Targeting cell types with gene therapy vectors for therapy

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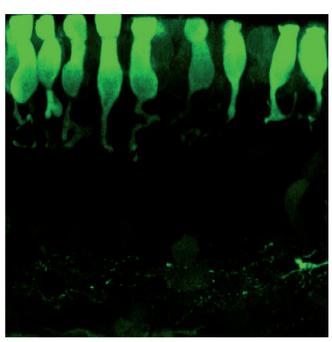
Targeting genes to specific neuronal or glial cell types could be essential in making gene therapies for the eye, or indeed for other neural systems in the brain or elsewhere. Adeno-associated viral vectors (AAVs) are the most promising approach for delivering gene therapy into the retina or the brain, but targeting expression to specific cell types is a challenge. If such therapies are not targeted to specific cell types, it is possible that they will be ineffective or even harmful.

At the core of cell targeting specificity is a DNA control element – promoter or enhancer – that when embedded into the AAV genome drives transgene expression in a cell-specific fashion.

An international team led by IOB scientists have created a library of 230 AAVs, each with a different synthetic promoter designed using four independent strategies. First, AAVs were tested for cell-type-specific expression in the eyes of mice. Next, a subset was analyzed in mouse brain and in the eyes of non-human primates. Finally, the library was tested in human post-mortem retinas. Remarkably, scientists identified a collection of AAVs that specifically targeted gene expression to neuronal and glial cell types in the mouse retina and brain, as well as in non-human primate and human retinas. The cell-type-specific AAVs target many retinal cell types or classes, including the photoreceptors, pigmented epithelium cells and ganglion cells affected in human blinding diseases like macular degeneration, retinitis pigmentosa and glaucoma.



Human cone photoreceptors targeted by specific AAV

In basic research, genetic labeling allows the isolation and molecular characterization of neuronal or glial cell types. Genetically encoded sensors and electrical recording targeted to neuronal cell types allow monitoring of activity; cell-type-targeted optogenetic or chemogenetic tools permit modulation of this activity. Using cell-type specific AAVs, the team demonstrated applications for recording, stimulation, and molecular characterization of targeted cells.

Furthermore, the scientists invented an approach using combinations of AAVs to target individual cell types that could not be marked by any one AAV alone. In addition, they successfully targeted particular sets of cells by using more than one AAV. This strategy may be used to analyze connectivity across different neuronal cell types.

The results demonstrate that different neuronal and glial cell types of mice, non-human primates, and humans can be efficiently targeted using AAVs. These resources and methods provide economic, fast, and efficient cell-type targeting in a variety of species, both for fundamental science and for the gene therapy of cell-type-specific human blinding diseases.