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substrate gelsolin (Furukawa et al., 1997; Kothakota et al., 1997). Such a mechanism might contribute to the shrinkage or loss of dendritic spines in response to LTD-inducing stimuli. The study by Li et al. introduces a new set of molecules at the center of the pathway underlying synaptic LTD and further demonstrates the resourcefulness of postmitotic neurons in borrowing signaling pathways traditionally associated with cell growth, differentiation, and death in dividing cells to perform specialized functions at synapses.

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A Bone to Pick with Compulsive Behavior

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Mice with mutations in the *Hoxb8* gene exhibit compulsive grooming behavior. Chen et al. (2010) now report that this behavior stems from *Hoxb8* deficiency in microglia, a type of immune cell in the brain derived from bone marrow. These findings provide intriguing connections between immune dysfunction and neuropsychiatric disorders.

Mice with mutations in the *Hoxb8* gene groom themselves at about twice the frequency of wild-type mice, resulting in hair loss and open skin lesions (Greer and Capecchi, 2002). The *Hoxb8* mutant mouse has been proposed as a model for a human behavioral disorder, trichotillomania (compulsive hair pulling), which may be related to obsessive-compulsive disorder (OCD; Chamberlain et al., 2006). Reporting in this issue, Chen et al. (2010) now investigate the cellular basis of the overgrooming behavior in *Hoxb8* mutant mice. Reasoning that lack of *Hoxb8* expression in the brain should play an important role in the behavioral phenotype, the authors ask what cell types in the brain normally express *Hoxb8*. They find that within the mouse brain the only *Hoxb8*-expressing cells are microglia that originate in bone marrow and migrate into the brain. To test whether bone marrow-derived microglia lacking *Hoxb8* are responsible for compulsive grooming behavior, the authors carry out bone marrow transplants. Strikingly, transplant of wild-type bone marrow into *Hoxb8* mutants restored normal, noncompulsive grooming behavior within a timeframe consistent with the migration of new microglia into the brain. These findings provide important new evidence that abnormalities of the immune system can produce compulsive behavior and strengthen the case that microglia play an important role in modulation of nervous system function.

Behaviors are said to be compulsive if they continue despite causing significant harm or distress. Compulsions are thought to result from abnormal functioning of neural circuits that connect the cerebral cortex and the striatum, a component of the basal ganglia (Figure 1). Parallel loops run from diverse regions of the cerebral cortex to the striatum, then, by way of the thalamus, back to prefrontal regions of the cerebral cortex. These loops facilitate the consolidation of repeated sequences of movements or thoughts into highly efficient modules that can be replayed automatically, that is, without conscious supervision (Graybiel, 2008). Depending on the precise movements or thoughts in the sequences, these automatic behaviors may range from skilled performances to habits or rituals. It is thought that when corticostriatal loops that control habitual behaviors become dysfunctional, compulsions can result.

How might mutations in the widely expressed Hox gene family member *Hoxb8* lead to compulsive grooming behavior in mice? The possible mechanism is not as straightforward as it would be if the gene encoded a synaptic protein such as the SAP90/PSD95-Associated Protein 3 (SAPAP3), which has been implicated in compulsive grooming (Welch et al., 2007). In the latter case,

the phenotype might result from abnormal synaptic transmission or plasticity occurring directly within the circuit responsible for habit formation. Chen et al. detected microglia expressing *Hoxb8* in the cerebral cortex, striatum, olfactory bulb, and brainstem of wild-type mice. Microglia are found in close proximity to neurons but do not participate in synaptic connections. Thus their effects on information processing in the nervous system likely result from paracrine actions of mediators that they release. The anatomical location of some of the *Hoxb8*-expressing microglia detected by Chen et al. positions them to influence the corticostriatal loops that are thought to support compulsive behaviors. The authors propose that cytokines released by *Hoxb8*-expressing microglia might be involved in the modulation of grooming behavior. However, these microglia might also release other chemical signals that modulate the activity of corticostriatal circuits. In any case, further investigation will be required to determine the precise mechanism by which bone marrow-derived microglia that express *Hoxb8* influence grooming behavior.

There is a precedent for microglia playing a potentially important role in neural signaling and plasticity. For example, both microglia resident in the brain and newly recruited bone marrow-derived microglia have emerged as potentially significant actors in the development of chronic pain (McMahon and Malacangio, 2009; Jarvis, 2010). In addition, immune dysfunction can cause neuropsychiatric syndromes that include OCD-like symptoms. Sydenham's chorea, which is characterized by involuntary rapid jerking movements (chorea) and psychological symptoms including obsessions and compulsions, can result from acute rheumatic fever, an autoimmune disorder triggered by infection with Group A streptococcal bacteria. It has been argued, in addition, that some cases of childhood onset OCD and tics occurring without acute rheumatic fever may be caused by an autoimmune response to infection by Group A streptococci. However, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, or PANDAS, as this syndrome has been called (Swedo et al., 1998), remains contested, at least with respect to its frequency (Schrag et al., 2009). The findings of Chen et al. (2010) do not contribute directly to the search for a mechanism by which PANDAS might occur. That said, this work should help to reinvigorate research on mechanisms by which disorders of the immune system might produce neuropsychiatric symptoms.

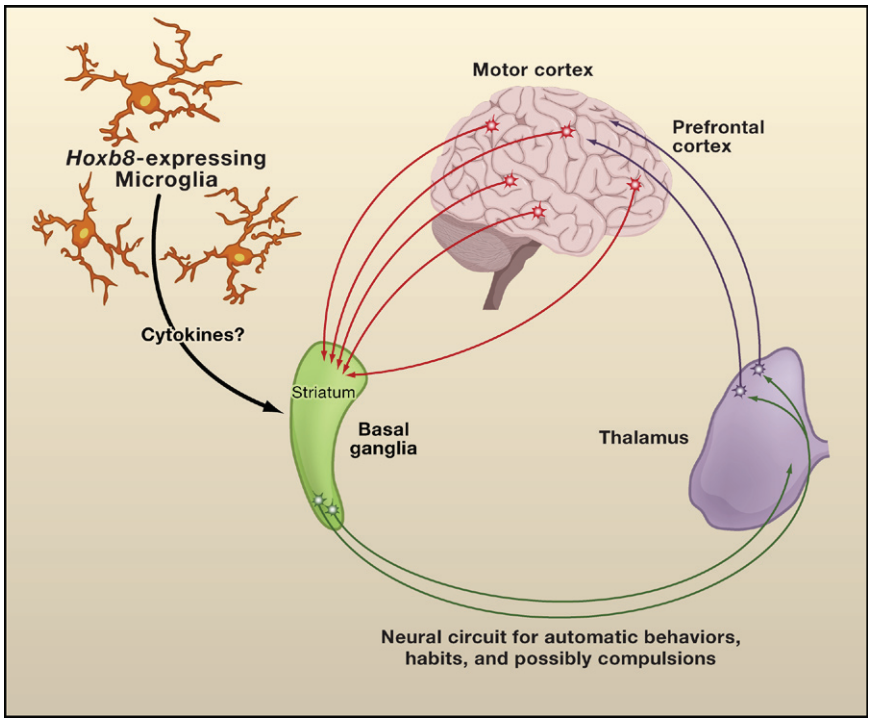

Figure 1. Bone Marrow-Derived Microglia and Compulsive Behavior
Neural circuits in the brain that connect the striatum, a component of the basal ganglia, with the cerebral cortex are thought to underlie engrained behaviors, whether learned or instinctual, that are performed independently of conscious control. Such behaviors range from highly practiced athletic or artistic performances to habits, rituals, and compulsions. Different types of behaviors are controlled by parallel loops that project from diverse regions of the cerebral cortex to the striatum and from there, via the thalamus, back to the cerebral cortex. Chen et al. (2010) report that microglia in the brain that are derived from the bone marrow are responsible for the compulsive grooming behavior of *Hoxb8* mutant mice. Bone marrow transplant from wild-type mice abrogates the compulsive behavior. The authors propose that cytokines or other mediators released by the bone marrow-derived microglia modulate the function of the circuits involved in grooming behavior.

The difficulty of generating truly useful animal models of human neuropsychiatric disorders has long impeded the detailed study of pathogenesis as well as the development of new therapies. One important obstacle to the production of animal models results from the nature of many neuropsychiatric symptoms. Some symptoms may appear to be uniquely human or may be ascertained only through a verbal report of subjective experience. For these reasons, it is difficult to produce a truly convincing animal model of OCD. Obsessions are intrusive thoughts, and compulsions are ritualized behaviors that are undertaken to neutralize the anxiety and tension that typically result from the obsessions. Both the presence of obsessions and the resulting anxiety would seem to require, at least for the present, a verbal report of both cognitive and emotional experience. Compulsive grooming can, in contrast, readily be studied in mice; however, its relevance to OCD or even to trichotillomania can reasonably be questioned.

To date genetic studies of OCD and other disorders associated with compulsive behavior have not yielded highly penetrant disease-associated (or disease-causing) gene variants. Thus, development of animal models of these disorders with clear relevance to human disease remains a substantial challenge. Indeed, it is unclear whether the *Hoxb8* mutant mice studied by Chen et al. (2010) or the previously reported SAPAP3

mutant mice (Welch et al., 2007) share significant pathophysiological mechanisms with any disorders that produce compulsive behaviors in humans. However, these mutant mice should prove extremely useful as tools for neurobiological investigations. Analysis of *Hoxb8* mutant mice should help to illuminate such matters as the roles of different populations of microglia in the brain. Moreover, these mice could give rise to sorely needed new hypotheses about the mechanisms underlying human disorders characterized by compulsive behaviors. Although recent genetic animal models of disease have tended to move from the human to the mouse, it is equally important to find ways of following up in human patients on observations made originally in mutant mice. If we are to understand the basis of human neuropsychiatric disorders, we will need great ingenuity, and we will have to exploit unexpected findings from mutant mouse strains when they appear to be relevant to the human condition.

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Viral Houseguests Undertake Interior Redesign

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As part of their life cycle some single-stranded RNA viruses remodel host cytoplasmic membranes into specialized organelles. In this issue, Hsu et al. (2010) demonstrate how the viruses selectively co-opt host machinery to make this unique organelle, which has a lipid composition favorable to viral replication.

Viruses are obligatory intracellular parasites that depend on a living host for reproduction. They have continuously probed the machinery of the cell to find new ways of exploiting their hosts, ensuring their continued success and, as an unintended corollary, providing many insights into cellular function. There are over two thousand species of viruses, which are classified by the nature of their genomes. Among these groupings are the positive-sense single-stranded RNA (ssRNA) viruses whose genomes can be directly translated into proteins. This collection includes deadly pathogens that are threats to humans (for example, dengue virus, hepatitis C virus, and yellow fever virus), animals (foot-and-mouth disease virus), and plants (tobacco mosaic virus). Despite being highly divergent in genome organization, host range, and morphology, these RNA viruses share a common replication strategy—they remodel host cytoplasmic membranes into specialized organelles that foster their replication (Miller and Krijnse-Locker, 2008). In this issue, Hsu et al. (2010) reveal insight into how RNA viruses selectively recruit host factors to make a specialized organelle with a lipid composition that is favorable to virus replication.

These specialized virus-induced organelles can arise from endosomal or mitochondrial membranes but most commonly derive from membrane compartments of the secretory pathway, including the endoplasmic reticulum, Golgi, and trans-Golgi network (Figure 1; Miller and Krijnse-Locker, 2008). Although the exact function of these organelles remains speculative, the replication of positive-sense ssRNA viruses requires the targeting and anchoring of RNA-dependent RNA polymerase within their membranes. The specialized membranes may provide a stable microenvironment that facilitates viral RNA