NEUROSCIENCE

It's a material world

The assembly of polymers can be genetically targeted to specific neurons or other cells to manipulate their properties.

The chemical assembly of polymers such as hydrogels within tissues has been explored extensively in the tissue clearing field. However, in these hydrogel–tissue chemistry (HTC) approaches, "structures with new functionality are chemically synthesized everywhere within intact tissue," says Karl Deisseroth from Stanford University in California. "But in none of the many HTC methods is the construction of the new material genetically targeted to specific cells," says Deisseroth. Furthermore, HTC approaches are typically not applied to living samples.

To overcome these limitations, "I sat down with Zhenan Bao (now chair of Chemical Engineering at Stanford) and together we brainstormed ways to target chemical assembly of materials to specific cells," says Deisseroth. This genetically targeted chemical assembly (GTCA) could then be harnessed to deposit materials with useful properties in the targeted, living cells.

While the concept of GTCA is flexible, Deisseroth and his colleagues focused on biocompatible polymerization that can be triggered by the enzyme APEX2. Small-molecule precursors are perfused into the intact tissue and polymerized in the cells expressing APEX2 through oxidative radical cation polymerization. Using this approach, the researchers deposited, for example, polyaniline (PANI) or poly(3,3′-diaminobenzidine) (PDAB) into APEX2-expressing cells. Notably, neurons remained viable and healthy under the reaction conditions used for polymerization. However, "we did not test for long-term effects — only short-term/immediate effects — but […] there could be accumulating (and indeed possibly adverse) effects in the long run with ongoing production of the synthesized material," says Deisseroth.

The researchers monitored the functional effects of PANI or PDAB deposition in cultured rat hippocampal neurons using whole-cell patch-clamp electrophysiology. Consistent with the chemical properties of the polymers, PANI-containing neurons showed increased capacitance, which coincided with reduced action-potential firing after current injection. In contrast, PDAB-containing neurons showed reduced capacitance and therefore increased action-potential firing after current injection. Similar effects were seen in acute brain slices.

Genetically targeted chemical assembly (GTCA) of functional materials. Golden color illustrates deposition of functional polymer. Blue diamond particles represent monomers diffusing globally through the tissue, with polymerization enabled in targeted cells only. Credit: Yoon Seok Kim/Jia Liu/Ella Maru: Deisseroth/Bao laboratories, Stanford

Of note, optogenetic or pharmacological manipulation of ion channels can change other cellular membrane properties, but Deisseroth says that "membrane capacitance changes typically only happen with natural processes such as growth and myelination."

Finally, Deisseroth and his colleagues applied the methodology to living animals; in particular, *Caenorhabditis elegans*. They expressed APEX2 in pharyngeal muscle cells and obtained robust PANI polymerization upon administration of the small-molecule precursors. PANI deposition in the pharyngeal muscle reduced the muscle's contraction frequency, without affecting other bodily functions of the worms. Furthermore, PANI deposition in excitatory motor neurons impaired forward locomotion while PANI deposition in inhibitory motor neurons increased the reversal frequency. According to Deisseroth, there should be no fundamental barrier to rodent tissue GTCA, since the team has already achieved GTCA ex vivo in rodent brain slices.

Nina Vogt

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