This Week in The Journal

● Cellular/Molecular

Genetic Stimulation of Neurogenesis Mimics Antidepressants

Yun Li, Yanjiao Li, Renée M. McKay, Dieter Riethmacher, and Luis F. Parada

(see pages 3529–3539)

Many treatments that relieve depression in humans—e.g., exercise, electroconvulsive shock, and serotonin reuptake inhibitors—stimulate neurogenesis in the dentate gyrus and reduce behaviors that model aspects of depression in mice. Blocking neurogenesis prevents treatment-induced behavioral modifications. The treatments also increase expression of neurotrophic factors, which probably stimulate neurogenesis by activating the small GTPase Ras and downstream signaling. Li et al. underscore the role of this pathway in antidepressant effects by conditionally deleting neurofibromin (NF1), a molecule that inactivates Ras, in adult mouse neural progenitor cells (NPCs). After 6 months of *Nf1* ablation, NPC proliferation, neurogenesis, and neuronal maturation were elevated in the dentate subgranular zone, and mice were less hesitant to eat in a novel environment (a model of anxiety) and spent less time immobile in forced-swim and tail-suspension tests (models of despair). Furthermore, these mice were resistant to increased immobility during tail suspension normally produced by chronic mild stress.

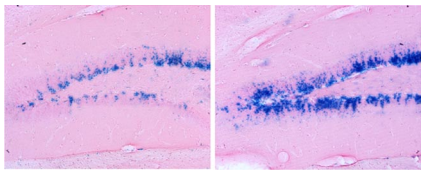
▲ Development/Plasticity/Repair

IGF2 Stimulates Neural Stem Cell Proliferation

Oliver Bracko, Tatjana Singer, Stefan Aigner, Marlen Knobloch, Beate Winner, et al.

(see pages 3376–3387)

Harnessing neurogenesis holds promise for treating neuropathological conditions besides depression (discussed above). Neurogenesis is reduced in mouse models of Alzheimer's, Parkinson's, and Huntington's diseases, and increased neurogenesis after seizures is thought to promote epileptogenesis. Many factors regulate neural stem cell



The number of NPCs and their progeny (blue) is larger in mice in which NF1 has been deleted from NPCs for 8 months (right), than in control mice (left). See the article by Li et al. for details.

(NSC) proliferation and differentiation, and a more complete knowledge of these factors should facilitate efforts to develop treatments. To this end, Bracko et al. identified genes that were differentially expressed in NSCs and immature neurons isolated from adult mouse dentate gyrus by fluorescence-activated cell sorting. One protein more highly expressed in NSCs was insulin-like growth factor 2 (IGF2), which has roles in cell proliferation during development. IGF2 was expressed in cultured NSCs and was downregulated upon differentiation. Knockdown of IGF2 reduced dentate NSC proliferation *in vitro* and *in vivo*. Additional results suggested that IGF2 promotes proliferation of NSCs in the adult dentate gyrus via the IGF1 receptor and downstream AKT signaling.

■ Behavioral/Systems/Cognitive

Merkel Cells Are Required for Texture Discrimination

Stephen M. Maricich, Kristin M. Morrison, Erin L. Mathes, and Brittany M. Brewer

(see pages 3296–3300)

Slowly adapting type 1 (SA1) mechanoreceptor afferents are sensitive to points, edges, and curvature. Mechanosensitive ion channels are present in the unmyelinated terminals of SA1 fibers, which densely innervate the skin. Each SA1 fiber is associated with numerous Merkel cells, which envelop the nerve terminals. Although Merkel cells produce numerous neuromodulators, they do not form obvious synapses with SA1 afferents, and their role in shaping SA1 activity is unclear. To address this question, Maricich et al. examined behavior in transgenic mice lacking Merkel cells. Surprisingly, despite similar densities of Merkel cells on foot surfaces, female, but not male, wild-type mice preferred rough to smooth floor surfaces. This preference was absent in females lacking Merkel cells, suggesting these cells are required for discriminating textures with the feet. Although mouse whisker follicles are also densely populated by Merkel cells, whisker-mediated texture discrimination appeared unaffected in transgenic mice, indicating that Merkel cells are not required for all texture perception.

♦ Neurobiology of Disease

Inhibiting ER Stress Response Attenuates α-Synucleinopathy

Emanuela Colla, Philippe Coune, Ying Liu, Olga Pletnikova, Juan C. Troncoso, et al.

(see pages 3306–3320)

Parkinson's disease (PD) is characterized by accumulation of α-synuclein in intracellular inclusions, but the relationship between this and degeneration of dopamine neurons is poorly understood. Impairment of several cellular processes, including the unfolded protein response (UPR), likely contributes to neurodegeneration. Membrane and secreted proteins are folded into their mature conformation in the endoplasmic reticulum (ER), guided by chaperone proteins. If the protein load exceeds the capacity of chaperones—for example, because synthesis of proteins prone to misfolding increases—misfolded proteins accumulate, causing ER stress and activation of the UPR. If ER stress continues, UPR programs trigger apoptosis. Colla et al. found that α-synuclein accumulated in ER of mice, and α-synucleinopathy produced by expressing a PD-linked form of α-synuclein was accompanied by activation of several UPR components. This increased cells' susceptibility to ER stress induced by other agents. A drug that inhibits the ER stress response reduced α-synuclein accumulation and slowed disease onset in mutant mice.