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SVZonChip: a paradigm shift in hydrocephalus research and treatment

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Abstract

Congenital hydrocephalus (CH) is an extreme cerebrospinal fluid (CSF) condition that affects brain development. Current medical treatments, such as ventriculoperitoneal shunting and endoscopic third ventriculostomy, are invasive and susceptible to complications. The subventricular zone (SVZ) is involved in CH, but investigations are hindered by conventional models. Here, we introduce SVZonChip, a dynamic 3D microfluidic device simulating SVZ physiology and CSF dynamics, presenting a proof-of-concept system that could be applied for studying CH. This bioengineered device provides a translational bridge between disease modeling and therapeutic discovery, opening up avenues for non-invasive treatments.

Keywords

Congenital hydrocephalus (CH), ependymal cells (ECs), subventricular zone (SVZ), neural stem cells (NSCs), 3D organotypic in vitro culture, organ-on-a-chip (OOC), microfluidics, tissue engineering

Author's opinion

Congenital hydrocephalus (CH) is a complex condition where there is abnormal accumulation of cerebrospinal fluid (CSF), causing progressive ventricular dilation, raised intracranial pressure, and devastating neurological disabilities [1]. Occurring in about 85 out of 100,000 people across the globe, CH is still a clinical problem, especially in low- and middle-income nations where access to sophisticated medical interventions is restricted [1]. Though the use of CSF shunting is still the standard treatment approach, shunt malfunction, infection, and late sequelae require a shift in focus toward other therapeutic strategies [2]. Recent findings propose that the subventricular zone (SVZ), a major neural stem cell (NSC) niche in the brain, is an important site for understanding CH pathophysiology [3]. The SVZ is involved in neurogenesis, ependymal barrier development, and homeostasis of CSF, but dysregulations in this zone are commonly found in CH disease [4, 5]. Conventional models for CH rely largely upon genetic mouse models, hydrocephalic rats, and transgenesis, which cannot adequately represent human SVZ cellular organization

and biomechanical forces [6]. In addition, such models raise ethical issues and have limitations in translation. There is, therefore, an urgent necessity for human-relevant in vitro models that can reproducibly mimic CSF-mediated hydrocephalus disease in humans. To overcome these challenges, our team created SVZonChip, a biomimetic microphysiological system that reproduces the SVZ environment in vitro (Figure 1). This system combines a region-specific decellularized extracellular matrix (ECM) from bovine SVZ tissue and a dynamic microfluidic culture system that mimics CSF flow [7]. The SVZonChip consists of co-cultured primary mouse radial glial cells (RGCs), ependymal cells (ECs) in a layered arrangement that reproduces native SVZ. In static conditions, RGCs preserve their progenitor-like state, whereas ECs adopt cilia and generate an epithelial barrier. When subjected to microfluidic CSF flow, SVZonChip shows improved ependymal ciliary growth, enhanced cellular polarization, and SRY-box transcription factor 2 (Sox2)+ and glial fibrillary acidic protein (GFAP)+ enrichment, resembling in vivo SVZ-like characteristics. Compared to conventional CH models as described in Table 1, SVZonChip offers a more physiologically relevant substitute by mimicking SVZ-specific cell-ECM interactions and mechanical stresses. SVZonChip captures essential features of SVZ pathophysiology relevant to CH, including ciliary architecture, flow-dependent signaling, and barrier formation. Although it does not model genetic mutations such as L1 cell adhesion molecule (*L1CAM*) or coiled-coil domain-containing protein 39 (*CCDC39*) directly, it offers flexibility for both disease modeling and therapeutic exploration. Experimental manipulation can be achieved using chemical agents (e.g., neuraminidase to disrupt ependymal cilia) or, in principle, gene delivery methods (e.g., viral or lipid-based transfection), enabling the recreation of hydrocephalus-associated phenotypes in a controlled in vitro environment. While the platform simulates CSF dynamics via microfluidic flow, it does not reproduce CSF secretion, which is primarily mediated by the choroid plexus (CP). Future integration with CP-on-chip systems, such as those described by Pellegrini et al. [8], may overcome this limitation and support more comprehensive modeling of hydrocephalus. *L1CAM* and *CCDC39* mutant genetic mouse models offer information on mutations associated with hydrocephalus but do not have essential elements for human ECM composition [9, 10]. Brain organoids from induced pluripotent stem cells (iPSCs) hold potential but are plagued by heterogeneity and failure to mimic fluid dynamics [11, 12]. Rat models for hydrocephaly offer a useful understanding of dynamics in CSF, but cannot mimic the mechanobiological functions of shear stress upon ependymal cilia [13]. SVZonChip fills this gap by incorporating biomimetic ECM, NSC science, and microfluidic CSF flow, and provides a reproducible and scalable system for mechanistic investigations and screening for drugs. Apart from its use in CH, SVZonChip is an attractive system for studying other neurodevelopmental and neurodegenerative diseases implicated in SVZ dysfunction. Periventricular leukomalacia, post-hemorrhagic hydrocephalus, and glioblastoma all entail SVZ niche dysregulation and are therefore strongly relevant to an extensive list of neurological disorders. SVZonChip further represents an innovative system for analysis of CSF flow dynamics in real-time, which reveals new information about mechanobiology's role in neural development and disease state progression. As the neuroscience field increasingly adopts organ-on-a-chip (OOC) technology, SVZonChip marks a revolutionary leap toward human-relevant disease modeling. By replicating SVZ neurogenesis and CSF-mediated pathophysiology in vitro, this system provides novel pathways for elucidating CH pathogenesis and non-invasive therapeutic development. Future directions should aim at incorporating patient-derived iPSCs in order to facilitate personalized disease modeling and further optimizing microfluidic parameters for maximizing physiological relevance. Additionally, integration with brain and CP organoids or OOC systems could enhance the physiological relevance of the SVZonChip model. Such combinations may enable multi-regional in vitro platforms that simulate interactions between CSF secretion (by the CP), flow dynamics, and SVZ-specific mechanobiology, offering a more comprehensive tool for studying CH and neurodevelopmental processes. With sustained inter-disciplinary efforts from bioengineers, neuroscientists, and clinicians, SVZonChip promises to reshape the terrain of hydrocephalus research and therapeutic discovery.

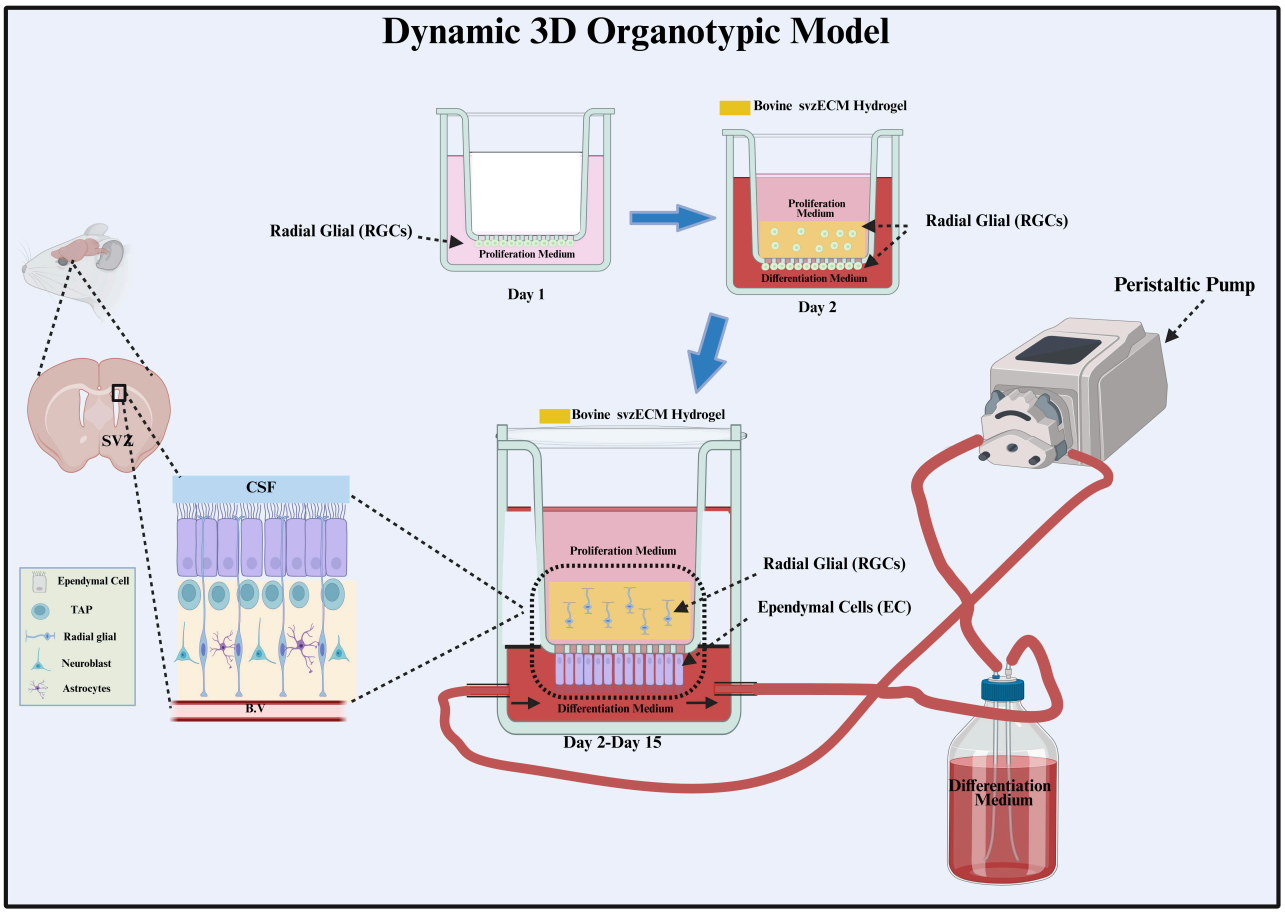

Figure 1. Dynamic 3D organotypic model for SVZonChip. This figure shows a schematic representation of the dynamic 3D organotypic subventricular zone (SVZ) model. Radial glial cells (RGCs) were seeded onto polycarbonate (PCF) membrane insert on day 1 in a proliferation medium. On day 2, a bovine SVZ equivalent extracellular matrix (ECM) hydrogel seeded with RGCs was applied atop this. The insert was connected with a peristaltic pump for the dynamic flow of medium, mimicking in vivo conditions and facilitating RGC proliferation, differentiation, and establishment of an epithelial barrier under dynamic conditions for 15 days. CSF: cerebrospinal fluid; EC: ependymal cell; TAP: transient amplifying progenitor; B.V: blood vessel. Reprinted from [7], CC BY

Table 1. Comparative evaluation of various models of hydrocephalus listing their respective strengths and weaknesses

Model type	Advantages	Limitations	References
Genetic mouse models	Replicates genetic mutations	Lacks human-specific ECM, limited CSF flow analysis	[9, 14]
iPSC-derived brain organoids	Human-relevant cellular architecture	Heterogeneous differentiation, lacks CSF dynamics	[11, 12]
Hydrocephalic rat models	Ventricular enlargement mimicry	Fails to capture the mechanobiological effects of CSF	[13, 15]
SVZonChip	Mimics SVZ-specific ECM and CSF flow, integrates microfluidic technology	Requires further validation for clinical translation	[7]

Genetic mouse models reflect hydrocephalus-related mutations but lack human-specific extracellular matrix (ECM) composition and cerebrospinal fluid (CSF) flow dynamics. Induced pluripotent stem cell (iPSC)-derived brain organoids have a human-relevant cellular organization but are plagued by heterogeneous differentiation and cannot mimic CSF dynamics. Hydrocephalic rat models simulate ventricular dilation but cannot capture the mechanobiological consequences of CSF dynamics for ependymal cilia. SVZonChip, an organ-on-a-chip system based on subventricular zone (SVZ)-specific ECM and dynamic CSF flow, has the potential for clinical translation but needs further verification

Abbreviations

CH: congenital hydrocephalus

CP: choroid plexus

CSF: cerebrospinal fluid

ECM: extracellular matrix

SVZ: subventricular zone

Declarations

Author contributions

IA: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Funding acquisition.

Conflicts of interest

The author declares that he has no competing interests.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

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