This Week in The Journal

β 1-Integrin Developmentally Required for Expectancy Updating

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(see pages 6644–6655)

Signaling molecules can play a critical role during development with far-reaching consequences, and then sometimes become dispensable in adulthood. Such is the case for β 1-integrin in the orbitofrontal cortex (OFC), a brain region that helps shape our responses to stimuli based on expectations, according to new work from DePoy, Shapiro, et al.

β 1-integrin is half of a protein complex that connects cytoskeletal signaling factors with the extracellular matrix, including at postsynaptic densities. The authors first knocked down expression of *Itgb1*, the gene encoding β 1-integrin, in neurons of the OFC by approximately a third in adolescent male mice [postnatal day (P)24] and then tested their behavior a month later. The mice learned to freeze in response to a tone paired with a foot-shock, similar to control mice. But when mice with reduced *Itgb1* expression heard the tone without the shock, they continued to freeze, suggesting an impairment in OFC-mediated conditioned fear extinction. The mice also showed deficits in learning in the context of a reward-related task. Finally, *Itgb1*-deficient OFC layer V excitatory neurons had fewer, shorter spines than did neurons in the same animals that were not affected by knockdown. In contrast, knockdown of *Itgb1* at P31 had no effect on reward-related responses or on dendritic spines.

The researchers next wanted to see how the loss of β 1-integrin affected OFC neurons' ability to process incoming information from prelimbic cortical areas, which is necessary to form memories linking actions and outcomes. They silenced *Itgb1* in the OFC in one hemisphere in early life. Later, during behavioral testing, they silenced prelimbic cortical neurons in the contralateral hemisphere, so that prelimbic neurons communicated only

with the β 1-integrin-deficient, ipsilateral OFC. The animals' behavior indicated that *Itgb1* was also required for processing of input from the prelimbic cortex that led to expectancy updating.

Surprisingly, knocking down *Itgb1* in the OFC of female mice at P24 had no effects on reward-related behaviors, but hippocampal knockdown impaired contextual fear memory. Because previous work suggested that estradiol-mediated activation of the neurotrophin receptor *trkB* boosted β 1-integrin-mediated signaling, the authors asked whether stimulating *trkB* in males might confer resilience against *Itgb1* deficiency. Indeed, treating *Itgb1*-deficient male mice with a *trkB* agonist rescued responses to reward. The work demonstrates a developmental role for β 1-integrin in the OFC that is key for updating expectations based on experience—behaviors that are needed well into adulthood.

Infographic depicting environmental enrichment-induced neurogenesis in hippocampus of mice expressing human wild-type PS1, including mature neurons (orange), neural stem cells (green), neuroblasts (red), progenitor cells (blue and purple), and microglia (yellow).

Microglia Mediate Deficits in Adult Neural Proliferation

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(see pages 6766–6780)

The proliferation and differentiation of hippocampal neural progenitor cells in adulthood contributes to emotional processing, learning, and memory, and exposure of mice to environmental enrichment increases proliferation of adult progenitor cells. Presenilins (PS) are linked

to early-onset forms of familial Alzheimer's disease (FAD) in humans, and PS1 regulates adult hippocampal neuron proliferation. Ortega-Martinez et al. previously observed that mice expressing FAD-linked mutant variants of PS1 did not display an environmental-enrichment-induced boost in neural proliferation. This week, the researchers wanted to determine the role of microglia, so they depleted the brains of mice almost entirely of this cell type by feeding mice an inhibitor (PLX5622) of the tyrosine kinase colony-stimulating factor 1 receptor (CSF1R), a microglial protein key to their proliferation and colonization of the brain. For 4 weeks, male mice ate a diet including PLX5622 or control diet, and then were housed either in standard housing or with environmental enrichment for an additional 4 weeks. Proliferation of adult hippocampal neurons (measured with BrdU) was similar between wild-type mice and those expressing FAD-linked PS1 variants housed in standard cages, but following exposure to environmental enrichment, wild-type mice showed increased neuronal proliferation compared with transgenic FAD mice. Importantly, however, mice with FAD-linked PS1 mutations that were fed PLX5622 showed no deficit in enrichment-induced proliferation. Microglial depletion with PLX5622 also rescued survival and differentiation of newborn neurons in the dentate gyrus of animals with FAD-PS1 variants.

In an effort to link the microglia-mediated deficits to behavior seen in Alzheimer's patients, the researchers measured anxiety-like behaviors in mice using a marble-burying task and by measuring the time mice spent in a dark versus light area of the cage. Mice expressing FAD-PS1 variants displayed higher baseline anxiety-like behaviors compared with wild-type mice under control conditions, a difference that widened further after environmental enrichment. FAD-PS1 mice fed PLX5622, however, were comparable to wild-type mice, suggesting that microglia also mediate some behavioral signs of FAD pathology.

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