Gene Therapy Untangles the Problem of Chronic Traumatic Encephalopathy

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CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE) is a common, progressive neurodegenerative disease occurring following significant and/or recurrent traumatic brain injury (TBI). The syndrome of chronic, progressive neurologic deficit as a result of recurrent TBI has been observed by clinicians for more than a century among prize fighters, in whom it was called dementia pugilistica or the “punch drunk syndrome.” Furthermore, repeated trauma has been postulated as a contributor to other specific neurodegenerative conditions, such as Parkinson’s disease and amyotrophic lateral sclerosis. The recent recognition of CTE in young people engaging in football or other contact sports and in U.S. war veterans returning from Iraq and Afghanistan has sharply increased interest in this condition. This represents a large group of otherwise healthy young people who may be at risk for this debilitating disorder.

A number of lines of evidence suggest that the accumulation of phosphorylated tau protein (pTau) is an important step in the pathogenesis of CTE. The accumulation of pTau is associated with the formation of neurofibrillary tangles, which are distinctive intracytoplasmic structures visible within neurons on neuropathologic examination of the brain, seen in a number of neurodegenerative conditions. In Alzheimer’s disease, pTau-related tangles are prominent. In that case, these occur in association with extracellular accumulations of an abnormal form of beta amyloid (A-beta amyloid plaques). In contrast, pTau tangles occur independently of amyloid plaques. CTE is only one of several conditions associated with pTau accumulation. As a group, these conditions are called tauopathies. There is evidence that the abnormal pTau accumulation can be self-propagating in a prion-like fashion, and that this progressive cascade can be interrupted by binding of pTau with anti-pTau antibodies. One major barrier to monoclonal antibody therapy for neurodegenerative disorders is the relatively poor penetration of antibodies through the blood–brain barrier (BBB) when given by intravenous or subcutaneous administration.

In this issue, Sacramento et al. in the laboratory of Dr. Ronald Crystal report utilizing a recombinant adeno-associated virus (rAAV) serotype rh10 (rAAVrh10) vector to deliver a vectored version of each of four different anti-pTau monoclonal antibodies directly to the central nervous system (CNS) in a mouse model of TBI and CTE. rAAVrh10-anti-pTau vectors were injected bilaterally into the hippocampus (5 x 10^10 genome copies per side) of mice who 3 weeks earlier had completed a series of stereotactic impacts designed to create a reproducible TBI and CTE lasting up to 6 months after the impacts. This model has previously been shown to lead to the progressive development of pTau-positive neurofibrillary tangles. Animals treated with two of the rAAVrh10-anti-pTau vectors, those expressing the IPN or PHF1 antibodies, showed a reduction in pTau protein by Western blot and by immunostaining and a reduction of neurofibrillary tangles compared to untreated or empty vector controls. This enhanced clearance of pTau was seen throughout the brain and was not associated with any detectable vector-associated pathology. The other two anti-pTau antibody vectors did not exert a detectable effect on pTau accumulation.

These findings suggest that direct CNS injection of rAAVrh10-anti-pTau can effectively reduce pTau after a single injection. This, in turn, suggests that rAAVrh10-anti-pTau may be a viable therapy for CTE in humans. Interestingly, the use of direct CNS injection of rAAV to deliver a vectored antibody enables one to bypass the BBB effectively and to do so in a fashion that is long lived. In the same vein, direct CNS injection has also been used to treat neurogenetic disorders. However, in those cases, an even distribution of the transgene product is quite difficult to achieve. This is much less of an issue with secreted transgene products, such as vectored antibodies, which are not cell autonomous and so do not have to reach the majority of neurons in order to exert their anti-tau effect.

An effective therapy for CTE with a rAAV-based CNS gene therapy would represent a remarkable achievement.
for this disorder, which currently can only be treated with supportive measures. It may also represent a generalizable advance in therapy for tauopathies and other progressive neurodegenerative diseases, such as Alzheimer’s disease and Parkinson’s disease. Future investment in this extremely promising platform would seem to be warranted.

REFERENCES


