Gene therapy strategies for Alzheimer Disease

INTRODUCTION

Alzheimer Disease is the neurodegenerative disorder with the highest prevalence, mostly present in elders. The neuronal degeneration and loss of synapses progresses over time spreading through the brain.

There are TWO main pathways that cause Alzheimer disease:

Degeneration of cholinergic neurons
Accumulation of extracellular insoluble aggregates composed by amyloid-β peptide (Aβ)

AMYLOID-β PEPTIDE AGGREGATION

Its production originates from the amyloid precursor protein (APP) through γ-secretase processing (Fig. 2).

Amyloid-β oligomers increase the neurons glutamate, leading to toxicity and posterior denervation (Fig. 1).

CHOLINERGIC NEURONS DEGENERATION

The cholinergic neurons are nerve growth factor (NGF) dependent, establishing its survival and synopsis formation through axonal stimulation.

There is a correlation between the aging and the reduction in the concentration of NGF and the efficiency of its signalling pathway.

There is a loss of synopsis present in the ascendant cholinergic projections from the nucleus basalis of Meynert to the hippocampus and neocortex.

This is followed by the loss of NGF producer neurons, and a decrease in the neuronal activity.

siRNA AND NEPRILYSIN GENE THERAPY

The delivery of siRNA against APP mRNA forms a silencing complex that induces its cleavage. However, it might effect on the physiological role of APP.

Neprilisin on the other hand, is an endopeptidase that cleaves peptides of 4-5 kDa, including the amyloid-β peptide.

Both experiments expressing neprilisin and siRNA against APP confirmed that recombiant gene therapy vectors successfully decreased the levels of amyloid-β peptide in vitro and in vivo conditions.

NGF GENE THERAPY

After the treatment, the patients showed a median reduction in the decline of the score in both tests, MMSE and ADAS-Cog.

Interestingly, some subjects not only stopped the degeneration in the early stages after treatment, but also showed an improvement.

CONCLUSION

However, none of the gene therapy techniques successfully showed a fully recovery and functional restoration of the impaired brain areas, the cease in the deterioration of cholinergic neurons as well as β-amyloid plaques elimination could bring symptomatic mitigation and also stop the development of Alzheimer disease.

Further studies are needed to clear the remaining uncertain molecular pathways involved in Alzheimer’s in order to enable the development of innovative gene based therapies.

REFERENCES

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