



Cerebrospinal Fluid: From the Sacred River of the Brain to an Emerging Reservoir of Neural Stem and Progenitor Cells

Jingzhong Ding¹, Chunru Xu², Thomas Boland³, and Yuanyuan Zhang^{2,4*}

¹Departments of Gerontology & Geriatrics, Internal Medicine, Epidemiology & Prevention, Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC 27101, USA

²Wake Forest Institute for Regenerative Medicine, Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC 27101, USA

³Department of Metallurgical, Materials & Biomedical Engineering, The University of Texas at El Paso, El Paso, TX 79968, USA

⁴Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, NC 27101, USA

*Corresponding Author: Yuanyuan Zhang, MD/PhD, Wake Forest School of Medicine, Email: Yuanyuan.Zhang@wfusm.edu

ABSTRACT

For centuries, cerebrospinal fluid (CSF) was regarded primarily as a protective and nutritive fluid surrounding the brain and spinal cord. Advances in developmental neuroscience, stem cell biology, and regenerative medicine have transformed this traditional view by demonstrating that CSF functions as a dynamic biological microenvironment enriched with growth factors, extracellular vesicles, cytokines, metabolites, and regenerative cellular populations. Emerging evidence suggests that CSF serves both as a critical signaling niche for neural stem cells and as a source of heterogeneous stem-like and progenitor cell populations that may contribute to central nervous system (CNS) development, homeostasis, and repair.

Unlike established stem-cell sources such as bone marrow, umbilical cord blood, or adipose tissue, the identity, origin, and functional significance of CSF-derived regenerative cells remain incompletely understood. Recent studies implicate multiple cellular sources, including the choroid plexus, ventricular-subventricular zone, ependymal-associated progenitors, and other periventricular stem-cell niches. Furthermore, growing recognition of the roles of the choroid plexus-CSF axis, glymphatic transport system, and age-associated changes in CSF composition has expanded our understanding of how the CSF microenvironment regulates neurogenesis and neurological health.

This review summarizes current knowledge of CSF-derived stem/progenitor cells, including their putative origins, biological properties, mechanisms of action, and potential applications in disease modeling, biomarker discovery, and regenerative medicine. We further highlight emerging engineering approaches, including choroid plexus organoids, biomaterial-based niche engineering, microphysiological systems, neural organoids, three-dimensional bio-printing, single-cell multi-omics, and artificial intelligence-driven analyses that may accelerate progress in the field. Finally, we discuss current challenges involving cellular identity, standardization, scalability, and clinical translation, as well as future opportunities for leveraging CSF-derived cellular and molecular components in precision neurology and next-generation regenerative therapies.

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Introduction

Cerebrospinal fluid has fascinated physicians and scientists for centuries. Ancient medical traditions considered the brain the seat of intelligence and vitality, while the fluid surrounding it remained mysterious and poorly understood. Early descriptions by Hippocrates recognized fluid accumulation in hydrocephalus, and Galen later linked the ventricular system to the circulation of “animal spirits” responsible for thought and movement. Although these

concepts were scientifically inaccurate, they reflected a long-standing recognition that intracranial fluids play fundamental roles in brain function.

Modern neuroscience has dramatically revised our understanding of CSF. Rather than serving merely as a mechanical cushion, CSF is now recognized as a dynamic biological compartment that supports nutrient transport, waste clearance, neuroendocrine signaling, immune surveillance, and neural development. Recent discoveries have further demonstrated

A Historical Perspective

- Ancient times**
Brain as the seat of intelligence and life force; mysticism, cranial fluid
- Hippocrates (460-370 BC)**
Concepts of cranial fluid and hydrocephalus
- Galen (129-216 AD)**
Ventricular system and "animal spirits"
- Modern era**
CSF recognized as an active signaling microenvironment containing cells and bioactive molecules

B Choroid Plexus-CSF Axis

Secretion into CSF

- Growth factors (e.g., IGF-1, BDNF, VEGF)
- Cytokines
- Extracellular vesicles
- Metabolites
- Hormones

Functions

- Regulates neural stem cell maintenance and quiescence
- Supports proliferation and differentiation
- Modulates aging and repair
- Maintains CNS homeostasis

CSF: A Dynamic Neural Stem Cell Niche

C Neural Stem Cell Niches Interfacing with CSF

Ventricular-Subventricular Zone (V-SVZ)

- Ependymal cells
- Type B (NSC)
- Type C (NPC)
- CSF (Ventricle)

Subgranular Zone (Hippocampus)

- Type B (NSC)
- Immature neurons
- CSF (Dentate Gyrus)

Other Periventricular Regions

- Ependymal-associated progenitors
- CSF

D Putative Origins of CSF-Derived Stem/Progenitor Cells

- Choroid plexus progenitors**
Choroid plexus cells and vesicles into CSF
- Ependymal-associated progenitors**
Ependymal cells with stem-like potential
- Ventricular-Subventricular Zone (V-SVZ)**
Neural stem/progenitor cells entering CSF
- Other neurogenic regions**
(e.g., hippocampus, periventricular areas)
Migratory progenitors and stem-like cells
- Injury or disease-induced mobilization**
Progenitors released in response to pathology

E CSF Composition Key Bioactive Components

Growth Factors: IGF-1, BDNF, NGF, GDNF, VEGF, FGF-2

Cytokines & Chemokines: IL-1, IL-6, IL-10, TNF- α , TGF- β , CXCL12, etc.

Extracellular Vesicles: Exosomes, microvesicles, apoptotic bodies

Metabolites: Lactate, lipids, amino acids, neurotransmitters

Hormones & Other Molecules: T3, cortisol, melatonin, etc.

Collectively modulate stem cell behavior and CNS physiology

F Mechanisms of Action

- Paracrine Signaling**
Growth factors and cytokines regulate proliferation, differentiation, and migration
- Extracellular Vesicles**
Transfer proteins, RNAs, and miRNAs to modulate target cells
- Neuroprotection**
Enhance cell survival, reduce oxidative, and oxidative stress
- Immunomodulation**
Regulate neuroinflammation and maintain immune balance

G Applications

- Disease Modeling**
 - Neurodegeneration
 - Neurodevelopmental disorders
 - Stroke/neurotrauma disorders
 - Brain genetic neurodegenerative diseases
 - Neuroinflammatory diseases
- Biomarker Discovery**
 - CSF cells, secretome proteins
 - Early diagnosis
 - Disease monitoring
 - Prognostic indicators
- Therapeutic Development**
 - Drug screening
 - Stem/progenitor therapies
 - Progenitor engraftment

H Future Regenerative and Clinical Translation

- Cell-based therapies**
(CSF-derived progenitors)
- Cell-free therapies**
(secretome, exosomes)
- Combination therapies**
(cell + exosomes)
- Personalized medicine**
(iPSC, gene editing)
- Homologous reconstitution**
for neurodegenerative disorders

Goals

- Enhance neural function
- Restore neurons
- Modulate inflammation
- Improve cognitive function
- Improve quality of life

Legend

- Neural stem cell (Type B)
- Neural progenitor cell (Type C)
- Neuron
- Astrocyte
- Oligodendrocyte
- Microglia
- Exosome

CSF flow

CSF is a dynamic and multifaceted niche that harbors stem/progenitor cells and bioactive molecules, playing critical roles in neurodevelopment, neurological disease, and emerging regenerative medicine.

As interest in regenerative medicine and neurological disease modeling continues to grow, cerebrospinal fluid (CSF) has emerged as a promising yet underrecognized biological resource. Among body fluid-derived stem cell populations [5, 6], CSF-associated neural stem/progenitor cells may play important roles in neuroregeneration, disease modeling, drug screening, and the early diagnosis and prediction of neurological disorders. Although definitive evidence for the existence of bona fide CSF-derived neural stem cells remains limited, accumulating studies support the presence of regenerative cellular populations and signaling networks within CSF that may contribute to central nervous system (CNS) homeostasis, repair, and functional recovery.

CSF is a clear, colorless fluid produced predominantly by the choroid plexus within the ventricular system. Approximately 500 mL is generated daily in adults, with complete turnover occurring several times each day. The fluid circulates through the ventricles and subarachnoid spaces before being reabsorbed into the venous system [7, 8].

Recent studies have established that the CSF-choroid plexus axis functions as an important regulator

of neural stem cell behavior throughout life. The choroid plexus secretes numerous factors into CSF that modulate proliferation, self-renewal, differentiation, and aging of neural stem cell populations [1, 4, 8].

Tissue Origins of CSF-Derived Stem and Progenitor Cells

The precise origins of stem-like and progenitor cells identified in CSF remain an active area of investigation. Current evidence suggests multiple potential cellular sources.

Choroid Plexus: The choroid plexus produces CSF and serves as an important neurosecretory organ. Beyond fluid production, it releases trophic factors and extracellular vesicles that regulate neural stem cell activity. Recent studies suggest that the choroid plexus-CSF axis represents a previously underappreciated component of the neural stem cell niche [1, 4, 8].

Ventricular-Subventricular Zone: The ventricular-subventricular zone (V-SVZ) is among the most extensively characterized neural stem cell niches in the adult brain. Neural stem cells residing in this region extend apical processes that directly contact CSF, allowing them to sense and respond to CSF-borne signaling molecules [4, 11-14].

Periventricular Neural Stem Cell Niches: Additional stem/progenitor populations may arise from periventricular regions and the hippocampus, where ongoing neurogenesis persists throughout adulthood. These cells may contribute to regenerative cellular populations observed in CSF [11-14].

Ependymal Cell-Associated Progenitors: Ependymal cells lining the ventricular system exhibit limited regenerative properties and may contribute precursor populations to the CSF under specific physiological and pathological conditions.

Collectively, available evidence suggests that cells recovered from CSF likely originate from multiple neural stem-cell niches rather than from a single identifiable source. Compared with established stem-cell sources such as bone marrow, umbilical cord blood, urine, and amniotic fluid, CSF represents a relatively underexplored but potentially valuable reservoir of regenerative cells and signaling factors (Table 1).

Stem-Like and Progenitor Characteristics:

Several studies have reported cellular populations within CSF that exhibit characteristics associated with neural stem and progenitor cells. These populations express markers commonly associated

Table 1: Comparative Stem Cell Source

Stem Cell Source	Collection Method	Invasiveness	Typical Cell Yield	Clinical Status
Bone Marrow	Bone marrow aspiration	High	High	Established
Umbilical Cord Blood	Collection at birth	Low	Moderate-High	Established
Adipose Tissue	Liposuction	Moderate	High	Established/Emerging
Amniotic Fluid	Amniocentesis or obstetric collection	Moderate	Moderate	Emerging
Urine-Derived Stem Cells	Voided urine collection	Minimal	Moderate	Emerging
Cerebrospinal Fluid (CSF)	Lumbar puncture or neurosurgical collection	Moderate	Low	Emerging
Induced Pluripotent Stem Cells (iPSCs)	Reprogrammed somatic cells	Variable	Expandable <i>in vitro</i>	Established research platform

with neural stemness, including Nestin, SOX2, Musashi-1, GFAP, CD133, and Vimentin [2, 12, 14],

In vitro studies have demonstrated that some CSF-derived cells possess proliferative capacity, limited self-renewal, and neurosphere-forming ability [2, 3]. These findings support the presence of stem-like or progenitor characteristics.

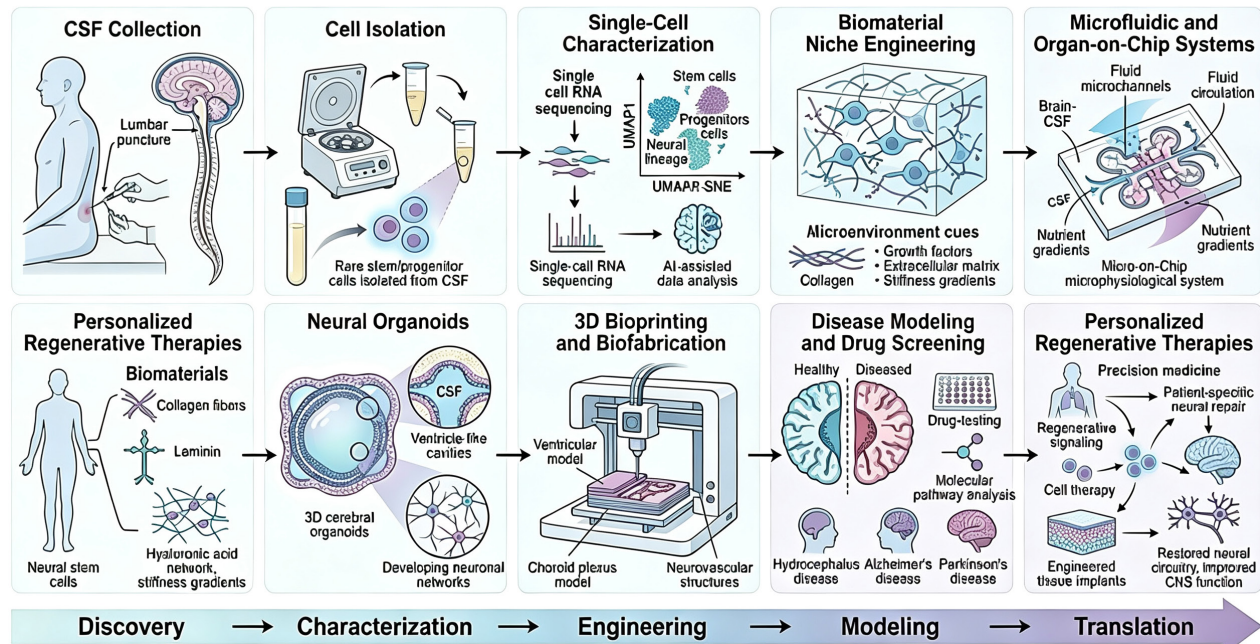
However, caution is warranted. Expression of neural stem cell markers alone is insufficient to establish definitive stem cell identity. Moreover, many studies involve heterogeneous cell populations isolated from fetal or disease-associated CSF samples. Consequently, current evidence supports describing these cells as **CSF-derived stem/progenitor cells or stem-like populations** rather than as established neural stem cells [14, 15].

Biological Functions

Regulation of Neurogenesis: One of the most important functions of CSF is regulation of neural progenitor proliferation and differentiation. Experimental studies have demonstrated that CSF provides critical growth-promoting signals that

Figure 2. Engineering and Translational Pipeline for CSF-Derived Stem/Progenitor Cells. Cerebrospinal fluid (CSF)-derived stem/progenitor cells may serve as a novel platform for regenerative medicine, disease modeling, and precision neuroscience. Following CSF collection and cell isolation, advanced single-cell and multi-omics technologies enable characterization of rare cellular populations. Biomaterial-based niche engineering, microfluidic organ-on-chip systems, neural organoids, and three-dimensional bioprinting provide increasingly sophisticated platforms for studying CSF-derived cells in physiologically relevant environments. These engineered systems facilitate disease modeling, drug discovery, and mechanistic investigations, ultimately supporting the development of personalized regenerative therapies for neurological disorders.

Engineering and Translational Pipeline for CSF-Derived Stem/Progenitor Cells



influence neural stem cell behavior during brain development and adulthood [2, 3].

Neural Differentiation: CSF-derived stem/progenitor cells have demonstrated the capacity to differentiate toward neuronal and glial phenotypes under specific experimental conditions. Although lineage potential varies among studies, these findings suggest a role in neural development and tissue remodeling [2, 3].

Neuronal Support: CSF contains numerous neurotrophic factors capable of promoting neuronal survival and functional maintenance. These trophic cues may help preserve neural networks and enhance endogenous repair mechanisms following injury [16, 17].

Neuroimmune Regulation: Beyond supporting neurogenesis, CSF serves as a critical interface between the nervous and immune systems. Cytokines and immune mediators present within CSF influence inflammatory responses that can either support or impair tissue regeneration [7, 8].

Mechanisms of Action:

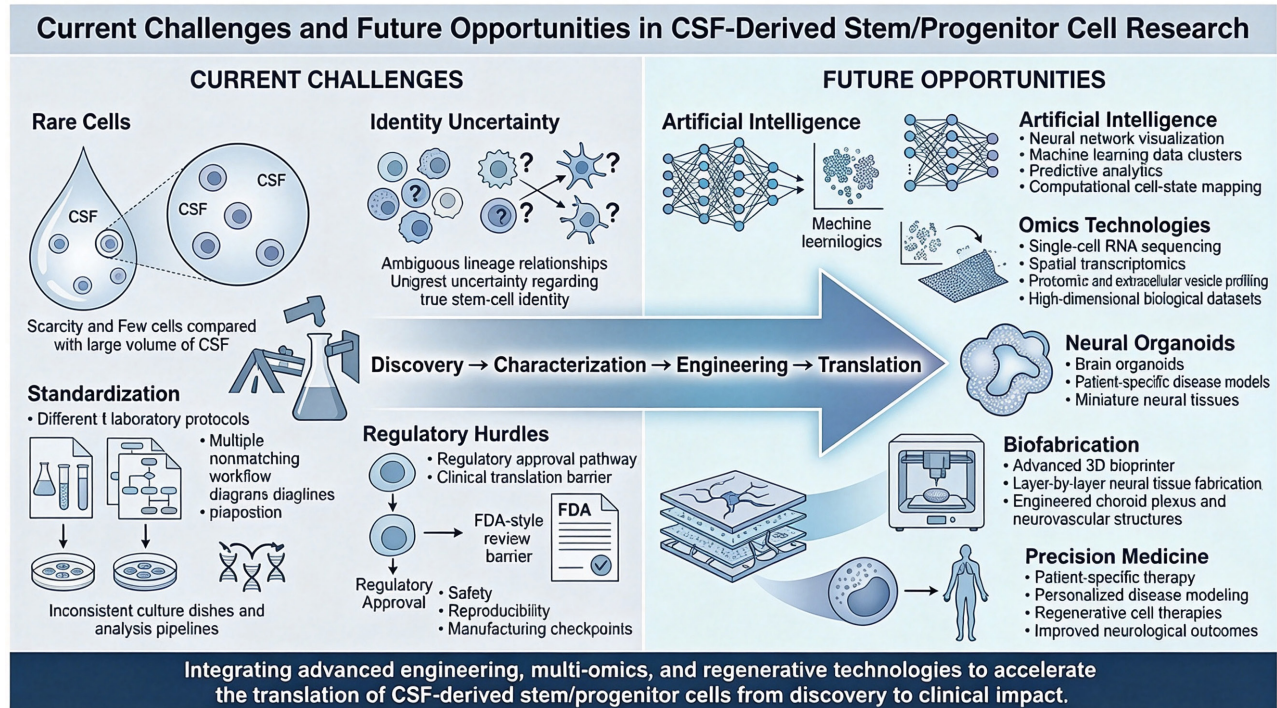
Several mechanisms may explain the biological effects of CSF-derived stem/progenitor cells and the CSF microenvironment.

Growth Factor Signaling: CSF contains multiple growth factors that regulate neural progenitor survival, migration, and differentiation, including: Insulin-like growth factor-1 (IGF-1), Brain-derived neurotrophic factor (BDNF), Nerve growth factor (NGF), and Vascular endothelial growth factor (VEGF) [3, 17],

Extracellular Vesicle Communication: Extracellular vesicles and exosomes within CSF transport proteins, mRNAs, microRNAs, and signaling molecules between cells. These vesicles are increasingly recognized as important mediators of neural development and regeneration [8, 15].

Neuroprotection: Recent investigations suggest that CSF-associated signaling pathways may reduce neuronal apoptosis, enhance survival of neural cells, and improve repair responses following ischemic injury [15, 18].

Figure 3. Current Challenges and Future Opportunities in CSF-Derived Stem/Progenitor Cell Research. Major barriers limiting the clinical translation of CSF-derived stem/progenitor cells include their low abundance, uncertain cellular identity, lack of standardized isolation and characterization protocols, and regulatory challenges associated with cell-based therapies. Emerging technologies, including artificial intelligence, multi-omics profiling, neural organoids, biofabrication, and precision medicine approaches, may help overcome these limitations. Together, these advances are expected to accelerate the development of CSF-derived cellular platforms for disease modeling, biomarker discovery, drug screening, and regenerative therapies for neurological disorders.



Immunomodulation: CSF-derived signaling molecules may suppress excessive neuroinflammation while promoting tissue repair, thereby contributing to maintenance of CNS homeostasis [15].

Choroid Plexus Organoids and Engineered CSF Systems

The choroid plexus is increasingly recognized as a central regulator of cerebrospinal fluid production and composition, serving as both a secretory organ and a signaling interface between the circulation and the central nervous system (CNS). Beyond its role in generating CSF, the choroid plexus secretes growth factors, cytokines, extracellular vesicles, and other bioactive molecules that influence neural stem-cell behavior, neurodevelopment, immune surveillance, and tissue homeostasis [1, 8]. The intimate relationship between the choroid plexus and CSF suggests that understanding CSF-derived stem/progenitor cells requires experimental systems capable of recreating this specialized microenvironment.

Recent advances in stem-cell engineering and organoid technology have enabled the generation of human choroid plexus organoids derived from induced pluripotent stem cells (iPSCs). These organoids recapitulate key structural and functional characteristics of the native choroid plexus, including epithelial organization, barrier function, and secretion of CSF-like fluids [19]. Importantly, choroid plexus organoids have demonstrated the capacity to reproduce aspects of human-specific CSF composition, providing a powerful experimental platform for investigating neurodevelopmental processes, CNS signaling pathways, and neurological disease mechanisms.

Engineered choroid plexus systems may also facilitate studies of CSF-derived stem/progenitor cell biology. By incorporating neural stem cells, extracellular vesicles, and patient-derived cellular populations into controlled in vitro environments, researchers can investigate how choroid plexus-secreted factors regulate stem-cell maintenance, proliferation,

migration, and lineage specification. Furthermore, integration of choroid plexus organoids with microfluidic brain-on-chip technologies may enable the development of advanced models that mimic CSF circulation and ventricular niche dynamics in ways not possible with conventional static culture systems. As interest in personalized medicine continues to expand, patient-specific choroid plexus organoids may provide unique opportunities for disease modeling, drug screening, and precision therapeutic development. Such systems could ultimately serve as critical tools for understanding the mechanisms governing CSF-mediated regulation of neural stem-cell niches and the origins of regenerative cellular populations within the ventricular system.

The Glymphatic System: Linking CSF Dynamics to Brain Homeostasis and Regeneration

In addition to serving as a signaling environment, CSF participates in a recently recognized waste-clearance pathway known as the glymphatic system. This network facilitates the exchange of CSF and interstitial fluid through perivascular spaces, thereby promoting removal of metabolic waste products, misfolded proteins, and neurotoxic molecules from the brain [20, 21]. The glymphatic system has emerged as a critical regulator of CNS homeostasis. During sleep, increased glymphatic activity enhances clearance of metabolites including amyloid- β and tau, proteins implicated in Alzheimer's disease and other neurodegenerative disorders [21, 22]. Dysfunction of glymphatic circulation has been associated with aging, traumatic brain injury, stroke, vascular disease, and neurodegeneration, highlighting the importance of CSF dynamics for long-term neurological health.

Emerging evidence suggests that glymphatic transport may influence neural stem-cell niches through the distribution of trophic factors, extracellular vesicles, cytokines, and metabolic signals present within CSF. Because neural stem cells located in ventricular and periventricular regions maintain direct or indirect contact with CSF, alterations in fluid transport and molecular exchange may affect cellular proliferation, differentiation, and regenerative capacity. Although the relationship between glymphatic function and CSF-derived stem/progenitor cells remains poorly understood, this interface represents an important area for future investigation. From a translational perspective, advanced imaging technologies, computational fluid-dynamics models, and microphysiological systems are beginning to provide

new opportunities for studying glymphatic transport mechanisms. Improved understanding of CSF circulation and glymphatic function may reveal previously unrecognized pathways through which regenerative signals are distributed throughout the CNS and could identify novel therapeutic strategies for enhancing tissue repair following neurological injury.

Neuroimmune Network: CSF as a Communication Highway

Traditionally viewed as an immune-privileged organ, the brain is now recognized as being in continuous communication with the immune system throughout life [23]. Beyond facilitating the presentation of cytokines, pathogens, and antigens to the peripheral immune system through meningeal and cervical lymphatic pathways [24], CSF serves as a critical neuroimmune interface between the central nervous system and immune cells, which plays an important role in the pathogenesis of neurodegenerative diseases [25]. Recent studies support a bidirectional communication network between the brain and peripheral immune system [26, 27], whereby peripheral immune cells, including T cells and monocytes, can infiltrate into the brain and contribute to neurodegeneration. Aging of the immune system, now recognized as a major driver of age-related disorders including neurodegeneration [28–32], is characterized by functional decline in both innate and adaptive immunity along with chronic low-grade inflammation [33]. Notably, two recent studies demonstrated that, with advancing age, infiltrating peripheral monocytes progressively replace resident microglia within the brain [34, 35]. Although the precise routes of infiltration remain unclear, brain border regions such as the choroid plexus [36, 37] and meningeal lymphatic vessels [38] are among the leading candidate gateways for peripheral immune cell entry.

The interactions between these immune processes and CSF-associated neural stem-cell niches can profoundly influence recovery and disease progression following neurological injury or disease. Depending on their activation state, infiltrating immune cells may either promote tissue repair or exacerbate neurodegeneration [39]. Beneficial immune responses can facilitate the clearance of cellular debris and damaged myelin while stimulating the proliferation of endogenous neural stem and progenitor cells [40]. In contrast, pro-inflammatory immune cells may impair stem-cell survival, inhibit differentiation, and contribute to ongoing neural damage [41].

Aging and Age-Related Changes in the CSF Stem Cell Niche

Aging is accompanied by profound alterations in both the composition of cerebrospinal fluid and the function of neural stem-cell niches. The age-associated decline in neurogenesis observed throughout the mammalian brain has been linked, in part, to changes in the molecular environment of the CSF and the secretory activity of the choroid plexus [4, 42].

Studies have demonstrated that aging alters the concentration of multiple growth factors, cytokines, and inflammatory mediators within CSF, resulting in reduced support for neural stem-cell self-renewal and neuronal differentiation. The aged choroid plexus exhibits transcriptional changes associated with increased inflammation and decreased secretion of factors that promote stem-cell maintenance and tissue regeneration [4]. Consequently, neural stem cells exposed to aged CSF frequently display diminished proliferative capacity and impaired regenerative potential compared with cells maintained in younger microenvironments. Age-related changes in CSF composition may also contribute to the pathogenesis of neurodegenerative disorders. Alterations in proteostasis, impaired glymphatic clearance, chronic inflammation, and disrupted intercellular signaling can lead to the accumulation of pathological proteins and progressive neuronal dysfunction. These processes have been implicated in Alzheimer's disease, Parkinson's disease, and other age-associated neurological conditions [21, 43].

Understanding how aging affects CSF-derived stem/progenitor cells may therefore be essential for the development of regenerative therapies targeting neurological diseases. Future investigations combining single-cell transcriptomics, proteomics, extracellular vesicle profiling, and artificial intelligence-based analyses may help elucidate age-dependent changes in both cellular and molecular components of the CSF environment. Such knowledge could inform strategies to rejuvenate neural stem-cell function, restore regenerative signaling pathways, and improve therapeutic outcomes in aging populations. Collectively, available evidence suggests that aging should be viewed not only as a process affecting neural cells themselves but also as a systems-level phenomenon involving dynamic changes in the CSF microenvironment, choroid plexus function, and glymphatic transport. These interconnected processes may ultimately determine the regenerative capacity of the aging central nervous system.

Disease Modeling Applications

Hydrocephalus: Hydrocephalus remains one of the most common neurological disorders requiring pediatric neurosurgical intervention. Increasing evidence suggests that abnormalities in neural progenitor biology contribute to disease pathogenesis, making CSF-derived cellular populations valuable tools for mechanistic studies [44].

Neurodevelopmental Disorders: Patient-derived CSF samples may provide unique opportunities to investigate developmental disorders affecting brain formation, neural connectivity, and cognitive function [9, 15].

Autism Spectrum Disorder: Although still exploratory, CSF-derived biomarkers and progenitor populations may contribute to understanding molecular pathways involved in autism spectrum disorder and related neurodevelopmental conditions [15].

Rare Genetic Neurological Diseases: Because CSF directly reflects CNS biology, patient-derived cells and extracellular vesicles may be useful for disease modeling, biomarker discovery, and therapeutic screening in rare neurological disorders.

Regenerative Medicine Applications

Although clinical applications remain largely experimental, interest in CSF-related regenerative strategies continues to expand.

Spinal Cord Injury: CSF-derived stem/progenitor cells and their associated signaling pathways may contribute to neuronal survival and endogenous repair following spinal cord injury [15, 45].

Ischemic Stroke: Experimental studies have shown that CSF-associated growth factors enhance stem cell proliferation, migration, and neuroprotection in models of ischemic injury [15, 17, 46].

Parkinson's Disease: CSF-based disease models may facilitate investigation of dopaminergic neuron degeneration and support development of future regenerative therapies [46].

Alzheimer's Disease: CSF contains disease-associated biomarkers as well as regenerative signaling molecules that may provide insights into disease progression and therapeutic development.

While these applications remain promising, substantial work is needed before clinical translation can be achieved.

Engineering Platforms for Cerebrospinal Fluid-Derived Stem and Progenitor Cells

While substantial progress has been made in defining the biological properties of cerebrospinal fluid (CSF)-derived stem/progenitor cells, translation toward clinically useful applications will require the development of advanced engineering platforms capable of isolating, expanding, characterizing, and directing the fate of these rare cellular populations. Like other stem cell systems, the behavior of CSF-derived cells is strongly influenced by their surrounding microenvironment. Consequently, biomaterials, biofabrication technologies, microphysiological systems, and computational tools are expected to play increasingly important roles in unlocking the therapeutic potential of this emerging cell source.

One of the primary challenges in studying CSF-derived stem/progenitor cells is the recreation of the specialized microenvironment that supports neural stem-cell maintenance *in vivo*. Within the ventricular-subventricular zone and other neurogenic niches, stem cells are exposed to highly regulated biochemical and mechanical cues delivered through the extracellular matrix, neighboring cells, and CSF-borne signaling factors [14, 47]. Traditional two-dimensional culture systems are often unable to reproduce these complex interactions, leading to altered cellular phenotypes and loss of stem-like properties.

Recent advances in biomaterials and tissue engineering have enabled the development of brain-mimetic hydrogels that more closely replicate the mechanical and biochemical characteristics of neural tissue. Hydrogels based on hyaluronic acid, collagen, gelatin methacrylate (GelMA), laminin, and decellularized brain extracellular matrix can provide a supportive microenvironment that promotes neural stem-cell survival, proliferation, and differentiation [48-50]. Such systems may ultimately facilitate the long-term expansion and characterization of CSF-derived stem/progenitor cells while preserving their native phenotypic characteristics.

The dynamic nature of CSF circulation presents additional challenges for conventional cell culture approaches. *In vivo*, neural stem cells are continuously exposed to fluid flow, nutrient exchange, extracellular vesicles, and soluble signaling molecules. Microfluidic systems offer unique opportunities to recreate these physiological conditions *in vitro*. Brain-on-a-chip and ventricle-on-a-chip platforms can simulate aspects of CSF flow, nutrient gradients, and cellular interactions within the neurogenic niche [51]. These systems enable precise control of mechanical and bio-

chemical stimuli while allowing real-time monitoring of cellular responses. Such devices may provide powerful tools for investigating how CSF-derived stem/progenitor cells respond to developmental signals, injury-associated factors, and disease-specific microenvironments. Furthermore, microphysiological systems could support high-throughput drug screening and mechanistic studies that are difficult to perform in animal models [52, 53].

The convergence of stem-cell biology and tissue engineering has driven remarkable advances in three-dimensional neural organoids and microphysiological tissue models. CSF-derived stem/progenitor cells may represent a valuable patient-specific cell source for generating neural organoids that recapitulate aspects of human brain development, neurodevelopmental disorders, and neurodegenerative diseases. Brain organoids have emerged as powerful platforms for modeling neural development, congenital abnormalities, and neurological diseases while preserving the three-dimensional architecture of developing neural tissues [54]. Incorporation of CSF-derived cells into organoid systems could provide unique opportunities to investigate disorders associated with abnormal ventricular development, hydrocephalus, autism spectrum disorders, and rare genetic neurological diseases. Moreover, organoids integrated with engineered CSF compartments may offer more physiologically relevant models for studying how CSF signaling influences neurogenesis, cellular maturation, and tissue homeostasis [55, 56].

Three-dimensional bioprinting has emerged as a powerful strategy for constructing complex tissue models with controlled spatial organization. Although the application of CSF-derived stem/progenitor cells in bioprinting remains largely unexplored, their integration into biofabricated neural tissues may create new opportunities for studying central nervous system development and regeneration. Bioprinting technologies have already been used to fabricate neural tissue constructs, neural-matrix interfaces, neurovascular tissues, and disease-specific brain models (Knowlton et al., 2018; Groll et al., 2016). These approaches enable precise positioning of cells, biomaterials, and signaling gradients that more closely mimic native CNS architecture. Bioprinting could therefore be used to generate ventricular wall models, choroid plexus constructs, and multicellular neural microenvironments for investigating CSF-mediated signaling and neurodevelopment. In the longer term, biofabrication approaches may contribute to implantable neural constructs designed to promote tissue repair

following injury or neurodegenerative disease [57].

A major challenge in the CSF stem-cell field is the remarkable heterogeneity of cellular populations recovered from CSF samples. Recent advances in single-cell RNA sequencing, spatial transcriptomics, proteomics, and extracellular vesicle profiling are enabling unprecedented characterization of rare cell populations within the CNS [58, 59]. The integration of these high-dimensional datasets with artificial intelligence and machine-learning approaches may facilitate identification of previously unrecognized stem/progenitor populations, predictive biomarkers, and regenerative signaling networks (Kimmel et al., 2019). Computational modeling may also help distinguish bona fide neural stem cells from transient progenitor populations and reveal how CSF composition changes across development, aging, injury, and disease. Such data-driven approaches are expected to become essential components of future CSF-based precision medicine strategies.

Despite the promise of CSF-derived stem/progenitor cells, substantial translational barriers remain. Cell yields obtained from clinical CSF samples are typically low, and standardized methods for isolation, expansion, quality control, and potency testing have not yet been established. Lessons learned from the development of mesenchymal stem-cell, induced pluripotent stem-cell, and cord-blood therapies may guide future efforts toward Good Manufacturing Practice (GMP)-compliant production of CSF-derived cellular products [60, 61]. Standardized bioprocessing workflows, automated cell-expansion platforms, and robust potency assays will be critical for ensuring reproducibility, safety, and regulatory compliance. Continued collaboration among neuroscientists, stem-cell biologists, clinicians, and biomedical engineers will be essential for translating emerging discoveries into clinically meaningful therapies [62].

Current Challenges

Despite increasing enthusiasm, several important challenges limit translation of CSF-derived stem/progenitor cells.

Cell Scarcity: The low abundance of regenerative cell populations within CSF complicates isolation and expansion procedures.

Uncertain Cellular Identity: A major unresolved question is whether CSF-derived cells represent bona fide neural stem cells, lineage-restricted progenitors, or cells shed from adjacent neural tissues [14, 15].

Lack of Standardized Protocols: Uniform meth-

ods for isolation, characterization, culture, and quality control have yet to be established.

Collection Limitations: Unlike urine or peripheral blood, CSF acquisition requires lumbar puncture or neurosurgical procedures, limiting accessibility.

Regulatory Considerations: Future clinical applications must satisfy stringent requirements regarding safety, reproducibility, and efficacy.

Future Perspectives

The transformation of CSF from a passive biological fluid into an active regulator of neural development and regeneration represents one of the most exciting advances in modern neuroscience. Emerging evidence suggests that CSF serves not only as a signaling niche for neural stem cells but also as a reservoir of stem-like and progenitor populations with potential relevance to disease modeling and regenerative medicine.

Future breakthroughs in single-cell transcriptomics, spatial biology, extracellular vesicle profiling, organoid technology, and artificial intelligence-assisted data analysis are expected to provide unprecedented insight into the cellular complexity of the CSF environment. Such approaches may clarify the identity, origin, and therapeutic significance of CSF-derived stem/progenitor cells.

Although CSF should not yet be considered an established stem cell source comparable to umbilical cord blood, amniotic fluid, or bone marrow, the growing body of evidence supports its emerging role as a reservoir of regenerative cells and signaling factors. Continued investigation may ultimately establish CSF-derived stem/progenitor cells as valuable tools for biomarker discovery, personalized disease modeling, and next-generation therapies for neurological disorders.

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Author Contributions

YZ conceived the article; YZ, JD, TB performed the literature review; YZ, JD, TB interpreted the literature; YZ, JD, TB wrote the manuscript, and YZ, JD, TB approved the final version.

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