Directed Evolution Of AAV Vectors That Undergo Retrograde Axonal Transport

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Technology description

Brain functions such as perception, cognition, and the control of movement depend on the coordinated action of large-scale neuronal networks, which are composed of local circuit modules that are linked together by long-range connections. Such long range connections are formed by specialized projection neurons that often comprise several intermingled classes, each projecting to a different downstream target within the network. Projection neurons have also been implicated in the spread of several neurodegenerative diseases. Selective targeting of projection neurons for transgene delivery is important both for gaining insights into brain function and for therapeutic intervention in neurodegenerative diseases.

Viral vectors constitute an important class of tools for introducing transgenes into specific neuronal populations, but their potential for biological investigation and gene therapy is hampered by excessive virulence. Other viruses can infect neurons when administered directly to the nervous system, with "pseudorabies", adenoviruses and lentiviruses used most commonly in animal research. However, these viruses mediate only modest levels of transgene expression, have potential for toxicity, and are currently not easily scalable for clinical or large animal studies. Recombinant adeno-associated viruses (rAAVs) are an effective platform forin vivogene therapy, as they mediate high-level transgene expression, are non-toxic, and evoke minimal immune responses. rAAVs have allowed retrograde access to projection neurons, but their natural propensity for retrograde transport is low, hampering efforts to address the role of projection neurons in circuit computations or disease progression.

UCB and HHMI researchers have produced a new rAAV variant (rAAV2-retro) that permits robust retrograde access to projection neurons with efficiency comparable to classical synthetic retrograde labeling reagents. The rAAV2-retro gene delivery system can be used on its own or in conjunction with Cre recombinase driver lines to achieve long-term, high-level transgene expression that is sufficient for effective functional interrogation of neural circuit function, as well as for CRISPR/Cas9-mediated and other genome editing in targeted neuronal populations. As such, this designer variant of adeno-associated virus allows for efficient mapping, monitoring, and manipulation of projection neurons.

Application area

Gene therapy, including the treatment of neurodegenerative disorders characterized by pathological spread through functionally connected and highly distributed networks.

Advantages

AAV can be endowed with robust retrograde functionality through directed evolution
Up to two orders of magnitude increase in retrograde transport over existing variants
Efficiency comparable to synthetic tracers in many circuits
Payload expression levels are sufficient for circuit interrogation and gene manipulation

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