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Organoid-engineered neurovascular units for drug discovery and neurodegeneration research

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Abstract

The highly selective permeability of the human blood-brain barrier presents a major obstacle to neurological disease modeling. Established 2D cell cultures and animal models are unable to accurately reproduce the physiological and molecular features of the human blood-brain barrier, limiting the translation of bench to bedside. Recent advances in the use of human induced pluripotent stem cells and organoid engineering have enabled the development of more physiologically relevant *in vitro* brain models for studying blood-brain barrier function. Blood-brain barrier organoids, mimic key structural and functional features of the blood-brain barrier. Moreover, integration of blood brain barrier organoids with brain organoids or microphysiological systems allows the formation of functional neurovascular units that better represent *in vivo* conditions. The development of scalable, reproducible, and partially vascularized blood-brain barrier organoid models holds promise for high-throughput drug discovery platforms, and the development of personalized therapeutic strategies for central nervous system disorders.

Keywords: Blood–brain barrier (BBB) models, Drug screening, Brain organoids, Human Stem cell–derived organoids, Precision medicine, Neurovascular modeling, BBB permeability assays, Translational neuroscience

Introduction

The human blood-brain barrier (hBBB) is a highly specialized and complex structure that precisely regulates the transport of chemicals and therapeutic compounds within the central nervous system (CNS).[1] It consists of endothelial cells, pericytes, the capillary basement membrane, and astrocyte end-feet, which together protect the brain from toxins, remove harmful substances, and supply essential nutrients to neural tissue. Proper functioning of this barrier is essential for maintaining homeostasis and normal physical functions of the central nervous system. The regulatory and selective nature of the BBB is so precise that most drugs, especially large molecules and biopharmaceuticals, are unable to efficiently cross the BBB and reach their therapeutic targets in the brain.[2] Despite significant advances in the understanding of the cellular and molecular structure of this barrier and the elucidation of the role of its dysfunction in the pathophysiology of diseases such as brain metastases and neurological disorders, effective drug delivery to the central nervous system remains a major challenge for the treatment of CNS disorders.[3]

Despite the critical physiological role of the BBB, no reliable and reproducible laboratory model has been developed to accurately recapitulate the development and function of the hBBB. The molecular profile and functional characteristics of the human BBB differ significantly from those of rodent models, and several lines of evidence have shown that drug permeability across the human BBB is greater than that of the mouse BBB.[4]

Significant differences in human blood-brain barrier and animal models permeability to drugs may contribute to the high failure rate of CNS drugs in clinical trials.[5] These issues highlight the urgent need to develop human-relevant BBB models to advance translational and applied research. The emergence of induced pluripotent stem cell (iPSC)-derived models, along with three-dimensional (3D) culture systems, has been a major milestone in overcoming the limitations of traditional two-dimensional (2D) and animal models. Models derived from iPSCs, which are capable of differentiating into brain endothelial-like cells, allow for the investigation of molecular permeability and the study of BBB dysfunction caused by genetic abnormalities.[6]

These models use a simple approach to recreate a neuro-vascular interface, often employing microfluidic devices, hydrogel, and transwell inserts.[7,8] Nevertheless, they are not ideal for modelling a fully functional BBB due to differences in differentiation trajectories that are relevant during development. Since human neurovascular

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development takes place in a 3D environment, creating precise and accurate 3D models of the hBBB that accurately capture this complex system could significantly advance CNS drug development.

Organoids are 3D, self-organizing cell aggregates that can be generated either directly from patient- derived tissues or by applying principles of developmental biology. These structures recapitulate key features of various organs from which they are derived.[9]

Development of functional BBB organoids is essential for creating a truly biomimetic platform for drug discovery and disease models. To accurately represent the blood- tissue interface the inclusion of vascular networks capable of perfusion is critical. Consequently, a natural progression in organoid research has been the development of BBB organoids designed to integrate into brain organoids.[3] Recent progress in development of BBB organoids have provided promising platforms for preclinical drug evaluation.[10] BBB organoids are generated by co-culturing endothelial cells, pericytes and astrocytes in a low attachment environment. These organoids recapitulate several key characteristics of the BBB, such as the presence of tight junctions, molecular transporters and drug efflux pumps, thereby providing a relevant model for studying drug transport across the BBB. The BBB organoid platform provides a reliable, adaptable, and cost-efficient *in vitro* system. Its compatibility with high-throughput systems makes it a valuable tool for modeling the BBB, potentially accelerating the development of therapies for a range of neurological disorders.[11]

Several research groups have developed a novel self-organized organoid- based human BBB using brain endothelial cells, pericytes and astrocytes. These 3D systems support direct interactions between different cell types without the use of synthetic membranes or scaffolds and successfully reproduce essential structural and functional characteristics of BBB- such as the formation of tight junctions, the expression and activity of efflux transporters moving forward, *in vivo* BBB research, the generation, handling, and characterization of these organoids still demand considerable manual effort. Even so, the approach offers a marked enhancement in the efficiency and fidelity of BBB modeling compared to previous methods.[10] In separate studies, researchers generated BBB spheroids by co-culturing primary endothelial cells, pericytes, and astrocytes establishing an *in vitro* platform for screening brain penetrating compounds.[11, 12] Lan Dao et al., developed hBBB assembloids that faithfully recapitulate the principal structural and functional characteristics of the hBBB, offering insights into mechanisms underlying cerebral cavernous malformations (CCMs).[7]

Simonneau et al. established a high-throughput platform for generating BBB organoids by employing hydrogel-based micro patterned scaffolds. This approach enabled the production of over 5000 viable and size- consistent organoids within a 96 well plate format. Utilizing the Gri3D micro patterned hydrogel system, the researchers achieved scalable and reproducible organoid formation characterized by rapid growth and minimal heterogeneity. This method represents a significant advancement in the standardized and efficient generation of homogeneous, well- defined BBB organoids for large scale experimental applications.[10] Earlier studies have demonstrated that organoids are more effective than transwell representations in modeling angiopep-2 transcytosis.[13] In addition to providing more physiologically relevant barrier properties and model dynamic interactions between the vascular and neural components, BBB organoids can also be integrated with cerebral organoids to generate complex neurovascular assemblies that better resemble the *in vivo* brain environment.

Although the 2D model is appreciated for fundamental research and high-throughput analysis, it lacks the capacity to accurately capture the complex and intricate physiology of the BBB, as it lacks any 3D architecture and intricate cell-cell interactions. In contrast, the 3D model possesses spatial architecture, components of the extracellular matrix, and more biologically accurate interactions between neuronal, endothelial, and glial cells, bringing it one step closer to the physiology of the hBBB, although issues with parameter control and standardization remain. The organoid-on-chip platform takes this process forward as it combines the use of iPSC organoids and microfluidic technology, which allows the simulation of shear stress, molecular concentration, and neurovascular interactions.

Compared to simpler BBB organoids, neurovascular organoids face a key limitation, i.e. the lack of a true blood-tissue barrier, as their vascular network is still not capable of perfusion. Integrating approaches such as microfluidic technology or advanced bio fabrication besides co culture approaches or bioengineered scaffolds may help address the challenge of creating functional vasculature. For example, microfluidic systems can connect cerebral organoids to microvascular networks composed of human umbilical vein endothelial cells enabling perfusion through the organoids vascular structure.

Conclusion

The reliable and consistent incorporation of organoids into vascular networks with full function, represents a critical advancement to developing a platform for personalized drug screening in neurodegenerative disorders. In the near future, hybrid approaches that combine disease-specific structures with organoids on chip technologies are expected to play a key role in both pre-clinical and clinical research. This progression may lead to precision medicine and precision drug screening, where emerging patient derived organoids closely mimic natural tissues

Study Highlights

What is the current knowledge?

- The blood-brain barrier in humans (hBBB) restricts the transportation of drugs into the CNS.
- The animal models and 2D models fail to accurately mimic the human BBB.

What is new here?

- Developed BBB organoids mimicking the interaction between endothelial, pericytes, and astrocytes.
- Organoids allow for more accurate modeling of drug transport and neurovascular interactions.
- Microfluidic integration enables perfusable vascular networks useful for high-throughput drug screening.

and are connected to a stable, consistent BBB vascular network, allowing for reliable results. Collectively the abovementioned features position BBB organoids as a versatile and efficient tool for drug screening and drug discovery approaches.

Competing Interests
Author declares no competing interests for this article.

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References
1. Dao L, You Z, Lu L, Xu T, Sarkar AK, Zhu H, et al. Modeling blood-brain barrier formation and cerebral cavernous malformations in human PSC-derived organoids. *Cell Stem Cell* **2024**; 31: 818-33. e11. doi: 10.1016/j.stem.2024.04.019
2. Nakhlband A, Omidi Y. Barrier functionality of porcine and bovine brain capillary endothelial cells. *Bioimpacts* **2011**; 1: 153-9. doi: 10.5681/bi.2011.021
3. Sharma A, Fernandes DC, Reis RL, Gołubczyk D, Neumann S, Lukomska B, et al. Cutting-edge advances in modeling the blood-brain barrier and tools for its reversible permeabilization for enhanced drug delivery into the brain. *Cell Biosci* **2023**; 13: 137. doi: 10.1186/s13578-023-01079-3
4. Engelhardt B, Liebner S. Novel insights into the development and maintenance of the blood-brain barrier. *Cell Tissue Res* **2014**; 355: 687-99. doi: 10.1007/s00441-014-1811-2
5. Nakhlband A, Farahzadi R, Saeedi N, Barzegar H, Montazersaheb S, Razi Soofiyani S. Bidirectional relations between anxiety, depression, and cancer: a review. *Curr Drug Targets* **2023**; 24: 118-30. doi: 10.2174/1389450123666220922094403
6. Vatine GD, Barrile R, Workman MJ, Sances S, Barriga BK, Rahnama M, et al. Human iPSC-derived blood-brain barrier chips enable disease modeling and personalized medicine applications. *Cell Stem Cell* **2019**; 24: 995-1005.e6. doi: 10.1016/j.stem.2019.05.011
7. Vatine GD, Al-Ahmad A, Barriga BK, Svendsen S, Salim A, Garcia L, et al. Modeling psychomotor retardation using iPSCs from MCT8-deficient patients indicates a prominent role for the blood-brain barrier. *Cell Stem Cell* **2017**; 20: 831-43.e5. doi: 10.1016/j.stem.2017.04.002
8. Huntley MA, Bien-Ly N, Daneman R, Watts RJ. Dissecting gene expression at the blood-brain barrier. *Front Neurosci* **2014**; 8: 355. doi: 10.3389/fnins.2014.00355
9. Rossi G, Manfrin A, Lutolf MP. Progress and potential in organoid research. *Nat Rev Genet* **2018**; 19: 671-87. doi: 10.1038/s41576-018-0051-9
10. Bell L, Simonneau C, Zanini C, Kassianidou E, Zundel C, Neff R, et al. Advanced tissue technologies of blood-brain barrier organoids as high throughput toxicity readouts in drug development. *Heliyon* **2025**; 11: e40813. doi: 10.1016/j.heliyon.2024.e40813
11. Bergmann S, Lawler SE, Qu Y, Fadzen CM, Wolfe JM, Regan MS, et al. Blood-brain-barrier organoids for investigating the permeability of CNS therapeutics. *Nat Protoc* **2018**; 13: 2827-43. doi: 10.1038/s41596-018-0066-x
12. Cho CF, Wolfe JM, Fadzen CM, Calligaris D, Hornburg K, Chiocca EA, et al. Blood-brain-barrier spheroids as an in vitro screening platform for brain-penetrating agents. *Nat Commun* **2017**; 8: 15623. doi: 10.1038/ncomms15623
13. Kassianidou E, Simonneau C, Gavrilov A, Villaseñor R. High throughput blood-brain barrier organoid generation and assessment of receptor-mediated antibody transcytosis. *Bio Protoc* **2022**; 12: e4399. doi: 10.21769/BioProtoc.4399