emory University, Atlanta, GA) has found that a brief pulse of oxytocin in one part of the brain restores the ability of the mice to recognize each other as strangers or familiar friends.

As a readout of social behavior, Young measured how long mice investigated a new mouse placed into the same cage. If a mouse is familiar, a normal mouse spends relatively little time sniffing around it, but mice lacking oxytocin keep sniffing away as if they have never seen their long lost friend.

The mice lacking oxytocin can be tricked, however, if the familiar mouse is always painted with a lemon scent. This acts like a name tag that the test mouse can now recognize. If a third, unfamiliar mouse is now added with the same name tag (i.e., it is also lemon-scented), the mutant mouse is tricked into thinking that its friend has once again entered the room. Conversely, the familiar friend can be disguised with an almond scent, which makes the mutant think that the friend is a newcomer.

In previous work, Young and colleagues rescued these and other defects by flooding the mouse brain with 1 ng of oxytocin. But now they have achieved the same rescue by adding just 0.1 pg of oxytocin to a brain region called the medial amygdala. A similar addition to the olfactory bulb had no such effect.

In humans, the amygdala is known to help make sense of faces, emotional expressions, and social cues. Autistic patients, who have difficulties in social interactions, often have defects in the amygdala and lowered levels of oxytocin.

Thus, oxytocin may be acting as some kind of social switch. But Young does not yet know whether oxytocin is specifically released during a social interaction. “The oxytocin is probably involved in differentiating social versus nonsocial interactions,” he said. “It may help in routing the olfactory information to proper brain areas.”

Reference: Ferguson, J.N., et al. 2001. J. Neurosci. 21:8278–8285.
Learning for a lifetime

Retrieving a memory turns out to be a risky proposition. For at least some types of memories, an active retention process must take place during retrieval, or else the original memory will be lost. Now researchers have found that the machinery driving the new memory acquisition and the later memory retention shares some, but not all, components.

The idea that memory can be unstable is nothing new to psychologists, but goes against the recent trend in molecular memory research, which has focused on how memories become more and more secure as time progresses. Then, Karim Nader (McGill University, Montreal, Canada) and Joseph LeDoux (New York University, New York, NY) found that they could ablate a memory. They infused a protein synthesis inhibitor soon after inducing the recall of a memory. This disrupted the recall of that memory a full day later. Addition of the inhibitor had no such disruptive effect if it was not tightly paired with the earlier recall.

“The work was so clean and so clear,” said Alcino Silva (University of California, Los Angeles, CA), and yet “everyone was so surprised because we always think of memory consolidation as this closed process. The memory should be cemented.”

Memory may be labile because the act of remembering requires that the same nerve cells fire as they did when the memory was formed. During this rehearsal, said Nader, the memory “can be updated or associated with new information.” A dose of inhibitor applied in the middle of the update can, however, bring the whole performance crashing down, obliterating not only the modification but also the original memory.

This theory emphasizes the similarities between learning and remembering. But, says Silva, “the mechanisms during learning are not the same that you need during remembering.” To study this problem, Silva came up with ways of switching on and off two critical memory proteins: α-CaMKII and CREB. He found that CREB was required for both memory formation and retention, but α-CaMKII only for memory formation.

“It’s an interesting lead in terms of what is different between storage of a new memory and the reprocessing of a memory,” said Nader. Now the race is on to decipher the logic underlying these differences.

Reference: Nader, K., et al. 2000. Nature. 406:722–726.

Translational guidance

If axons are to turn on a dime, then translation would not be the first suspect as a way of regulating direction-finding. But, in results that she said came as “a complete surprise,” Douglas Campbell and Christine Holt (Cambridge University, Cambridge, UK) have found that common axon guidance molecules work by turning on translation at the tip of the growing neurite.

The work is part of Holt’s attempt to understand a series of guidance decisions in the developing eye. Axons of retinal ganglion cells (RGCs) start off by slithering along the laminin coating of the retina, before a roadway of netrin induces a turn into the brain. Ephrin at the midline controls how many neurons cross into the other side of the brain, and then semaphorin 3A bumps the neurons onto a course headed for the optic tectum. Entry into the tectum is controlled by FGF.

Detailing all these decision points is all very well, but it doesn’t tell us how the guidance molecules make the axon turn. This is where the translation switch comes in. The hardware needed for such a switch is certainly present in the axon—ribosomes were localized to axons decades ago. “But that old literature seems to have been forgotten,” said Holt.

In 2000, Mark Bear (Brown University, Providence, RI) found that rapid induction of local translation was important in changing the activities of dendrites. So, Holt added cycloheximide to inhibit translation in her axon guidance assays. Even in severed neurites, the drug prevented turning either toward attractants, such as netrin, or away from repellents, such as semaphorin 3A.

The target of this regulation appears to be a translation initiation factor called 4E. Within five minutes of attractant or repellent addition, 4E and its binding protein are phosphorylated. Holt does not yet know if this change is sufficient to induce guidance, nor does she know which target mRNAs are critical to changing the behavior of the axon. Guidance molecules increase the incorporation of hot leucine in axons, so as a first step Holt is looking to see how many new proteins are labeled during this procedure.

Reference: Campbell, D.S., and C.E. Holt. 2001. Neuron. 32:1013–1026.