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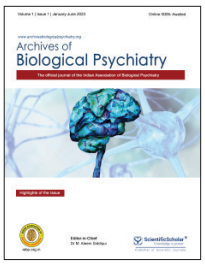

Review Article *Neuropathology*

Modern cell culture technologies: Revolutionizing neuroregeneration in neuropsychiatry

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ABSTRACT

This review highlights the latest developments in current cell culture methods, including three-dimensional culture, organoids, coculture systems, microfluidics, and nanofiber scaffolds to support neuroregeneration in major neuropsychiatric illnesses. Due to the enhanced *in vitro* modeling of human brain structure and function, these state-of-the-art methods allow for investigations of disease processes and drug screening, and pathophysiological research on neuroregeneration has increased. We examine recent research on the relationship between these technologies and neuropsychiatric conditions such as stroke, Alzheimer's, traumatic brain injury, and spinal cord injury. The advancements present encouraging prospects for augmenting neuroregeneration and could facilitate stem cell-based therapies for neuropsychiatric ailments that were previously untreatable.

Keywords: Regeneration, Neuropsychiatry, Three-dimensional cell culture, Organoids, Coculture technique, Microfluidic, Scaffold cell cultures

INTRODUCTION

Neuropsychiatry is a medical field that includes both neurology and psychiatric disorders.[1] Research on neuroregeneration has revolutionized treatments for many of the ailments in this sector. The dynamic discipline of neuroregeneration focuses on the development, maintenance, and connectivity of neurons. In adults, neuronal cells exhibit limited regenerative capabilities. Consequently, severe peripheral nerve injuries often remain unresolved, culminating in paralysis. The placement of a nerve graft is typically necessitated for the restoration of function. Neurogenesis, neuroplasticity, and neurorestoration are three areas of research that show promise for enhancing brain health and curing neuropsychiatric disorders.[2]

This study aims to provide a concise overview of the uses of contemporary cell culture technologies, including microfluidics, organoids, coculture systems, three-dimensional (3D) culture, and nanofiber scaffolds, in neurodegenerative therapy for major neuropsychiatric disorders. Thanks to these state-of-the-art methods, research on neuroregeneration has progressed significantly, as human brain shape and function can now be better modeled *in vitro*. We examine current research that models neuropsychiatric illnesses and creates novel treatment strategies using these technologies.

In neuropsychiatry and neuroregeneration research, cell culture techniques are widely employed to investigate and develop treatments for a range of neurological diseases. For the purpose of study and drug development, scientists can cultivate and modify brain cells through the use

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of cell culture. Cell culture research can help find shared pathways across diverse diseases and potential therapy targets for neuronal preservation and repair, which is beneficial for neurodegenerative disorders, which are common in neuropsychiatry.[3,4]

3D CULTURE

The intricacy of the human nervous system and the limited accessibility of living brain tissue represent considerable hurdles in the research of nervous system and brain development.[5] To address these issues, 3D cultures [Figure 1] have emerged as a viable way to investigate human brain function. Unlike two-dimensional systems, which are incapable of capturing the delicate interactions between neural cells, 3D neuronal cultures have shown the ability to duplicate human neuron properties such as transcriptional patterns[6] and *in vivo*-like neuron-neuron interactions,[7] including the extracellular matrix (ECM) and its interactions with neurons.[8] These 3D models expand beyond neurons to incorporate glial cells,[9] allowing for a better understanding of their interactions with neurons[5] and reproduction of oligodendrocyte function.[10] Notably, 3D brain organoids with induced pluripotent stem cell (iPSC)-derived human microglia-like cells that mimic their functional features and transcriptomic profile have been generated.[11]

ORGANOIDS MODELLING NEUROLOGICAL DISEASES

Researchers have created *in vitro* neurological organogenesis models employing iPSCs to grow human cerebral organoids. These organoids closely resemble the human brain's multilayered structure [Figure 2] and numerous cell types, which include astrocytes, oligodendrocytes, neuroepithelial cells, neuronal cells, and radial glial cells. They can even reproduce specific layers inside the cortical plate and be used to build different brain areas, allowing researchers to examine and imitate neurological illnesses. These cerebral organoids' neurons have synapse structures and respond to stimuli with calcium action potentials.

Furthermore, these cerebral organoids can be made up of a variety of cell types, including neural stem cells (NSCs), mature and immature neurons, and glial cells, promoting neuronal connections comparable to that found in the human brain *in vivo*. This enables the investigation of structural phenotypes as well as a better knowledge of the cellular and molecular mechanisms behind human brain development, disease-induced neuronal abnormalities, and cognitive deficits.[12]

Aside from typical organoids, region-specific spheroids have been used to examine cell migration and brain circuit creation in formations[13] known as "assembloids." These organoids can be utilized to study neuronal connections in various brain regions. Furthermore, organoids maintained at the air-liquid interface have improved neuronal survival and maturation, allowing for the formation of long, dense bundles of axons with precise orientations.[14]

Recent advances in the field have resulted in the production of microglia-containing human brain organoids, which mimic essential aspects of the human brain and open up new avenues for research into brain development and pathology.[15] These organoids are useful for studying the underlying causes of neurological illnesses because they may develop intricate brain networks and exhibit spontaneous electrical activity.

COCULTURE

Coculturing [Figure 3] is a novel technique in neuroregeneration research that is propelling the field forward. Barberio *et al*. study, for example, produced a unique coculturing system comprising endothelial cells, astrocyte cells, and neuronal cells. This method allows for the investigation of the neurovascular unit's barrier functions, which is critical for understanding drug distribution to the central nervous system (CNS). Because many medications have difficulty crossing the blood-brain barrier (BBB), this coculturing strategy provides a platform for future drug testing and delivery pathways, potentially resolving this issue.[16]

There is also a study on the development of human iPSCs (hiPSCs) into microglia-like cells through specific factor exposure and coculturing with astrocytes. These iPSC-derived microglia (iPS-MG) have the phenotypic, gene expression profile, and functional features of brain microglia. In treating mouse syngeneic intracranial malignant gliomas, murine iPS-MG produced using a similar approach displayed equivalent efficacy to primary brain-isolated microglia. This breakthrough opens up new avenues for research into human microglia and their potential uses in personalized medicine.[17]

MICROFLUIDICS

Microfluidics-based cell culture platforms [Figure 4] are game-changing drug screening and development technologies, seamlessly merging ideas from biology, biochemistry, engineering, and physics. They use microfluidics, which includes precise manipulation of small liquid volumes in microscale channels, to establish controlled settings for cell culture. These platforms enable 3D cell culture by simulating native tissue conditions. This is critical for understanding cell behavior in physiologically relevant situations. Microfluidic devices enable fine control of fluid flow, concentration gradients, and cell configuration, resulting in precise experiments. Many microfluidic systems are automated, which allows numerous experiments to run at the same time, saving time, and resources.

Cell culture systems based on microfluidics are used in a variety of sectors, including drug discovery, tissue engineering, and biological research. They make it easier to investigate cell activities and reactions to stimuli. These platforms allow for real-time observation of cell activities, which aids in dynamic studies. Microfluidic systems frequently save money since they require fewer reagent and cell quantities. They enable investigations using fewer cells and animals, which aligns with ethical concerns about animal testing and cell procurement.[18]

NANOFIBER SCAFFOLDS

There has been a tremendous increase in interest in electrospun nanomaterials derived from cellulose and its derivatives during the past two decades. These materials have attracted interest for a variety of clinical applications, with a particular emphasis on their use in cell culture for tissue engineering. The exceptional mechanical resilience of cellulose filaments is due to their hierarchical structure and the varying presence of crystalline domains. This extraordinary stability is critical in the creation of materials for tissue engineering, ensuring that these structures can efficiently assist cell proliferation and tissue synthesis.

Cellulose and its derivatives have been shown to be biocompatible with a wide range of cell lines. This means they are well tolerated by cells and cause no harmful effects. This biocompatibility is important when creating materials for cell culture since it ensures that the cells can survive in their surroundings. These materials have led the way for the development of polymeric matrices with nanofibrous ECM-like properties. These matrices are useful for tissue engineering applications because they imitate the natural environment that cells experience within tissues and organs. Within these matrices, cells can attach, develop, and interact, promoting the formation of functional tissues [Figure 5].[19]

We present the latest reports at the interface of these modern cell culture technologies and specific neuropsychiatric disorders [Table 1].[20,21]

Table 1: Modern cell culture technologies and their targeted neuropsychiatric disorders.

Modern cell culture technology	Neuropsychiatric disorders[20,21]
3D culture	AD, Stroke, SCI
Organoid	AD, Stroke, SCI
Coculture	AD, Stroke, SCI
Microfluidics	Stroke, peripheral nerve damage
Scaffolds	Stroke, TBI, SCI

AD: Alzheimer's disease, SCI: Spinal cord injury, TBI: Traumatic brain injury

ALZHEIMER'S DISEASE (AD)

AD is a type of dementia characterized by gradual loss of mental faculties such as memory, attention, calculation, and judgment. The AD neuropathological signatures include amyloid beta-plaques and neurofibrillary tangles (NFT), leading to neurodegeneration.[22] With increasing prevalence across the globe, neurogenerative therapies are the hope for this debilitating disease.

3D culture and organoid

The role of galangin protein in neuroregenerative therapy is the most recent scientific highlight of 3D culture and organoid technology in AD. Galangin treatment restored

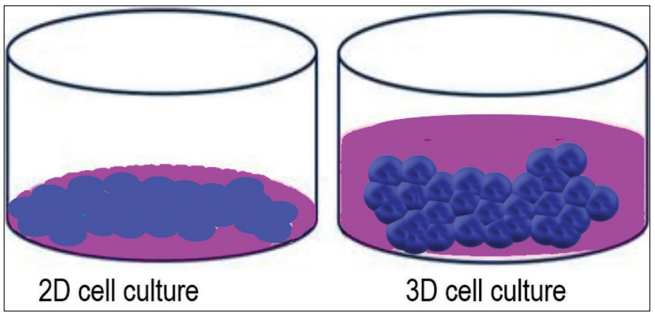

Figure 1: 3D cell culture.

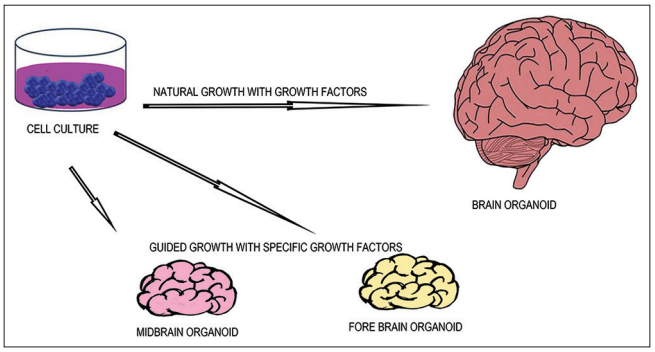

Figure 2: Brain organoids.

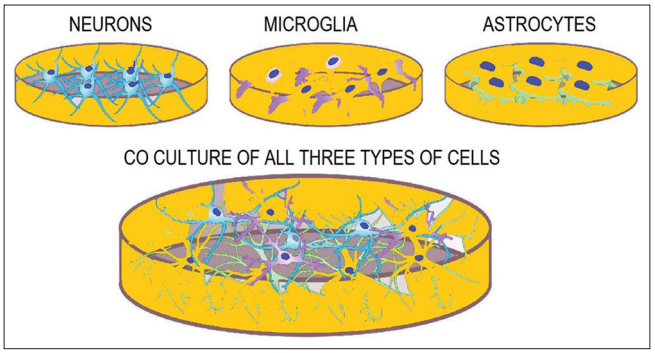

Figure 3: Coculture of neurons, microglia, and astrocytes.

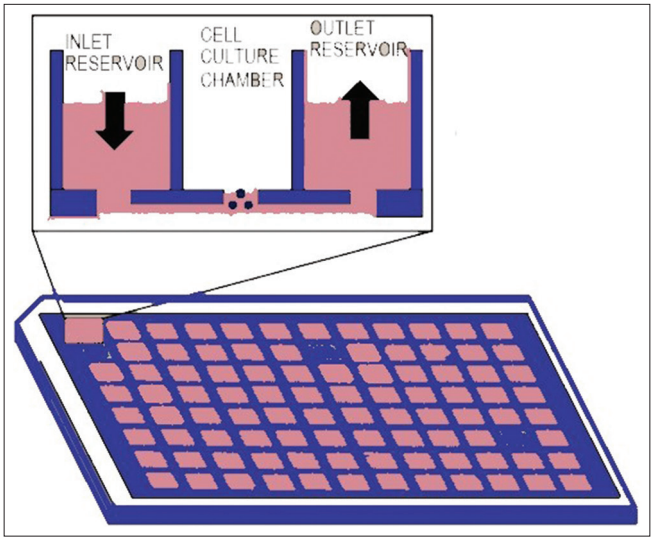

Figure 4: Microfluidics-based cell culture platform.

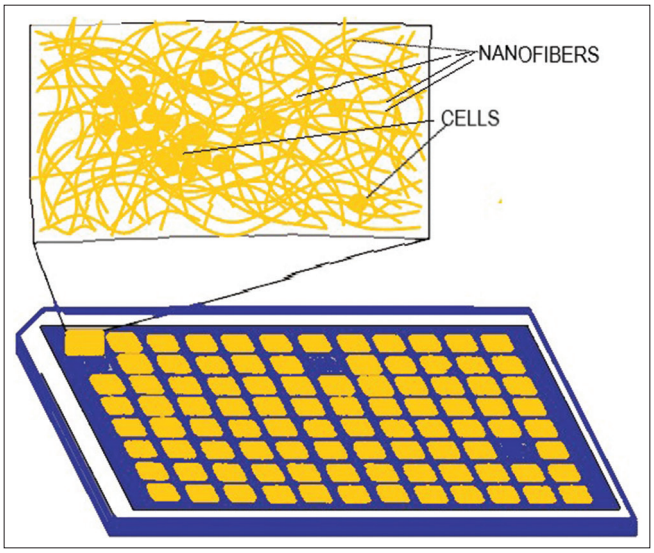

Figure 5: Nanofiber cell culture platform.

mitophagy and organoid growth, which were suppressed by A, in a unique 3D human brain organoid culture system. The mitophagy inhibitor prevented galangin's action, implying that galangin may have served as a mitophagy enhancer to alleviate AD-induced pathology. These findings highlighted the importance of mitophagy in the etiology of AD and suggested that galangin could be employed as a novel mitophagy booster to treat the disease.[23]

Coculture

The experiment with primary hippocampus neuronal and astrocytic cocultures was described in a recent publication of coculture technology in neuroregeneration. Before applying Amyloid142 oligomers to neuron-astrocyte cocultures, astrocytes were pretreated with an N-methyl-D-aspartate receptor (NMDAR) agonist or antagonist. Astrocytic NMDARs protect against AD-induced synaptotoxicity by influencing NGF production, maturation, and secretion in astrocytes. This new insight contributes to the search for a specific targeted therapeutic strategy to delay the start of AD.[24] Another seminal work used bone marrow-derived mesenchymal stem cells (BM-MSCs) cultivated with a cocktail of growth factors in consenting patients with severe spinal damage; no side effects were noted, and a significant therapeutic benefit was documented. The protocol was used in three further cases of amyotrophic lateral sclerosis (ALS) and one case of CNS multisystem atrophy. Two of the ALS patients experienced significant initial improvement or stabilization, followed by continued deterioration many months later.[25] In patients with progressive multiple sclerosis (MS), repeated MSC treatments were demonstrated to be safe in the short- to intermediate-term and produced clinical improvements that lasted up to 4 years, with short-term immunomodulatory effects that were particularly evident in patients treated with more than two injections.[26]

Other approaches

A groundbreaking adult brain gene therapy experiment used an *ex vivo* approach. Patient fibroblasts were isolated from skin biopsies and genetically engineered with retroviral vectors to generate and release nerve growth factor (NGF). These modified fibroblasts were subsequently implanted into the brain, acting as small biological pumps for constant localized NGF supply. This novel technique demonstrated the expansion of cholinergic fibers toward the cellular source of NGF, a classic trophic response, as well as the activation of cortical metabolic activity, as measured by fluorodeoxyglucose-positron emission tomography imaging[27] in AD patients.

STROKE

In medical terminology, "stroke" refers to a wide range of disorders involving the blockage and/or hemorrhaging of blood vessels. The restriction and blockage invariably result in a lack of blood supply and interrupted blood flow. This causes devastating brain deficits, which can sometimes be irreversible. Novel cell culture technologies are being used to try to find treatments for this crippling disease.[28]

3D culture and organoid

A significant amount of neuregeneration research is focused on stroke therapy. Human cerebral organoids generated from hiPSCs were cultivated and transplanted into the intersection of the infarct core and the peri-infarct zone of NOD-SCID (brand of immunodeficient laboratory mice) mice treated to stroke in a recent study. Months later, they discovered that

the grafted organoids survived well in the infarcted core, differentiated into target neurons, repaired infarcted tissue, sent axons to distant brain targets, and integrated into the host neural circuit, eliminating sensorimotor defect behaviors in stroke mice, whereas transplantation of dissociated single cells from organoids did not repair the infarcted tissue. Their research provides a new technique for regenerating infarcted tissue through organoid transplantation, potentially correcting stroke-induced impairment.[29]

Coculture

In a recent experiment, human hippocampus neurons (N), astrocytes (A), microglia (M), and brain microvascular endothelial cells (BMEC) (E) were used to create hNAME, a novel coculture system for stroke. After reoxygenation, hNAME-neurons and endothelial cells were more severely damaged than monolayer cells (oxygen-glucose deprivation [OGD]48/R24). The release of inflammatory factors rose gradually as the OGD and reoxygenation times increased, peaking at OGD48/R24. Human umbilical cord mesenchymal stem cells (hUMSCs) verified the hNAME value. Treatment with hUMSCs significantly reduced the severity of neuronal and endothelial cell injury in hNAME. This study demonstrates a neuroregeneration *in vitro* model replicating the immunological microenvironment of the human brain.[30]

Microfluidics

Microfluidic technology has significantly advanced stroke research. A functional neurovascular unit on a microfluidic chip as a microphysiological model of ischemic stroke that recapitulates the function of the BBB as well as interactions between therapeutic stem cells and host cells (human brain microvascular endothelial cells, pericytes, astrocytes, microglia, and neurons) was developed and tested in a recent study. The model was utilized to track the infiltration of a number of putative stem cells as well as evaluate the expression levels of genes linked with post-stroke disorders. The researchers discovered that each type of stem cell had distinct neurorestorative effects, primarily by promoting endogenous recovery rather than direct cell replacement, and that synaptic activity recovery correlated with the structural and functional integrity of the neurovascular unit rather than with neuron regeneration.[31]

Nanofiber scaffolds

In a new study using coculture and nanofiber scaffolds, researchers created a dual growth factor sustained-release delivery system composed of electrospun Polycaprolactone nanofiber (PCL NF) that continuously releases vascular endothelial growth factor and basic fibroblast growth factor on primary BMECs, hippocampal neurons, and an Neurovascular unit (NVU) model after OGD injury. The unique NF membrane created directly protected NVUs treated to OGD by inhibiting the JAK2/STAT3 pathway, leveraging the synergy of two growth factors. These findings could lead to a new treatment method for ischemic cerebrovascular disorders.[32]

TRAUMATIC BRAIN INJURIES (TBIS)

TBI is described as short- or long-term brain damage caused by external mechanical forces such as accelerating, decelerating, and spinning forces that cause direct physical disturbance of neural tissues.[33] At present, there is no clinically validated therapy for repairing cerebral parenchyma loss caused by TBI. As a result, neurogenerative technologies are urgently needed to address this problem.

Nanofiber scaffolds

Collagen scaffolds have shown potential in healing the CNS after TBI by including hydrogels, which can contain water molecules. Collagen hydrogel gelates in physiological circumstances, making it suitable for TBI healing. In a recent experiment, collagen fibers infused with alginate hydrogel were loaded with iPSC-derived neurons, and neuronal maturation and neural network formation were observed.[34] Collagen-chitosan scaffolds loaded with mesenchymal stem cells (MSCs) were found to improve motor function in a rat TBI model.[35] Functional hyaluronate collagen scaffolds have been shown to enhance NSC differentiation into functioning neurons during TBI repair.[36] In the rat TBI model, the scaffold enhanced cognitive and locomotor function, reduced apoptotic response and neuroinflammation, and restored neural networks.[37] This suggests that scaffold implantation could be a novel method of repairing brain damage.

SPINAL CORD INJURY (SCI)

SCI produces terrible paralysis, which may end in the patient being permanently bedridden and imposing a lifelong physical and mental strain on the patient's family. The neurological condition is characterized by primary mechanical injury and secondary inflammatory response-mediated harm, neither of which has an effective treatment.[38]

3D culture and organoid and coculture

A bioengineered transplantable spinal cord-like tissue (SCLT) was constructed *in vitro* by replicating the white matter and gray matter composition of the spinal cord utilizing an NSC-based tissue engineering approach in a recent advanced experiment. Organotypic coculturing with dorsal root ganglion (DRG) or muscle cells revealed that the SCLT uses spinal cord organogenesis potentials to connect to the targets. In rats,

SCLT transplantation into the transected spinal cord resulted in considerable motor function recovery of the paralyzed hind limbs. There was greater remyelination and increased innervation in the tissue. The pro-regeneration environment aided the donor neurons in the establishment of a neural relay.[39]

Another study looked at how combined olfactory ensheathing cells, Granulocyte colony-stimulating factor, and lipopolysaccharide therapy affected cell viability after scratch damage generated by a cataract knife on cells in an *in vitro* model of spinal-derived neural injury with mixed neuronal-glial cultures. The combined therapy prevented cell death and gradually reduced the size of the gap. By establishing a neuroprotective environment for cells, the combined therapy improved cell survival after spinal damage. As a result, the findings shed new light on the combined therapy, which might be considered a viable preclinical therapeutic method for SCI as it advances into clinical trials.[40]

Nanofiber scaffolds

The use of NSCs may benefit people with SCI. Due to the inflammatory environment, NSCs often grow into astrocytes rather than neurons. Paclitaxel (PTX), a microtubule-stabilizing medication, has been demonstrated to boost NSC differentiation into neurons after SCI. Stromal cell-derived factor 1 (SDF-1) has the ability to attract NSCs and so direct stem cell migration. The collagen scaffold was produced by loading SDF-1 and nanoparticle-encapsulated poly (lactic-co-glycolic acid) (PLGA) containing PTX (PLGA-PTX) into a 3D collagen porous scaffold, which allowed for progressive PTX release. There was neural regeneration through the conduit channel for NSC migration and neuronal differentiation when the functional scaffolds were introduced into the lesion site. There was improvement in motor function and less glial scar formation. A 3D collagen porous scaffold mixed with PLGA-PTX and SDF-1 was found to be effective in the study.[41]

PERIPHERAL NERVE DISEASE

In adults, neuronal cells exhibit limited regenerative capabilities. Consequently, severe peripheral nerve injuries often remain unresolved, culminating in paralysis. The placement of a nerve graft is typically necessitated for the restoration of function. Modern cell culture methods offer novel avenues that could revolutionize the treatment of even severe peripheral nerve injuries by neuroregeneration.

Microfluidics

In recent years, a new microtube containing gradient decellularized porcine sciatic nerve ECM hydrogel (pDScNM-gel) from microfluidics for sciatic nerve regeneration has been produced. The pDScNM improved axon development and proliferation of primary DRGs in a concentration-dependent way. When cells were cocultured in a gradient pDScNM microtube, these characteristics were likewise seen. The *in vivo* regeneration and functional recovery of the sciatic nerve was also achieved by combining the gradient pDScNM microtubes with a medical silicon tube. These findings suggested that microtubes with gradient pDScNM could be a feasible alternative for healing peripheral nerve deficits and have a high therapeutic potential.[42]

A recent update described a 3D peripheral nervous system (PNS) microfluidic platform that mimicked the entire range of myelination, demyelination, and remyelination utilizing primary Schwann cells (SCs) and motor neurons (MNs). Based on three independent design parameters, the platform enabled repeatable hydrogel patterning and long-term stable coculture of MNs and SCs *in vitro* for 40 days. Furthermore, the detachable substrate on demand allowed for in-depth biological examination. It revealed the ability of lysophosphatidylcholine to simulate segmental demyelination and the recovery of myelin structure with the use of two drugs: benzatropine or methylcobalamin. This 3D PNS disease-on-a-chip could be used to better understand the pathophysiology of demyelination and to screen medications for remyelination.[43]

BIPOLAR DISORDER

In the treatment of depression, stem cell therapy has shown potential. Neurogenesis plays an important role in depression, as decreased neurogenesis in the hippocampus is frequently reported in depressed individuals, potentially leading to depressive symptoms. On the other hand, increased neurogenesis has the potential to mediate antidepressant effects.[44]

Zhang *et al*. performed a study in which they used HUC-MSCs to treat depression-like symptoms associated with myocardial infarction. They discovered that infusing HUC-MSCs dramatically enhanced cardiac function and depression-like behavior by regulating microglial polarization through Jmjd3 gene downregulation and microglia polarization.[45]

Furthermore, evidence indicates that glutamatergic anomalies and glial pathology, as well as monoaminergic system malfunction, play an important role in depression. Mesenchymal stem cells expressing glutamate transporters, for example, might restore normal glutamatergic transmission and brain-derived neurotrophic factor levels, potentially reducing depression symptoms.[46]

Furthermore, increased proinflammatory cytokine release, such as monocyte chemoattractant protein-1, interleukin-1, interleukin-6, and tumor necrosis factor-alpha, might result in depression-like behaviors. Therapy using adipose-derived mesenchymal stem cells has been found to reduce these cytokines and alleviate depression symptoms.[47]

Overall, stem cell therapy has the potential to modulate depressive illnesses through mechanisms such as neurogenesis, glutamatergic transmission modulation, and anti-inflammatory effects. These findings suggest possible therapeutic implications in the treatment of depression.[48]

AUTISM

Recent research has investigated the use of cell-based techniques to treat autism spectrum disorders (ASD). One study focused on fetal stem cell (FSC) transplants in autistic children. Pre-transplantation, six months, and 12 months after the procedure, the participants were thoroughly observed. FSCs were injected both intravenously and subcutaneously. Autism Treatment Evaluation Checklist and Aberrant Behavior Checklist assessments were used. The findings revealed no substantial adverse events, such as infections or immunological problems. When compared to pre-treatment values, statistically significant improvements were detected in a variety of domains, including speech, sociability, sensory perception, and general health, as well as reductions in total scores.[49]

Another study looked at the use of mesenchymal stromal cells (MSCs) to treat neuroinflammation in children with ASD. Children were given intravenous infusions of human cord tissue mesenchymal stromal cells (hCT-MSCs) in this open-label phase I research. Except for a few episodes of agitation during administration, these therapies were well-tolerated. Some youngsters produced anti-human leukocyte antigen (HLA) antibodies, but they had no clinical consequences. Importantly, six of the 12 participants improved on ASD-specific assessments.[50]

Furthermore, some studies have revealed that hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) may help alleviate ASD symptoms by lowering inflammation and boosting stem cell mobilization, proliferation, and differentiation in tissues. These findings point to promising improvements in the use of cell-based treatments to treat ASD, with an emphasis on safety and efficacy.[51]

SCHIZOPHRENIA

A recent study concluded that a single intracerebroventricular injection of bone marrow-derived MSC can suffice for long-term reversal of changes in adult hippocampal neurogenesis and improve schizophrenia-like behavioral phenotype inflicted by developmental exposure to ketamine in mice.[52]

OTHER TECHNOLOGIES

1. Dental pulp stem cells (DPSCs): At present, the transplanted DPSCs alone or in combination with several novel nerve conduits, such as ethyl acrylate collage, are being used in 3D culture. Several current studies have successfully applied DPSCs in nerve regeneration.[53] In an *in vivo* rat sciatic nerve injury, nerve conduit preloaded with DPSCs promoted functional repair.[54] Hypoxia-treated DPSCs transplantation into damaged rat spinal cord increased vascularization and oxygenation of the injured spinal cord.[55] Pre-differentiated human DPSCs (hDPSCs) were injected into the striated urethral sphincter and transplanted into the pudendal nerve of female rats whose pudendal nerves had been surgically severed to cause stress urinary incontinence. After four weeks, the external urethral sphincter's thickness significantly recovered as a result of the hDPSCs' effective engraftment. These transplanted stem cells also showed *in vivo* loyalty to the myogenic lineage. It is significant to note that the hDPSCs supported vascularization in the afflicted area. There was a discernible increase in incontinence as a result of these cellular treatments, emphasizing the regenerative potential of hDPSCs in treating stress urinary incontinence.[56] In a DPSC auto-transplantation in the unilateral hindlimb of diabetic rats, *in vivo* in diabetic rat sciatic nerve injury, improved blood flow, nerve conduction velocity, capillary number, and intradermal nerve fiber density.[57] The results of a recent study suggested that dental follicular cells could be a viable source of dopaminergic neurons for functional transplantation, and they also prompted further thorough research on the subject's potential as a PD treatment.[58]
   Mead *et al*.[59] conducted retinal damage studies and discovered substantial results. They discovered that DPSCs produce many neurofibrillary tangles (NTFs). This NTF release resulted in increased proliferation of neural III-tubulin+ retinal cells and prolonged neuritis. Furthermore, transplanting DPSCs into the vitreous fluid of mice following optic nerve injury enhanced the survival of Brn-3a+ retinal ganglion cells and encouraged axonal regeneration. About 44% of DPSCs in conditioned medium from the damaged retina expressed the photoreceptor marker rhodopsin. These findings point to a novel and intriguing mechanism with potential therapeutic implications, highlighting the necessity of additional research in this field. Mead *et al*. found that DPSCs secreted a large number of NTF, which enhanced neural βIII-tubulin+ retinal cell proliferation and lengthened the neuritis.[59] In addition, transplantation of DPSCs into the vitreous humor of mice after optic nerve injury promoted Brn-3a+ retinal ganglion cell survival and axonal regeneration. It has been reported that 44% of DPSCs expressed a photoreceptor marker rhodopsin in a conditioned medium from the damaged retina. This promising novel mechanism should be further explored for clinical applications.[53]
2. Therapies using translocator protein (TSPO) ligands have been found to be very useful in many central

and peripheral injury models.[60] In a recent study, neuroinflammation in a mouse model of prion-induced chronic neurodegeneration (ME7) was controlled by a colony-stimulating factor receptor 1 inhibitor through TSPO modulation.[61]

3. Other cell culture experiments also targeted Parkinson's dementia, including the development of a unique procedure for effectively differentiating hiPSCs into high-purity midbrain dopaminergic (mDA) neurons. This breakthrough holds potential for studying the causes of neurological illnesses, conducting drug screening investigations, and using hiPSC-derived mDA neurons for cell transplantation.[62]
4. Another study concentrated on the metallothionein (MT) family, which includes MT1 through MT4. MT1 and MT2 are present largely in astrocytes and are thought to aid in neuronal survival and axonal regeneration. Exogenous MT1 and MT2 experiments revealed enhanced neuronal survival and axonal development in cortical, hippocampal, and dopaminergic cultures.[63]
5. Neuroprotection through G protein-coupled receptor (GPR)37/GPR37L1: Prosaptide, which acts on the receptors GPR37 and GPR37L1, has been shown in studies to protect cultured astrocytes from oxidative stress, indicating a potential function in neuroprotection. Ongoing research aims to understand how these receptors regulate astrocytic function and, as a result, neuronal activity and survival. It is yet unclear if these effects are limited to specific neuron subtypes, such as catecholaminergic neurons. Notably, small molecule GPR37 and GPR37L1 ligands are currently unavailable, leaving the pharmacology of these receptors as an unknown territory with the potential to provide significant therapeutic medicines.[63]
6. In mice, bone marrow-derived mesenchymal stem cells (BM-MSCs) suppressed chronic experimental autoimmune encephalomyelitis (EAE), a model of MS. These cells provided neuroprotection and preserved the majority of axons in the central nervous system of successfully treated animals, showing their therapeutic potential in the context of EAE and, by extension, MS.[25]
7. iPS cells have shown potential in the treatment of SCI patients by restoring motor function without tumorigenicity.[64] However, challenges such as establishing iPS cells, inducing them into neural stem/progenitor cells (NS/PCs) *in vitro*, and quality control are significant. A collaborative team is planning iPS-based cell therapy for SCI patients in the subacute phase using clinical-grade integration-free human iPS cell lines. Clinical trials are planned for chronic phase SCI and stroke, with the aim of using iPS cell-derived NS/PC stocks for regenerative medicine.[65]
8. Another study looked into the use of mesenchymal stromal cells (MSCs) to treat neuroinflammation in children with ASD. Children in an open-label phase I study received intravenous infusions of hCT-MSCs. These therapies were well-tolerated, with only a few occurrences of agitation during administration. Some youngsters produced anti-HLA antibodies, which did not cause any clinical problems. Notably, six of the 12 participants improved on ASD-specific measures.
9. Furthermore, some research has suggested that HSCs and mesenchymal stem cells (MSCs) may be beneficial in easing ASD symptoms by reducing inflammation and encouraging stem cell mobilization, proliferation, and differentiation in tissues. These findings point to hopeful improvements in the use of cell-based treatments to treat ASD, with an emphasis on safety and efficacy.[66]

Although stem cell-based treatments have great promise for neuroregenerative therapy, there are still many obstacles to overcome before these experimental methods may be used in clinical settings. To achieve medical manufacturing requirements, one major difficulty is increasing the production of clinical-grade stem cells and differentiation methods.[67] Our incomplete knowledge of the best cell dosages, delivery strategies, and mechanisms of action for patient safety and efficacy is another significant obstacle.[68] Concerns about transplanted cells' propensity to cause tumors and immunological rejection still exist.[69]

Current research endeavors to tackle these obstacles by means of interdisciplinary partnerships that combine proficiencies in stem cell biology, biomaterials, clinical medicine, and industry. For instance, large-scale cell therapy production is being facilitated by the establishment of Current Good Manufacturing Practice (cGMP) facilities with a focus on stem cell manufacturing.[70] In addition, to maximize cell distribution and survival after transplantation, improved biomaterial scaffolds are being developed.[71] Mechanisms underlying stem cell variability and fate are being elucidated with the use of computational modeling techniques.[72] To turn the promise of stem cell technology into practical regenerative treatments, advancements in these fields will be essential.

CONCLUSION

This review emphasizes how greatly advanced cell culture methods have the potential to change neuroregenerative therapy for severe neuropsychiatric illnesses. Our understanding of disease causes is accelerated by techniques such as 3D culture, organoids, coculture systems, microfluidics, and nanofiber scaffolds, which allow for enhanced modeling of human brain anatomy and function *in vitro*. The reviewed research demonstrates how these technologies can be used to test drug candidates, find new therapeutic targets, and create stem cell-based treatments for diseases that were previously thought to be incurable.

Although the emphasis here is on applications in neurologic

conditions such as Alzheimer's, stroke, and SCI, as our understanding of the underlying biological processes deepens, these state-of-the-art cell culture techniques will probably also spur advancements in the treatment of psychiatric disorders. Further exciting developments in the field of cell-based therapy for neurologic and mental illnesses include the use of DPSCs, iPSCs, and *ex vivo* modified cell transplantation.

There is a promise for solving and treating these urgent health issues thanks to the quick advancements in *in vitro* modeling and neuronal healing that this study highlights. Although stem cell-based therapies have enormous promise, more work has to be done to convert these experimental strategies into secure and efficient therapeutic interventions. Upgrading stem cell production, streamlining delivery systems, and clarifying mechanisms of action continue to be major obstacles. These obstacles will be addressed, and the potential of stem cell technologies for neuroregenerative medicine will be realized with the aid of devDevelopments in manufacturing, biomaterials, and computational modeling. Also, to fully achieve the potential of neuroregenerative medicine, more research is needed at the nexus of stem cell biology, tissue engineering, and neuropsychiatry.

Authors' contributions

SA was involved in the conception design of the work, the acquisition of data, and preparing the draft of the manuscript. SA, VCRA, and JPJ were involved in the analysis, interpretation of data, and review of the final draft of the manuscript. All have approved the submitted version and have agreed both to be personally accountable for the contributions and to assure the accuracy or integrity of any part of the work.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient consent is not required as there are no patients in this study.

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There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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