



## Articles of Significant Interest Selected from This Issue by the Editors

### **L2hgdh Deficiency Causes Brain Defects**

L-2-Hydroxyglutarate aciduria (L-2-HGA) is an autosomal recessive neurometabolic disorder caused by a mutation in the L-2-hydroxyglutarate dehydrogenase gene (*L2HGDH*) and characterized by the accumulation of L-2-hydroxyglutarate (L-2-HG) in the body fluids. The progression of this disease is poorly understood. Ma et al. (e00492-16) generated *L2hgdh* knockout (KO) mice and observed a robust increase of L-2-HG levels in the brain and testis, which was accompanied by increased histone methylation. *L2hgdh* KO mice exhibit progressive leukoencephalopathy, impaired adult hippocampal neurogenesis, and late-onset neurodegeneration. These findings provide insights into how L-2-HG accumulation leads to L-2-HGA pathogenesis.

### **Deciphering the Role of FBXL5 during Brain Development**

FBXL5 (F box and leucine-rich repeat protein 5) mediates the degradation of iron regulatory proteins (IRPs) and is a key upstream regulator of intracellular iron levels. Yamauchi et al. (e00470-16) found that the loss of FBXL5 resulted in a progressive increase in the number of neural stem progenitor cells in the cerebral cortex of mouse embryos. The iron accumulation due to FBXL5 loss induced production of reactive oxygen species, which in turn activated signaling by the mammalian target of rapamycin (mTOR). The findings provide important new insight into the importance of iron homeostasis mediated by FBXL5 in the brain.

### **PP2A-B56 Prevents Autophosphorylation-Mediated Cyclin E Degradation**

The SCF<sup>Fbw7</sup> ubiquitin ligase targets cyclin E for degradation following cyclin E autophosphorylation at S384 by cyclin-dependent kinase 2 (CDK2). Davis et al. (e00657-16) investigated how cyclin E-CDK2 complexes—which have key roles in exit from quiescence and S-phase entry—can phosphorylate cell cycle proteins prior to initiating cyclin E destruction. They found that PP2A-B56 phosphatases dephosphorylate cyclin E specifically at S384. Additionally, preventing S384 dephosphorylation by PP2A-B56 knockdown decreases cyclin E kinase activity and half-life at the G<sub>1</sub>/S transition. Thus, cyclin E dephosphorylation counteracts its autocatalytic degradation during the portion of the cell cycle where its function is most important.

### **NDR1 Regulation of Kindlin-3 Controls High-Affinity LFA-1 Binding and Immune Synapse Organization**

LFA-1/ICAM-1 interactions play an important role in formation of the immune synapse (IS), a specialized adhesion structure between T cells and antigen-presenting cells. However, the dynamics and regulatory mechanism of adhesive interactions have been unclear. Kondo et al. (e00424-16) have established a novel method by which synaptic interactions of LFA-1/ICAM-1 can be measured at the single-molecule level and found that high-affinity binding occurred in a zone enriched for activated Rap1 and kindlin-3. The authors demonstrate that NDR1 activated by Rap1 signaling controls kindlin-3 recruitment to IS, which in turn mediates high-affinity binding and IS organization, resulting in antigen-triggered stopping and proliferation of T cells.

### Low Doses of Tumor Necrosis Factor Alpha Improve Osteogenesis by Modulating Gs-Coupled Receptor Signals

Daniele et al. (e00442-16) investigated the beneficial effects of the proinflammatory cytokine tumor necrosis factor alpha (TNF- $\alpha$ ) on mesenchymal stem cell (MSC) differentiation to osteoblasts. The effect of the cytokine was probed for modulation of expression/activity of the A<sub>2B</sub> adenosine receptor (A<sub>2B</sub>AR), a G-protein-coupled receptor (GPCR) that exerts anabolic effects on bone. Low TNF- $\alpha$  concentrations induced a prodifferentiating effect on MSCs and, by regulating GPCR-regulated kinase 2 turnover/expression, impaired A<sub>2B</sub>AR desensitization, increasing in turn the pro-osteogenic effects elicited by A<sub>2B</sub>AR agonists. Thus, receptor desensitization plays a pivotal role in osteogenesis, and its manipulation may be useful to favor bone remodeling.