This Week in The Journal

DREADDs Enable *In Vivo* Monitoring of Transplanted Cells

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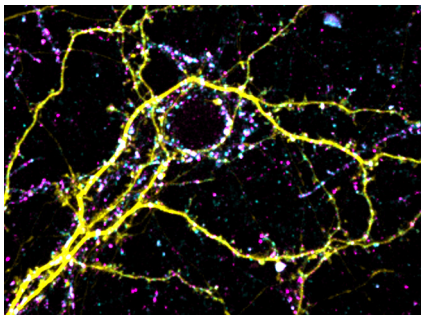
(see pages 11544–11558)

A major goal of neuroscience research is to develop treatments for neurodegenerative diseases and CNS injuries. Strategies for doing this include promoting growth of damaged or spared neurons and replacing damaged neurons with transplanted cells. The latter strategy includes the generation of neurons *in vitro* or *in situ* from pluripotent stem cells. Much progress has been made toward generating specific neuronal classes, and preclinical trials have shown promise for using these cells to treat Parkinson's disease and spinal cord injury. To further develop these treatments for clinical use, being able to monitor and control the function of transplanted cells *in vivo* would be helpful. Ji et al. achieved this by using designer receptors exclusively activated by designer drugs (DREADDs).

The authors first generated transgenic mice expressing the inhibitory DREADD hM4Di selectively in neurons. The mice were injected with the hM4Di-selective ligand CNO, which was labeled with ^{11}C. This allowed activation of hM4Di to be monitored with positron emission tomography (PET). In addition, hM4Di-mediated neuronal inhibition was monitored with arterial-spin-labeling perfusion magnetic resonance imaging (ASL-MRI), which detects activity-induced changes in cerebral blood flow.

Having verified that hM4Di could be localized and its activation could be monitored with PET and ASL-MRI, respectively, Ji et al. generated induced pluripotent stem cells (iPSCs) from mouse fibroblasts expressing hM4Di under control of a neuron-specific promoter. The cells were cultured to enhance production of neural precursor cells, which were transplanted into wild-type mouse hippocampus. ^{11}C-CNO binding measured by PET was at background levels 20 d after transplantation, but increased by 40 d, and remained elevated at 60 d after transplantation. Consistent with this, ASL-MRI detected no effect of ^{11}C-CNO 20 d after transplant, but showed decreased cerebral blood flow in the hippocampus 40 d after transplant. Postmortem immunolabeling of hippocampal sections containing transplanted cells confirmed that hM4Di was expressed in iPSC-derived neurons, but not in astrocytes, 40 d after transplantation.

These results demonstrate that expressing DREADDs in iPSCs under the control of a neuron-specific promoter allows the location, differentiation, and function of these cells to be monitored repeatedly over time with ^{11}C-CNO-based PET and ASL-MRI. This ability will help researchers optimize parameters to ensure long-term functional effectiveness of transplanted cells.



Differently labeled Aß oligomers (magenta and cyan) bound to overlapping sites in hippocampal dendrites (yellow). See Sinnen et al. for details.

Aß Oligomers Reduce Ca^{2+} Influx at Individual Spines

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(see pages 11532–11543)

Cognitive decline in Alzheimer's disease (AD) may begin with the accumulation of ß-amyloid (Aß) oligomers at synapses. Acute treatment of neurons with soluble Aß oligomers promotes long-term depression (LTD) and subsequent loss of dendritic spines. Although these effects require activation of NMDA receptors (NMDARs), the molecular mechanisms linking Aß oligomers to NMDAR-dependent LTD have been debated. While some studies suggest that Aß activates calcium influx through NMDARs containing GluN2B subunits, others suggest that Aß reduces calcium influx, and still others show that Aß promotes NMDAR internalization (Mota et al. 2014 Neuropharmacology 76:16).

To elucidate how Aß oligomers interact with NMDARs, Sinnen et al. added oligomers to cultured hippocampal neurons expressing the genetically encoded calcium indicator GCaMP6s. Before Aß treatment, spontaneous synaptic release events produced NMDAR-dependent calcium transients in most dendritic spines. Addition of Aß oligomers reduced the frequency and/or amplitude of these transients at ~63% of spines. These effects occurred at low concentrations (~40 pM) of Aß and saturated at concentrations well below those required for NMDAR internalization. Blocking NMDARs with magnesium or APV during oligomer exposure prevented the reduction in calcium transients. Moreover, the effects of oligomers were both mimicked and occluded by treatment with a selective blocker of GluN2B-containing NMDARs.

The greatest Aß-induced reduction in calcium transients occurred at synapses that had had the largest or most frequent transients before Aß exposure. In addition, the effect of Aß oligomers was significantly greater at synapses that bound Aß oligomers than at those that lacked such binding. The amplitude and frequency of calcium transients did not appear to influence Aß binding, however, and blocking neurotransmitter release at a subset of synapses did not prevent binding of Aß oligomers at those synapses. Aß oligomers applied at different times adhered to neurons in a largely overlapping pattern, suggesting the oligomers bound to specific sites.

These results suggest that at low concentrations, Aß oligomers bind to specific excitatory synapses, where they reduce NMDAR-dependent calcium influx. At higher concentrations, this binding leads to NMDAR internalization. Which—if either—of these mechanisms underlies cognitive impairment remains unclear. Identifying Aß binding partners might help answer this question and suggest new targets for preventing cognitive decline in AD.

This Week in The Journal was written by Teresa Esch, Ph.D.