Targeting microRNA-485-3p blocks Alzheimer's disease progression

Poster

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INDRODUCTION

Alzheimer's disease (AD) is a form of dementia characterized by progressive memory decline and cognitive dysfunction, which affects more than 44 million people worldwide. Currently, there is no effective therapy for AD despite its increasing global incidence; thus, effective treatment strategies for AD are urgently needed. While several drugs that decrease amyloid beta (Aβ) production or increase Aβ clearance in the brain have been identified, treatment with these drugs is poorly correlated with improvements in AD severity and cognitive dysfunction.

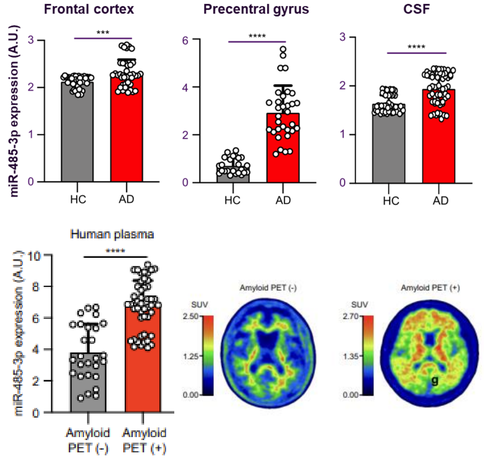
METHODS

Expression of miR-485-3p was analyzed by real-time PCR in the human frontal cortex (8 healthy controls (HC), 7 AD patients), precentral gyrus (6 HC, 8 AD), cerebrospinal fluid (CSF) (6 HC, 7 AD), plasma exosomes (10 HC, 17 mild cognitive impairment (MCI), 12 AD). Aβ 1–42 plaque immunofluorescence and tau pathology were imaged in primary cultured mouse neurons after lentivirus-derived miR485-3p transduction. MiR-485-3p antisense oligonucleotide (ASO, 1.5 μg) or control oligonucleotide formulated with the in vivo jetPEI reagent was injected into 8-month-old 5XFAD mice by ICV injection once weekly for two weeks. Behavioral tests were performed at 8 months and their brain pathology was examined after 8-week-washout at 10 months.

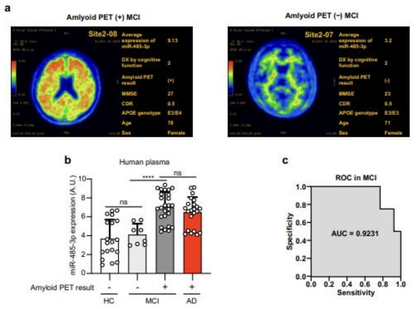
RESULTS

1) AD biomarker (miR-485-3p)

• Expression in human brain and peripheral tissues



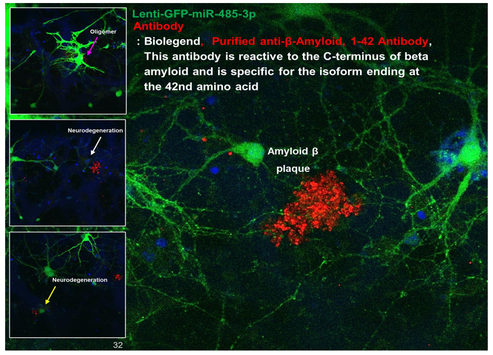
• miR-485-3p expression is upregulated in positive Aβ PET MCI patients compared to that in negative Aβ PET MCI patients.



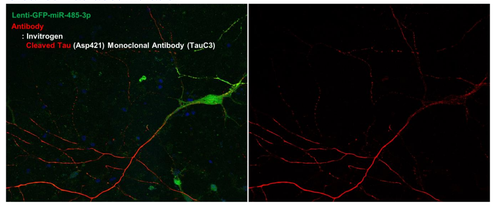
2) miR-485-3p pathophysiological role

• miR-485-3p induces AD pathology

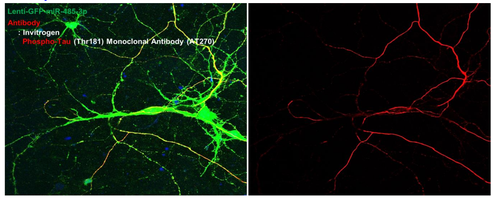
Aβ plaque production (Amyloidogenic pathway)



Cleaved-Tau accumulation

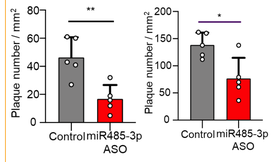


Phospho-Tau accumulation

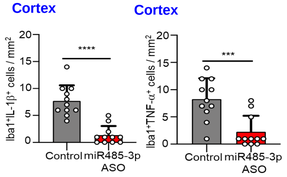


3) ASO (Antisense-oligonucleotide) as a therapeutic potential in AD (5XFAD)

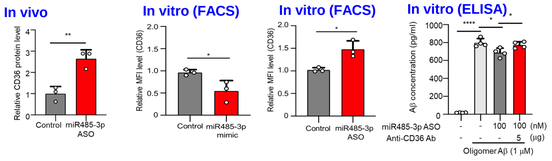
• miR-485-3p ASO reduces Aβ plaque



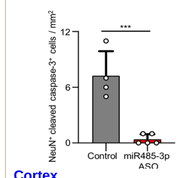
• miR-485-3p ASO reduces neuroinflammation

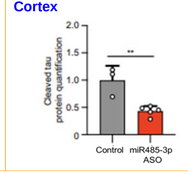


• miR-485-3p ASO enhances phagocytosis of Aβ by regulation of CD36 in vitro and in vivo.

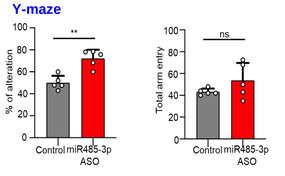


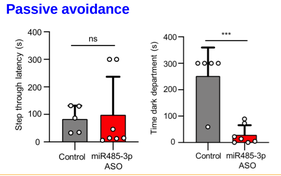
• miR-485-3p ASO reduces apoptosis and truncated tau





• miR-485-3p ASO rescues cognitive impairment





CONCLUSION

We found that miR-485-3p was overexpressed in brain tissues and CSF of AD patients, and the therapeutic ASO reduced Aβ plaques, tau pathology, neuroinflammation (cytokines, IL-1β and TNF-α), and eventually relieved cognitive impairment in a transgenic mouse model of AD. Mechanistically, the ASO enhanced Aβ clearance via CD36-mediated phagocytosis of Aβ *in vitro* and *in vivo*. We found that the ASO reduced apoptosis, which effectively decreased truncated tau levels. Collectively, our findings suggest that miR-485-3p is a useful biomarker as well as a causative factor of the inflammatory pathophysiology in AD. Furthermore, the ASO represents a therapeutic candidate for AD pathology and cognitive decline, establishing a new paradigm in the AD field.

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