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Alzheimer's Disease

Reducing the burden with ApoE2

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A new approach to gene therapy for Alzheimer's disease (AD), recently published in PNAS, shows efficacy in prevention and promises reversal in an animal model of the disease.[1]

AD is a devastating, progressive, and age-related neurologic disorder for which no effective therapies exist. Studies of the pathogenesis of AD have increasingly focused on the accumulation of the peptide known as Aβ. Aβ fragments of 40 or 42 amino acids collect in the extraneuronal space when β- and γ-secretases sequentially proteolyse the amyloid precursor protein (APP).[2,3] Here, they undergo progressive assembly into oligomers, protofibrils, fibrils, and ultimately senile plaques.[4–6] Growing evidence implicates the oligomeric Aβ forms as the mediator of neuronal dysfunction. Synaptic failure appears to be an early and perhaps reversible phase of AD and as such warrants attention in efforts to develop therapeutic strategies that might halt the progression of the disease.[7]

AD occurs in two forms: the relatively rare and highly penetrant familial forms (FAD), which are caused by mutations in APP or the presenilin (PS1) component of the γ-secretase, and the more prevalent late onset form (LOAD). An allele of the gene that encodes apolipoprotein E confers genetic vulnerability for LOAD. Three alleles, E2, E3, and E4, which only differ by a few amino-acid residues, occur within human populations. While insufficient to cause AD, individuals harboring the ApoE4 allele are at increased risk for disease development.[8,9] ApoE participates in peripheral cholesterol clearance; however, in the CNS it appears to have additional functions, including facilitating the metabolism of pathogenic Aβ forms. In this regard, ApoE2 and 4 appear, respectively, most and least effective forms of the protein. This observation suggests that enhancing the activity of ApoE2 might diminish Aβ levels and attendant pathogenic plaques.

In the new study, Jean-Cosme Dodart and co-workers exploited this concept through the development of lentiviral vectors to transduce the different allelic forms of ApoE. Their experimental system used an Alzheimer's mouse model that harbors a human FAD APP mutant transgene. In this mouse APP is expressed ubiquitously, which leads to CNS accumulation of pathogenic Aβ forms and the concomitant cognitive deficits. CNS gene transfer produces localized expression of the transduced gene product, so the investigators directed their attention to the hippocampal formation, which is always involved in AD.

The authors separately transferred each of the ApoE alleles and a control vector (expressing eGFP) into the hippocampal CA3 regions of AD model mice. These experiments allowed them to identify several interesting patterns. First, in the absence of the mouse endogenous ApoE gene, transfer of ApoE4 into older (11–12 months) mice accelerated disease pathogenesis, a pattern that is consistent with an ApoE4 role in LOAD vulnerability. Second, gene transfer of ApoE2 into middle-aged mice with an endogenous ApoE gene attenuated Aβ deposition and burden. Third, unexpectedly, lentiviral vector delivery irrespective of transduced gene resulted in neuron loss within the hippocampus and an adjacent region, the dentate gyrus. This concerning observation propelled an additional study of gene transfer into another hippocampal region, CA1. This experiment, also performed in PDAPP mice that harbor the murine ApoE gene, revealed no neuron loss and indicated that lentivirus vector delivery of only ApoE2 tended to reduce amyloid burden.

This study, while a proof-of-concept, does not address several key issues that bear on the potential for the treatment of AD. Among these is the fact that although the disease starts to develop in a small region of the CNS, it progresses to involve multiple brain regions. Given this an extensive CNS gene transfer strategy, which is likely to be neurosurgically challenging, might be a more appropriate one for AD. However, if localized ApoE2 gene transfer produces more widespread Aβ reduction, then the question of whether such an extensive strategy is required might be moot.

Another issue that needs to be addressed is the effect of the endogenous ApoE status of the subject. At present we do not know whether ApoE2 gene transfer will mitigate the action of an endogenous ApoE4 allele. Without any evidence that gene transfer of ApoE2 can counteract the negative effect of endogenous ApoE4 alleles, it is possible that this approach might only be applicable to those individuals that harbor an ApoE3 allele. Moreover, it is not clear whether increased or supraphysiologic levels of ApoE2 can provide benefit in ApoE2 subjects and whether increased levels will have deleterious consequences. Finally, the mechanism(s) that underlie lentivirus vector mediated cell death must be characterized and all efforts made to eliminate this show-stopping activity.

Of the demographically important diseases, none appear to have a more pervasive and dire societal impact than AD. Consequently, it is of paramount importance that new and effective strategies are sought to alter the natural history of disease progression. Whether CNS gene transfer such as that described by Dodart and co-workers will truly offer this possibility remains uncertain. However, their important observations pertaining to ApoE functioning in the adult CNS further underscore its importance as an AD target. ■

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