Perfecting ChR2

Two new reports describe variants of channelrhodopsin 2 with improved properties.

Channelrhodopsin 2 (ChR2) has been a godsend tool to study brain function. This protein—originally found in tiny algae—is a membrane-ion channel that opens up in response to pulses of light, producing a change in the membrane potential of charged cells. Algae use ChR2 to signal the presence of light and trigger their swimming away or toward it in the pond; neuroscientists, after ‘transplanting’ ChR2 into neurons, use it to provoke light-triggered action potentials in cells embedded deep in brain tissue. Not surprisingly, some of ChR2’s natural properties are not exactly ideal for this purpose.

In particular, the channel’s small currents and slow kinetics still limit the potential applications of ChR2 in neuroscience. Improving these properties would enable researchers to more reliably induce action potentials (‘spikes’) in cells located farther away from the applied light source, use lower light powers to stimulate them or get away with weaker transgene expression. One way to improve ChR2’s performance is by mutagenesis. Although this strategy has already yielded several ChR2 variants that exhibit faster kinetics or larger currents, so far one thing has always come at the expense of the other.

The search for the ‘perfect ChR2’ continues in many laboratories around the world, and two independent teams have now reported several improved ChR2 variants. A joint three-laboratory team composed of the labs of Peter Hegemann at Humboldt University, Karl Deisseroth at Stanford University and Thomas Oertner at the Friedrich Miescher Institute have developed a ChR2(T159C) mutant, the ‘TC’ mutant, which, when expressed in neurons, elicits photocurrents almost twofold larger than those of wild-type ChR2. In nonneuronal cells, CatCh’s modest preference for calcium ions elicits approximately three times higher currents and a slight slowdown of its kinetics compared to wild-type ChR2. But surprisingly, when expressed in neurons, the group saw a nearly 70-fold increase in the cell’s light sensitivity and a surprisingly rapid and complete repolarization of its membrane after each spike.

Behind these properties, Bamberg explains, are the indirect effects triggered by the local increases in calcium produced by CatCh at the neuron’s membrane. “CatCh can be seen as a light-gated membrane-bound calcium source,” he says. For one, local increases in calcium result in the activation of voltage-gated sodium channels and result in the fact that you need much less light to get a depolarization event. Secondly, calcium activates channels that are responsible for the membrane’s repolarization, accelerating this process. CatCh could also be used to modulate calcium levels in subcellular compartments in response to light in any kind of cell.

One exciting lesson from these studies is the potential of combining mutations to refine the properties of channelrhodopsin, promising yet better tools to come for optogenetics.

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