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Multi-physics physiological human brain models for elucidating mechanisms in Alzheimer's disease

Alzheimer's disease (AD), the prevalent age-related dementia, has emerged as a critical societal challenge, with over 6 million patents in the US alone. Despite urgent demands for effective treatments, our understanding of AD remains limited partially due to restricted access to human brain tissue, poor translational reliability of animal models, and the lack of physiologically relevant in vitro systems. A major challenge in replicating the human brain in vitro is the intricate interplay of brain vasculature, particularly the blood-brain barrier (BBB) and meningeal lymphatics (ML). These structures form a highly selective entry-exit system regulating brain metabolism, including the clearance of toxic molecules such as amyloid-β (Aβ) peptides, a hallmark of AD pathology. Emerging evidence underscores the role of BBB dysfunction and ML disruption in AD progression. However, the dynamic interactions among neurons, the BBB, and ML, as well as fluid transport pathways across these systems, remain poorly understood. Existing in vitro models often lack the three-dimensional (3D) complexity or vascularized ML systems needed to accurately recapitulate human brain physiology.

To address this gap, we developed multi-physics 3D in vitro human brain models within microfluidic devices that replicate physiologically relevant tissue structures and functions. These models feature in a single device perfusable BBB networks and ML-like vessels that sprout toward neurovascular networks, mimicking in vivo interactions. We use this model to show that human neural progenitor cell (NPC)-derived cultures establish an AD environment with Aβ deposition, enabling the study of hallmark AD pathologies such as BBB integrity loss and impaired ML drainage. Our quantitative analyses reveal changes in Aβ deposition, BBB permeability, vessel stability, and ML drainage, shedding light on the role of the BBB-ML system in AD. Furthermore, mechanosensitive pathways, including Piezo1, are implicated in vascular dysfunction, identifying novel therapeutic targets. This model is the first to integrate perfusable BBB networks, lymphatic systems, and AD neurons in a unified platform, offering

a powerful tool for investigating AD pathophysiology and accelerating drug discovery. Ongoing studies aim to uncover molecular and cellular mechanisms, identify biomarkers, and drive therapeutic development. Beyond AD, this versatile platform holds promise for studying a range of brain-related diseases, advancing both basic and translational research