Healthcare Innovations
How practice has changed

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Overcoming the blood-brain barrier with focused ultrasound to improve therapeutic antibody delivery in neurodegenerative diseases.

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Introduction

The blood-brain barrier (BBB) is formed by brain endothelial cells in every vessel of the brain (Fig. 1.). It protects the brain from harmful molecules, but also limits drug delivery in neurodegenerative disorders, including Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS).

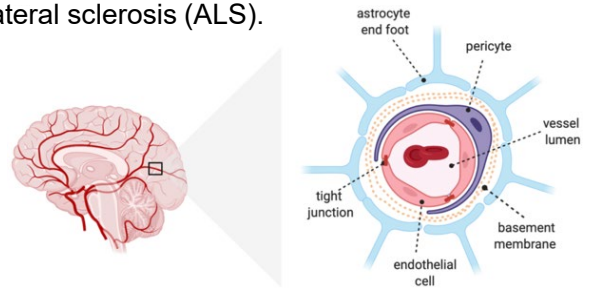

Fig. 1. The cellular architecture of the blood-brain barrier.

Recently, the application of focused ultrasound (FUS) emerged as a method of transient and reversible BBB opening. However, detailed understanding of the mechanisms of FUS-mediated human-BBB opening and its secondary effects is still urgently needed to ensure safety of long-term application in patients, and to induce improved drug delivery into the human brain.

Methods

Human induced pluripotent stem cell (hiPSC) obtained from familial AD patients carrying *presenilin-1* (*PSEN1)* mutation, sporadic AD patients carrying the apolipoprotein (*APOE*) *E4* allele and ALS patients carrying *C9orf72* mutation were used to generate brain endothelial-like cells (iBEC) and develop patient-derived *in vitro* AD and ALS BBB models (Fig. 2).

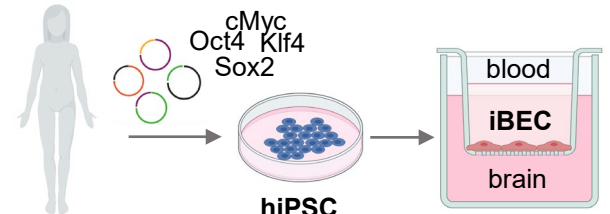

Fig. 2. Generation of *in vitro* BBB model.

FUS was applied with microbubbles (MB) to induce BBB opening *in vitro* (Fig. 4). Permeability of therapeutic antibody Aduhelm™ (α-amyloid antibody) and α-TDP-43 antibody through AD and ALS iBEC monolayer was evaluated.

Results

AD and ALS hiPSC were differentiated into iBEC expressing BEC-characteristic markers (Fig. 3).

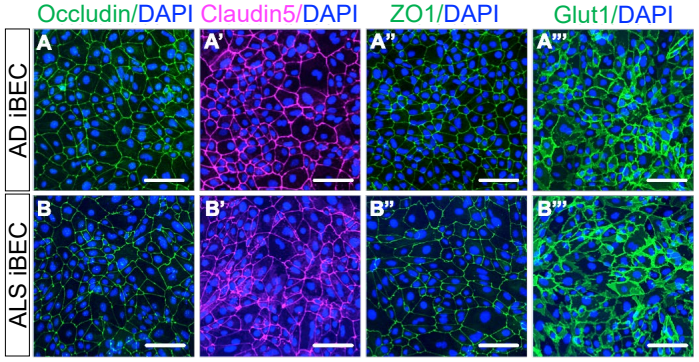

Fig 3. Expression of brain-endothelial cell markers in AD and ALS iBEC monolayer.

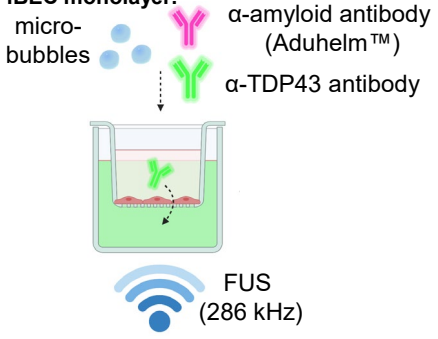

Fig. 4. Schematic of *in vitro* antibody delivery.

FUS-mediated iBEC monolayer opening resulted in improved antibody delivery in familial and sporadic AD, as well as in ALS BBB models (Fig. 5).

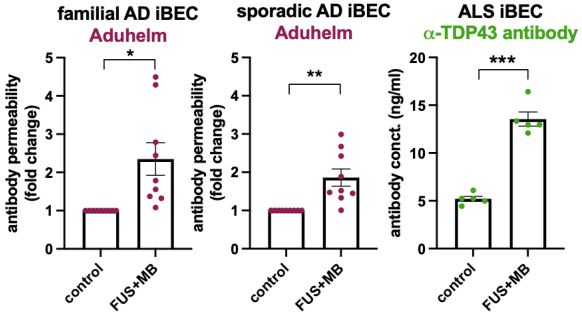

Fig 5. Improved therapeutic antibody delivery in AD and ALS iBEC using FUS+MB.

Conclusions

- hiPSC can be used to generate patient-derived AD and ALS *in vitro* BBB models and study drug delivery
- application of FUS with MB may transiently increase the permeability of the human BBB *in vitro,* leading to increased penetration of therapeutic antibodies, including recently FDA-approved α-amyloid antibody Aduhelm™
- FUS+MB can be used as a non-invasive method of improved drug delivery in neurodegenerative diseases

Fig 1,2 and 4 were created with Biorender.com

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