Neurons inhibit neurogenesis

Recent advances in the study of neural regeneration have prompted a significant shift in the way neurobiologists view brain repair. Assumptions regarding the inherent limitation of the mature central nervous system (CNS) in replacing lost neurons have given way to a perspective that focuses upon the local cellular and molecular microenvironment as the primary impediment to neural repair. One idea is that chemical signals produced by glia or neurons may directly influence the proliferation of endogenous neuronal progenitors.

In the 23 January 2003 issue of Neuron, Wu et al. present a study of the olfactory epithelium in which they identify an endogenous molecule that inhibits neurogenesis. Their results show a molecular mechanism for regulating the number of neurons produced by the olfactory epithelium and propose a general means by which tissue growth may be controlled in various organs, including the brain.

The olfactory epithelium, including the olfactory receptor neuron population, exhibits a remarkable capacity for regeneration, both naturally and in response to experimentally induced damage. As a result, the olfactory epithelium, though part of the peripheral nervous system, has long been viewed as a useful model for studying regenerative processes that are diminished in or absent from the adult CNS. Recent studies have revealed unanticipated similarities between the regenerative properties of the olfactory epithelium and the adult brain. In light of such findings, understanding the mechanisms that regulate olfactory receptor neuron production and recovery of function after damage may provide important clues for dealing with the seemingly intractable problem of brain repair.

Wu et al. identify a member of the transforming growth factor (TGF)-β protein superfamily as an endogenous inhibitor of neurogenesis. The TGF-β superfamily comprises a large group of structurally related cytokines with functions including the inhibition of mitosis. The molecule studied by Wu et al., growth and differentiation factor-11 (GDF11), is expressed within the embryonic olfactory epithelium during development.

Because TGF-β-like molecules inhibit cell proliferation in a number of systems, Wu et al. hypothesized that GDF11 might have a role in neurogenesis. To address this idea, they examined cell proliferation in the olfactory epithe-
fluorescent protein–positive cells. markedly decreased the number of green transgenic mouse in which the precursor cells test this, they examined another trans- rons by limiting the prolifer- tors, was examined. It was 
found that these animals 
also fail to produce GDF11, indicating that either the neurons themselves, or their immediate progenitors, are the endogenous source of GDF11. The authors suspected that GDF11 might inhibit the production of new olfactory receptor neu- rons by limiting the prolifer- ation of their immediate progenitors. To test this, they examined another transgenic mouse in which the precursor cells were specifically marked with green fluo- rescent protein. In olfactory epithelium explants derived from these mice, GDF11 markedly decreased the number of green fluorescent protein–positive cells.

How might GDF11 limit the number of the immediate neuronal progenitors? The authors ruled out the possibility that GDF11 induces apoptosis of imme-
diate progenitors. Instead, they found that GDF11 regulates cell production in a manner similar to that of GDF8, a closely related molecule in muscle tis-

sue. Both molecules seem to arrest the division of progenitor cells by upregulat-
ing the expression of cyclin-dependent kinase inhibitors. In the case of the ol-
factory epithelium, GDF11 seems to work through p27kip1. The actions of GDF11 within the olfactory epithelium, and analogous functions of related mol-
ecules in other tissue types such as muscle and brain, suggest a general mechanism for controlling the growth of tissues: when the number of differentiated cells reaches a certain level, their production of anti-proliferative factors helps to inhibit the division of progenitors.

In cases of brain damage, some compensatory neurogen-

esis is now known to occur in many brain regions. When mature neurons are damaged or destroyed, inhibitory cues may be superceded by proliferative chemosignals, such as fi-
broblast growth factor or related molecules, perhaps se-
creted by dying neurons or nearby glial elements. Destruction of neuronal popula-
tions may also remove the source of signals that inhibit neurogenesis. The work of Wu et al. supports this latter no-
tion by identifying an endoge-

cious inhibitory cue, GDF11, and characterizing its natural antagonist follistatin.

TGF-β molecules such as GDFs are expressed by neurons in the adult brain. Although the function of these mole-
cules in the CNS remains un-
clear, their involvement in regulating neurogenesis within the CNS seems plausible.

In most instances of brain damage, recovery of function is limited and significant neu-
ropathology remains or is even exacerbated after 
compensatory neurogenesis. Identifying the factors that impair efficient migration and incorporation of new neurons into damaged circuits will be an important step in the de-

velopment of brain repair strategies. Once these obstacles are identified, mole-
cules such as GDF11 and follistatin may be useful for stimulating a controlled in-
crease in the production of new neurons, which might be directed to the necessary 
locations to form appropriate connections and restore function after disease or damage.

2. Gould, E. & Tanapat, P. Lesion-induced proliferation
Successful drugs have high specificity for their molecular targets. In theory, nucleic acids, whose base-pairing interactions are highly specific, could be effective drugs. The challenge has been to create artificial nucleic acids, such as antisense oligonucleotides and ribozymes, that reach cells in adequate amounts to regulate specific gene function, yet are nontoxic. Efforts to date have focused on altering the phosphodiester linkages or modifying the ribose sugar to improve the stability, efficacy or cellular uptake of nucleic acids.

The work of Song et al. in this issue suggests that one type of entirely natural nucleic acid, small interfering RNAs (siRNAs), may hold promise as a therapeutic agent even without further engineering. These investigators provide the first in vivo evidence that infusion of siRNAs into an animal can alleviate disease, in this case hepatitis.

siRNAs are double-stranded RNA (dsRNA) molecules of 21–23 nucleotides with characteristic 2-nucleotide overhangs 3′ ends. They act as intermediates in the RNA interference (RNAi) pathway, which is thought to protect cells from harmful transposons and highly repetitive sequences by targeting their RNA transcripts for endonucleolytic cleavage and subsequent exonucleolytic degradation (Fig. 1). In culture, exogenously added siRNAs can protect mammalian cells from infection by a variety of viruses, but it is not yet known whether RNAi is a component of the mammalian antiviral response. In contrast, siRNA-directed RNA degradation is central to the antiviral response in plants, where it represents a potent form of sequence-based immunity.

The ribonuclease Dicer generates siRNAs by cleaving long dsRNAs. In siRNA-directed RNA interference, the two strands of an siRNA separate in a process probably mediated by specific protein ‘helicases,’ after which the individual siRNA strands associate with another set of proteins to form a protein–enzyme complex—the RNA-induced silencing complex (RISC). The RISC has the remarkable property of using the sequence of its tightly bound siRNA strand to direct the complex to mRNAs with perfect or nearly perfect complementarity. Tethered to the mRNA by its siRNA guide, the RISC destroys the mRNA by cutting it once, across from the center of the siRNA. Cleavage completed, the RISC departs, with the unperturbed siRNA ready to begin anew the cycle of target recognition and cleavage.

The power of siRNAs springs from the cellular biochemistry of the RNAi pathway.