TWO IS BETTER THAN ONE: COMBINATION GENE THERAPY

Gene therapy, by definition, is the replacement of a malfunctioning or missing gene to correct a genetic disease. While several gene therapies have been approved for monogenic diseases, therapies targeting more complex polygenic diseases pose challenges. For example, if the expression of a specific ligand is downregulated in the disease state, simply increasing ligand expression via a gene vector may not be sufficient to ameliorate the disease if receptor expression is also downregulated due to low intrinsic ligand expression. In other words, correcting a single gene deficiency is likely not sufficient to reverse or improve the disease state if multiple genes are involved. Recently, groups from Cambridge University and University of Melbourne published a proof-of-concept paper[1] where they successfully demonstrated gene expression of 2 genes delivered using a single adeno-associated virus (AAV).

While a combination gene therapy approach has been published before[2], it has utilized individual vectors to deliver each gene. A study from George Church's lab showed that a combination of 3 genes associated with increasing longevity - FGF21, αKlotho and soluble TGFβ receptor2 - had a positive impact on 4 age related diseases including obesity, type 2 diabetes, heart failure and renal failure. Systemic delivery of AAVs singly or in various combinations showed a positive effect on all 4 disease models. The combination of TGFβ receptor2 and FGF21 expression showed synergistic improvement of therapeutic efficacy in all 4 diseases, but the combination of FGF21 and αKlotho had a negative effect on the renal and heart failure disease models. This interesting finding suggests that designing gene combinations should be done carefully and validated in preclinical models for synergy. Nevertheless, the study by Davidsohn *et al.* highlight a new approach to gene therapy for polygenic diseases but this approach has some limitation including differences in expression level of the individual genes that are under the control of different promoters and concerns with viral burden.

The recent work from Khatib *et al.* has advanced combination gene therapy by combining expression of 2 genes in a single viral vector under the control of one promoter - BDNF or brain derived neurotrophic factor and its receptor TrkB. The two open reading frames are separated by a viral 2A peptide that is cleaved by the host cell machinery resulting in the expression of both genes in the same cell and at similar expression levels. This novel viral vector was tested in 2 animal models of disease – experimental glaucoma and tauopathy. Glaucoma is an optic neuropathy that causes optic nerve damage so the glaucoma phenotype was induced via injury to the optic nerve. The increased expression of both BDNF and TrkB was shown to improve axonal transport along the optic nerve compared to single expression of each gene and there was improved vision suggesting that this combination gene therapy could potentially restore vision loss due to glaucoma.

There have been reports that showed correlation in amyloid-related pathology in the eye and brain so the effect of improved axonal transport along the optic nerve was tested in the P301S mouse model of tauopathy measured by measurement of improvement of short-term and long-term memory. The study showed moderate increase in short-term memory after AAV administration but no significant change in long-term memory.

It is clear that combination gene therapies have the potential to improve gene therapy and there are signs of pharma interest in this area. The group from Cambridge University spun out a company called Quethera that is focused on the next generation of combination gene therapies. Astellas recently acquired Quethera in a deal valued at up to $109M[3, 4] suggesting that combination gene therapies for polygenic diseases is the next frontier of gene therapy development.

References:

[1] Khatib *et al.* Receptor-ligand supplementation via a self-cleaving 2A peptide–based gene therapy promotes CNS axonal transport with functional recovery Science Advances 31 Mar 2021: Vol. 7, no. 14, eabd2590.
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