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Biomaterials and stem cells targeting the microenvironment for traumatic brain injury repair: progress and prospects

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Traumatic brain injury (TBI) disrupts neural pathways, leading to sensory, motor, and autonomic dysfunctions, with no fully restorative therapies currently available. The pathophysiology of TBI involves two phases: primary injury and secondary injury. These stages are characterized by dynamic alterations in cellular death, glial activation, and inflammatory cytokine profiles, collectively establishing a regeneration-inhibitory microenvironment. Biomaterials, such as hydrogels and nanofiber scaffolds, mimic the extracellular matrix (ECM) to provide structural support, modulate local inflammatory responses, and degrade glial scar components. However, standalone biomaterial applications face limitations in dynamically addressing the multifaceted pathological progression. Combinatorial therapies integrating stem cells overcome these constraints: stem cells promote angiogenesis and synaptic remodeling through paracrine secretion of exosomes and cytokines, while differentiating into functional neural cells. Concurrently, biomaterials shield transplanted stem cells from hypoxia and cytokine toxicity, enhancing their viability and differentiation efficiency. Further combination with targeted strategies, such as functionalized material delivery of anti-inflammatory drugs, gene editing stem cell overexpression of nerve growth factor BDNF, precisely intervenes in the key pathways of secondary injury. This review systematically summarizes synergistic approaches combining biomaterials with cells, pharmaceuticals, and cytokines, emphasizing the critical roles played by spatiotemporal dynamic regulation and personalized design. These integrated strategies provide novel insights into developing multidimensional therapeutic frameworks to address TBI repair challenges.

1. Introduction

TBI is a complex form of brain injury that may be caused by external mechanical forces that result in brain dysfunction or other evidence of brain pathology.[1] TBI is a major central nervous system (CNS) injury and represents a significant clinical challenge. The prognosis of TBI is complex because it includes any physical event that results in an injury—typically primary (direct) mechanical injury and secondary (indirect) peripheral parenchymal injury. TBI is a complex form of brain injury caused by external mechanical forces that result in brain dysfunction or other pathological evidence. It is currently estimated that up to 69 million people worldwide experience TBI each year, and the annual cost of TBI to the global economy is approximately $400 billion,[2] resulting in healthcare costs and financial burden for patients and families.[3] TBI is the leading cause of morbidity and mortality worldwide and may become the third leading cause of death in the world by 2020.[4]

TBI in humans is primarily traumatic, and depending on the severity brought about by the trauma, TBI has long been categorized as mild (GCS 14–15), moderate (9–13), and severe (3–8) based on the Post-Resuscitation Glasgow Coma Scale score.[5] After TBI, the brain undergoes a complex pathophysiologic process, and injuries from TBI are categorized into primary and secondary injuries. Pathological consequences after primary brain injury may include diffuse axonal damage, blood–brain barrier (BBB) damage, hypoxia, and hematoma. Primary injury is caused by mechanical shock, which induces a series of pathological and biochemical changes that induce secondary injury, exacerbate primary cellular damage or even lead to new injury.[4] Secondary injury is caused by neuronal depolarisation, generation of oxygen free radicals and activation of pro-inflammatory cytokines. Reconstruction of tissue

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injury requires inhibition of secondary injury and repair of the tissue at the site of injury. However, unlike other tissues, the brain cannot repair itself normally after injury.[6]

TBI can be treated using a range of modalities, including pharmaceutical interventions, bioactive molecule delivery, cellular and biomaterial transplantation, therapeutic processes, and electrical stimulation. Neurocompatible biomaterials show great promise for therapeutic intervention in TBI, either as single or combined grafts. Biomaterials have multiple functions in TBI repair. Some of these roles include acting as extracellular matrix (ECM) to occupy the injury space and reestablishing connections to the damaged brain, carrying potential cells or bioactive substances to the site of the injury, guiding axonal regeneration, drawing in endogenous neural stem progenitor cells (NSPCs), and stopping the formation of scar tissue. A growing number of studies have reported the ability of functional biomaterials to modulate the TBI microenvironment and contribute to efficient repair of the damaged brain.[7]

The objective of this study was to thoroughly and systematically assess the pathophysiological alterations that transpire following TBI. We examine the transplantation of diverse biomaterials, either alone or in conjunction with cells and biomolecules, to modify the microenvironment and promote the healing of TBI as a means to identify novel therapeutic targets.

2. Pathophysiology

In pathophysiology, TBI is categorized into two separate phases: the main damage phase and the subsequent injury phase. The first phase starts promptly after an external mechanical trauma, including acceleration, deceleration, or rotating forces. The secondary phase may occur minutes to days following the initial injury.[8,9] The assessment of TBI severity depends not only on the degree of severity of the primary injury but also on the subsequent secondary response. The timing and presentation of these phases may vary between animal models and human patients. This analysis will concentrate on the two phases frequently observed in human cases of TBI (Fig. 1).

2.1 Primary stages of TBI

The pathophysiology of TBI involves a two-step process, commencing with the primary injury, which results directly from the mechanical forces that caused the injury. A series of molecular and biochemical events ensues, contributing to secondary brain injury, which is typically characterized by increased intracranial pressure, nerve damage, vascular impairment, tissue swelling, and hypoxic injury.[10]

While this stage cannot be treated, preventive measures may be implemented to delay its onset. Following the occur-

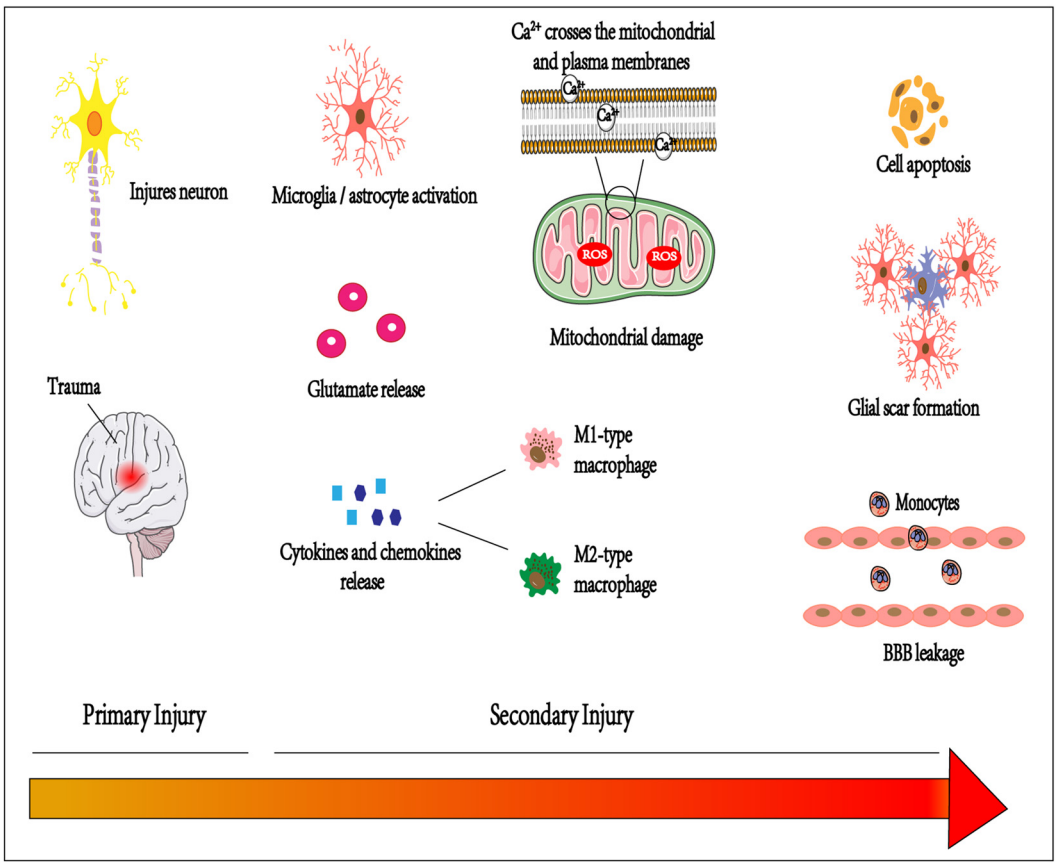

Fig. 1 Timeline of events in the primary and secondary stages of TBI.

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rence of TBI, localized damage can present as either focal or diffuse brain injury; both types encompass the stages of primary and secondary injury.

2.2 TBI secondary to injury

Excessive release of excitatory neurotransmitters, particularly glutamate, results in a significant influx of Ca^{2+} into the post-synaptic terminal. This influx causes depolarization, initiating a hypermetabolic response that may culminate in metabolic depression lasting several days. Elevated calcium concentrations interfere with various intracellular processes, including the induction of a cellular hypoxic condition. During hypoxia, the brain transitions to the glycolytic pathway, resulting in the accumulation of lactate.[11,12] Mitochondria are integral to the pathology of TBI. Elevated calcium ion concentration results in heightened mitochondrial calcium ion uptake, causing mitochondrial membrane permeabilization, dysfunction, and an augmented state of oxidative stress, as evidenced by the generation of reactive oxygen species (ROS).[13] Oxidative stress intensifies additional pathological mechanisms linked to traumatic brain injury, including cytoskeletal damage *via* calpain activation and neuroinflammation through the activation of glial cells.[14–16] Following brain injury, oxidative stress modifies the essential structure of tight junction proteins within the BBB. The BBB is a crucial element of a healthy brain, functioning as a barrier between the CNS and the peripheral body.[17] The disruption of the BBB in TBI results in heightened paracellular permeability.[18] The adverse microenvironment surrounding the lesion site predominantly influences the transformation of activated natural neural stem cells (NSCs) into astrocytes. This process results in glial fibrosis, which occludes the interstitial spaces among nerve cells.[19] Secondary injury typically represents the body's effort to mitigate damage and address the ramifications of the primary injury, aiming to restore both the structural and functional integrity of the brain.[20]

The primary phase of TBI is initiated by neuronal damage resulting from brain trauma. This injury subsequently activates astrocytes and microglia during the secondary phase. The activation of these glial cells is associated with an increase in glutamate levels, which leads to excitotoxicity and a subsequent influx of Ca^{2+} into damaged neurons and mitochondria. Excessive accumulation of Ca^{2+} can result in mitochondrial damage, production of reactive ROS, and ultimately, neuronal apoptosis and necrosis. Furthermore, mitochondrial dysfunction contributes to heightened ATP consumption, which may induce cerebral hypoxia and reduce the efficiency of glycolytic metabolism. The disruption of the blood–brain barrier allows for neutrophil infiltration, triggering an inflammatory response. This process is accompanied by the release of various cytokines and chemokines, facilitating the activation of M1 and M2 macrophages. The proliferation of astrocytes further contributes to the formation of glial scars, which impede neurotransmission and hinder the recovery process.

3. Biomaterial scaffolds in TBI

Stents designed for the repair of TBI must meet several multifunctional requirements. Firstly, biocompatibility is essential, necessitating that the stent can be implanted with minimal inflammatory response or rejection.[20] The scaffold must also be biodegradable and adaptable to the *in vivo* environment to ensure optimal integration with surrounding tissues. The scaffold must integrate trophic factors, cells, drugs, and additional pertinent components. The scaffold is essential for guiding axonal development and promoting cell proliferation.[21] The scaffold material must facilitate optimal conditions for cell adhesion, proliferation, and differentiation. Scaffolds have been widely employed in tissue engineering,[22] underscoring the significant role they play in advancing therapeutic strategies.

3.1 Hydrogel

Hydrogels are cross-linked hydrophilic polymers capable of retaining substantial amounts of water, which makes them suitable for a diverse range of experimental and clinical applications. Their high water content creates a hydrated biological microenvironment, while their reactivity, injectability, and degradability render hydrogels promising candidates as immunomodulatory materials.[14,23] Hydrogels can be made from many different materials, such as natural organic materials like decellularized tissues and ECM-derived macromolecules like chitosan, collagen, and hyaluronic acid (HA). Additionally, they can be derived from synthetic polymers, such as polyethylene glycol (PEG) and polyacrylamides, as well as from synthetic supramolecular gels, including self-assembling peptides (SAPs) and monosaccharides. The application of hydrogels in the treatment of TBI can be categorized into three main types: (1) the use of hydrogels alone; (2) the use of hydrogels as drug delivery vehicles; and (3) the use of hydrogels for cellular therapeutic delivery. The following sections will discuss various hydrogels in terms of their composition and functional roles.

3.1.1 Chitosan hydrogel. Chitosan is a cationic polyelectrolyte derived from the deacetylation of chitin. Compared with traditional inorganic flocculants, chitosan offers several advantageous properties, including non-toxicity, biodegradability, biocompatibility, and robust mechanical strength. Notably, chitosan does not contaminate biological systems, as polysaccharides similar to chitosan are naturally found in the cell walls of various microalgal species, establishing it as a bio-based, non-toxic polymer[24] (Fig. 2). Chitosan is characterized by its high reactivity due to its cationic charge and adhesive properties, and its cationic nature enables electrostatic interactions with anionic glycosaminoglycans in glial scars, facilitating localized scar component degradation (*e.g.*, CSPGs). Chitosan has been extensively studied as a potential biomaterial for various applications, such as drug delivery systems, wound healing agents, and tissue engineering frameworks. Loaded with neurotrophic factors (*e.g.*, BDNF) or anti-inflammatory agents (*e.g.*, IL-10), chitosan hydrogels reduce oxidative stress and enhance endogenous NSC migration.[25,26]

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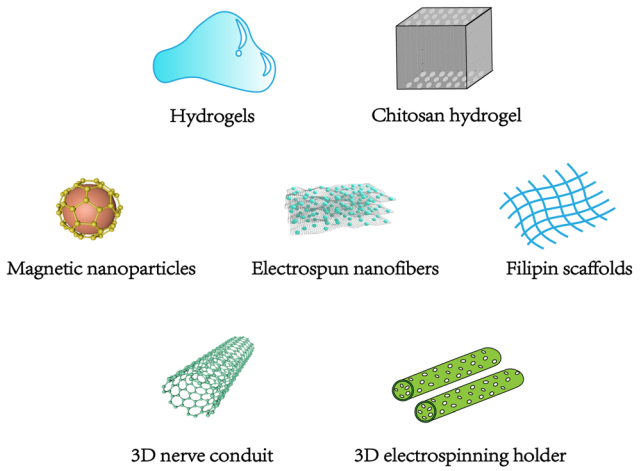

Fig. 2 Introduction of biomaterial scaffolds.

Furthermore, the role chitosan plays as a membrane sealant and effective neuroprotectant has been explored, with numerous *in vivo* and *in vitro* studies demonstrating that its application at the injury site promotes the sealing of neuronal membranes and restores nerve impulse conduction in the affected region.[27–29] Chitosan and chitosan-functionalized nanoparticles are extensively used for gene transfer; however, chitosan is typically not used in isolation due to its comparatively low transfection efficiency.[30]

Chitosan is commonly reconstituted with various materials to improve its properties, including the grafting of polyethyleneimine (PEI) onto chitosan or the formation of chitosan–PEI composites, which have demonstrated efficacy in both *in vitro* and *in vivo* gene delivery applications.[31] Furthermore, multiple studies have demonstrated that collagen–chitosan composite scaffolds possess favorable biocompatibility and mechanical properties. Collagen, a natural extracellular matrix protein, exhibits favorable biocompatibility and low immunogenicity, and is essential for cell adhesion and migration, thereby facilitating the microenvironment necessary for tissue repair.[32] However, collagen degrades rapidly and has limited mechanical strength, making it unsuitable as a standalone scaffold for TBI applications. The collagen–chitosan composite scaffolds address each other's limitations and enhance nerve repair and functional recovery in TBI.[33,34]

PEG and chitosan polymers possess the capability to seal or fuse compromised cell membranes. The hydrophilic properties of polyethylene glycol and its derivatives facilitate the reconstruction of the phospholipid bilayer in compromised cell membranes by addressing defects in the plasma membrane. Moreover, owing to its biodegradable characteristics, chitosan can be efficiently isolated from polyethylene glycol and associated constructs, including silica-based structures, in solution. Chitosan is synthesized *via* the *N*-deacetylation of chitin, which is the second most prevalent naturally occurring polysaccharide. The primary amine group facilitates covalent coupling with a range of chemicals and drugs. Chitosan exhibits significant biocompatibility and biodegradability, and it has been thoroughly investigated as a potential drug carrier and for various tissue engineering applications.[35]

The short half-life of neurotrophic factors and growth factors under physiological conditions poses challenges for maintaining their biological functions in the brain. Biodegradable chitosan loaded with various neurotrophic factors,[36] such as neurotrophic factor-3 (NT3), was utilized. The NT3–chitosan formulation allows for sustained and stable release of NT3, prolonging its functional duration and enhancing biological efficacy, exhibiting both neuroprotective and neurogenic properties.[37] NT3–chitosan not only promotes neuronal differentiation and facilitates blood transport but also exerts anti-inflammatory effects, creating a favorable microenvironment for regenerating and reconstructing neural tissue, thereby restoring sensory and motor functions after TBI. NT3–chitosan, as a composite scaffold, effectively minimizes the quantity of NT3 needed to sustain long-term biological effects while inhibiting NT3 denaturation and protein hydrolysis.[38] Ferulic acid, a common plant phenol, exhibits significant antioxidant properties and offers numerous health benefits, such as anti-inflammatory, glucose-lowering, anticancer, anti-apoptotic, anti-aging, hepatoprotective, and neuroprotective effects.[39] Research indicates that chitosan hydrogels can release over 85% of ferulic acid within 24 hours, with the release of active molecules being adjustable through modifications to the cross-linking density of the chitosan hydrogel matrix. Given that oxidative stress significantly increases following TBI,[40] controlling oxidative damage and protecting neuronal cells from free radicals is crucial. Experimental evidence indicates that the antioxidant properties of ferulic acid can reduce oxidative damage caused by H_2O_2. Modulating the release of ferulic acid from chitosan effectively inhibits oxidative stress following TBI.

3.1.2 Composite hydrogels. SAP hydrogels are hydrogels developed through the rational design of supramolecular peptide scaffolds, where the peptide sequence can be tailored to modify the physical and biochemical properties of the hydrogel.[41] Analyses of the physicochemical properties of SAP hydrogels indicate that modifying the 2D or three-dimensional (3D) structure, stiffness, porosity, nanomorphology, wettability, surface charge, and molecular characteristics can establish a conducive environment for the treatment of injured areas. Hybrid systems (*e.g.*, chitosan–gelatin, collagen–hyaluronic acid) integrate mechanical robustness (*via* covalent cross-linking) with bioactivity. Composite hydrogels synergize ECM-mimetic topography with tunable stiffness (1–10 kPa) to match brain tissue mechanics. Dual-delivery systems within composites enable sequential release of vascular endothelial growth factor (VEGF) and NT-3, addressing both vascular and neuronal repair. This is accomplished by the continuous administration of inflammatory agents and the modulation of the host immune response of stem cells, thus creating a favorable environment at the injury site. Injectable SAP hydrogels demonstrate the capability to penetrate the BBB, facilitating direct interaction with the injured region. The SAP hydrogel-

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mediated immunomodulation facilitates the controlled release of therapeutic agents, including small-molecule drugs, neurotrophic growth factors, and anti-inflammatory drugs, thereby improving drug utilization and demonstrating significant potential in TBI treatment.[42] The self-assembled scaffolds demonstrate a soft and deformable structure attributed to the internal non-covalent interactions among their monomers, allowing them to adapt to the contours of injured tissues or organs upon injection.[43,44] Additionally, SAP hydrogels can fill cystic cavities resulting from trauma and provide physical support to neighboring brain tissue, thereby preventing further damage caused by the collapse of the injured area. Nonetheless, their utilization has certain hazards, including the accumulation of chemical breakdown byproducts and increased inflammatory indicators, which may facilitate glial scarring, immunological responses, and cellular apoptosis.[45,46] The prolonged degradation of permanent or non-resorbable implants can provoke immunogenic and inflammatory responses. Successful integration into neural networks necessitates that the material's chemical composition permits a sufficiently slow degradation rate to support cellular integration and tissue growth, while producing only biocompatible degradation products to avoid adverse immune responses. Strategies to enhance hydrogel stability commonly involve the modification of amino acids and peptides or the alteration of their conformations.[47]

3.1.3 Stimulus-responsive hydrogels. A photoresponsive hydrogel is a functional hydrogel that can respond to ultraviolet, visible, and infrared light by converting light signals into chemical signals. This transformation is induced by changes in structure or properties through isomerization and dimerization reactions. Photoresponsive hydrogels consist of a polymer network containing a photosensitive component, enabling reversible cross-linking and photothermal capabilities.[48] The gelation mechanisms of photoresponsive hydrogels include: (1) the incorporation of chromophores into the gel system, which weakens hydrogen bonding forces and alters the structure and properties of the hydrogel;[49] (2) changes in hydrogel structure due to photocleavage and photooxidation of the added chromophore following light stimulation, leading to non-crosslinking of the hydrogel;[50] and (3) stimulation of photosensitive molecules by light, resulting in the production of ions that create an ionic concentration gradient inside and outside the gel, thereby increasing osmotic pressure and causing the gel to swell.[51]

Thermoresponsive hydrogels are reactive hydrogels characterized by varying hydrophobic groups that alter their physical and structural properties with temperature changes. Hydrogels may consist of natural and synthetic polymers. Natural examples include cellulose and HA, whereas synthetic alternatives comprise PEG esters and dimethylamine. The formation of thermoresponsive hydrogels is based on the principle that below the lower critical solution temperature (LCST), hydrogen bonds establish between hydrophilic groups and hydrophilic molecules, enhancing the solubility of the hydrogel, which can initially be administered as a solution. As the temperature rises, hydrogen bonding diminishes, interactions between hydrophobic groups increase, and solubility decreases. Thermoresponsive hydrogels have been widely employed for drug release and cell encapsulation.[52] Pan *et al.* incorporated black phosphorus nanosheets (BPNs) into platelet-rich plasma (PRP)–chitosan thermoresponsive hydrogels. With rising temperature, proton transfer from amino groups on chitosan diminished electrostatic repulsion between chitosan molecules, facilitating the aggregation of hydrophobic groups and leading to hydrogel formation. This thermoresponsive hydrogel enables the controlled, gradual release of degradation products from BPNs in response to thermal stimuli, which is beneficial for the treatment of rheumatoid arthritis (RA).[53] In conclusion, thermoresponsive hydrogels hold significant promise for future drug delivery applications. However, translating this hydrogel technology to clinical settings requires further in-depth studies to enhance biocompatibility, safety, and experimental reproducibility.

Magnetically responsive hydrogels are synthesized by doping cross-linked polymers with magnetic nanoparticles, which can modify the structure, properties, and response functions of these particles to magnetic fields (Fig. 2). Magnetic nanoparticles within nanohydrogels, when exposed to a magnetic field, can self-assemble into ordered structures that anisotropically alter the hydrogel's surface, thereby enhancing cell proliferation, neural regeneration, signal transduction, and extracellular matrix regeneration.[54] Magnetic nanoparticles vibrate in an alternating magnetic field, resulting in increased temperature. This elevation in temperature enhances the movement of drug molecules and accelerates polymer degradation, thereby facilitating drug release.[55] However, the aggregation of magnetic nanoparticles under a magnetic field can reduce the pore space between them, potentially limiting drug release.[56]

The importance and necessity of hydrogels in the treatment of TBI can be elaborated from the following points. (1) Biomimetic architecture and microenvironment compatibility: hydrogels replicate the 3D ECM of native brain tissue, offering structural and biochemical support for neural cells and stem cells. This biomimetic design enhances neural regeneration and synapse reformation while minimizing immune rejection, outperforming traditional rigid implants (*e.g.*, titanium meshes) in cell adhesion, proliferation, and differentiation within lesion sites. (2) Dynamic regulation of pathological microenvironments: post-TBI microenvironments are characterized by neuroinflammation, oxidative stress, and vascular disruption. Functionalized hydrogels enable targeted modulation through anti-inflammatory reprogramming: citrate-based nanoparticle-incorporated hydrogels polarize macrophages toward the M2 phenotype, suppressing pro-inflammatory cytokine release. Such strategies mitigate microglial hyperactivation in TBI models. Hydrogels can load VEGF or neurotrophic factors to promote angiogenesis and neurite outgrowth. (3) Stem cell delivery and functional augmentation: hydrogels address key challenges in stem cell therapy, including low post-transplant viability and poor integration.

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Mechanical protection: hydrogel encapsulation shields cells from shear stress during injection and pulsatile cerebrospinal fluid flow. Lineage-specific differentiation: tunable stiffness (1–10 kPa), porosity, and biochemical gradients (*e.g.*, BDNF gradients) direct stem cell fate toward neurons or glia. (4) Tissue-matched mechanical properties: conventional implants often induce secondary injury due to stiffness mismatch (brain tissue: ~1 kPa *vs.* titanium: ~100 GPa). Hydrogels achieve mechanical harmony with cerebral tissue while offering customizable strength. (5) The injectability and biodegradability of hydrogels make them suitable for minimally invasive treatment.

3.2 Nanofiber material scaffolds

Nanofiber scaffolds can be fabricated *via* electrospinning with fiber diameters of 50–500 nm, mimicking the nanotopography of native brain ECM. Aligned fibers guide axonal growth (*e.g.*, oriented fibers increase neurite extension by 2.5-fold). Functional adaptability includes (1) topological signal guidance: random fibers enhance astrocyte migration, while aligned fibers direct neuronal polarity; (2) multifunctional coatings: fiber surfaces modified with cell-adhesive peptides or conductive polymers enhance electrical signaling.

A viscoelastic polymer solution was uniaxially stretched to form a nanofiber network, and electrospun nanofibers offer distinct advantages over other biomaterials, including ease of preparation, high loading capacity, and tunable mechanical properties.[57] Synthetic polymers such as polyglycolic acid (PGA), poly-L-lactic acid (PLLA), and polycaprolactone (PCL), along with their copolymers, have been extensively utilized in the preparation of neural tissue nanofibers through electrostatic spinning. The mechanical strength, physical properties, and biomolecular recognition of natural materials closely align with those of natural soft tissues, rendering them especially appropriate for tissue engineering.[58] Collagen, gelatin, laminin, and chitosan have been utilized in the development of electrospun nanofibers for neural tissue engineering applications[59] (Fig. 2). Electrospun nanofibers mimic the layered fiber arrangement of collagen, laminin, and other ECM protofibers. The hydrophilic or hydrophobic nature of the nanofibers can be precisely tuned to enhance compatibility with brain tissue and promote therapeutic efficacy. Additionally, electrospun nanofibers replicate other characteristics of cellular ECM, such as a high surface area-to-volume ratio, high porosity, and similar mechanical properties.[60] These attributes enable electrospun nanofibers to improve drug delivery efficiency and facilitate faster, longer-lasting drug responses.

Research has also explored the application of electrostatically spun nanofibers in the treatment of TBI. The effectiveness of L-lactic acid-caprolactone copolymer nanofiber mesh dressings has been investigated, showing their capacity to postpone and alleviate injury processes, such as neurodegeneration, systemic inflammatory cell infiltration, and excessive glial scar formation.[61] The anti-inflammatory properties of electrostatically spun nanofibrous scaffolds merit thorough examination. A recent study demonstrated the covalent attachment of galactose to the surface of poly(lactic acid) nanofiber scaffolds, resulting in the formation of a polymer termed poly (lysine-lactic acid) (PLL-LBA). In a mouse model of traumatic brain injury, the implantation of this scaffold led to enhanced neuronal survival 21 days after implantation, suggesting a possible therapeutic application. Additionally, uniaxially oriented electrostatically spun PCL nanofibers were electrostatically sprayed with microparticles of different densities to create topographical cues for cellular interaction (Fig. 2). *In vitro* experiments indicated that these nanofibers effectively directed axonal growth of PC12 and SH-SY5Y neurons, aligned Schwann cells, and enhanced the migration of NSCs.[62]

Electrospun nanofibrous neural scaffolds can be classified into four categories: randomly oriented nanofibers, aligned nanofibers, 3D nanofibers, and functionalized nanofibers.

3.2.1 Randomly oriented nanofibers. Initially, nanofibers were electrospun in a random orientation and employed in tissue engineering because of their resemblance to the ECM. Both synthetic and natural polymers have been utilized in electrospinning for this purpose. Poly(lactic acid) nanofibers with interconnected pores were synthesized to replicate the natural extracellular matrix structure of the human body. *In vitro* cell culture studies demonstrated that these nanofiber scaffolds supported NSC differentiation and neural synapse formation while also enhancing NSC adhesion.[63] Silk proteins (SF) were prepared for culture with Schwann cells (SCs), showing that regenerated electrospun SF nanofibers enhanced SC adhesion, growth, and proliferation, indicating favorable biocompatibility.[64]

3.2.2 Aligned nanofibers. In neural tissue applications, directing cell growth in a specific orientation is crucial for promoting neuronal alignment. Aligned nanofibers are more conducive to neural synapse growth compared with randomly oriented fibers, as highlighted in previous studies.[65,66] These aligned structures exhibit effective neurite guidance and cell alignment capabilities. Numerous attempts have been made in neural tissue engineering to produce aligned fibers, with evidence demonstrating their effectiveness in guiding cell behavior.

3.2.3 Functionalized nanofibers. Beyond the topographical features, the biological functionality of scaffolds is vital for neural tissue regeneration. Functionalization of neural scaffolds is often achieved through the incorporation of biomolecules, including proteins and associated peptides, into the nanofibers. This creates opportunities for advancing the development of bioactive neural scaffolds. The nervous system synthesizes macromolecular proteins that govern essential processes, including cell division, cell survival, and neurite outgrowth. Neurotrophic factors secreted by target nerve cells or surrounding glia are crucial during nervous system development; only neurons that receive adequate neurotrophic factors are able to survive. Besides neurotrophic factors, ECM-based proteins and other molecules have shown considerable effectiveness in facilitating neural tissue regeneration.[67]

3.3 Three-dimensional (3D) material support

Regeneration of brain tissue following TBI remains a significant challenge, prompting interest in 3D printing as a means

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to design improved brain implant replacements. Numerous studies have demonstrated the positive impact of 3D-printed scaffolds on neural regeneration. These scaffolds bridge the gap between engineered and natural tissues by serving not only as templates for new tissue generation but also by facilitating the exchange of oxygen and nutrients.[68,69] Biomaterials developed through 3D printing technology can effectively address these challenges by allowing customization of size and precise control over the microenvironment.[70] 3D bioprinted or porous scaffolds provide hierarchical porosity (50–200 μm pores) for nutrient diffusion, immune cell infiltration, and vascular network formation. Decellularized ECM scaffolds retain endogenous growth factors and topology for host cell recruitment. 3D graphene oxide scaffolds enhance electrical coupling between transplanted stem cells and host neurons, while microfluidic-integrated scaffolds enable real-time monitoring of metabolite exchange.

The development and investigation of composite natural biomaterials to enhance brain injury repair is essential. Collagen, a natural element of the ECM, is recognized for its excellent biocompatibility, minimal immunogenicity, and biodegradability, which facilitates its extensive use in diverse tissue engineering applications. Nonetheless, the mechanical and thermal properties of collagen are comparatively inadequate, which may impede its supportive function. The rapid degradation rate further restricts its efficacy in TBI therapy.[71,72] Silk proteins, on the other hand, offer superior mechanical strength and environmental stability, serving as viable biomaterials for tissue reconstruction and repair. Nevertheless, the fragility and high solubility of silk proteins can restrict their applications. The complementary properties of collagen and silk proteins can mitigate each other's limitations.[32,73] This study demonstrates that the 3D-printed scaffolds possess a more uniform internal pore size and improved compatibility for cytokine interactions relative to scaffolds produced by merely combining collagen and filipin protein. The intricate 3D scaffolds exhibited suitable porosity, water absorption, and degradation characteristics, enhancing the adhesion and controlled release of exosomes subsequently transplanted to the injury site. Collagen/silk protein scaffolds infused with natural exosomes exhibited enhanced biocompatibility and repair results relative to other scaffolds documented in the literature.

3D nanofiber artificial nerve grafts are designed to serve as structured conduits for bridging neuropathic lesions. Numerous 3D nerve conduits utilizing electrospun nanofibers of diverse compositions have been created. A scaffold comprising parallel fibers embedded within a collagen matrix has been presented. Furthermore, 3D electrospun PCL scaffolds modified with ethylenediamine were developed to facilitate the examination of interactions between rat brain-derived NSCs and randomly oriented submicron PCL fiber scaffolds. The modified scaffolds demonstrated improved hydrophilicity, a notable increase in adherent cell numbers, and enhanced cell spreading across the scaffold. On PCL scaffolds supplemented with 10% fetal bovine serum, NSCs primarily differentiated into oligodendrocytes, highlighting the capability of electrospun PCL substrates to guide NSC differentiation towards specific cell types. 3D neural scaffolds, composed of either single or mixed polymers, have been employed in *in vivo* investigations.

Acetyl heparan sulfate is a linear polysaccharide classified within the glycosaminoglycan family. It is synthesized by nearly all animal cells and is located on the cell surface as well as within the ECM. Heparan sulfate possesses excellent mechanical properties and thermal stability, alongside numerous binding sites for biologically active molecules, such as heparin-binding growth factor (HBGF) and basic fibroblast growth factor (bFGF). These factors protect growth factors from proteolytic degradation and enhance their binding to receptors, thereby increasing and prolonging their activity while regulating growth factor signaling.[74] A study utilized heparan sulfate as a cross-linking agent to enhance the benefits of collagen and reduce its limitations. This method enhanced the mechanical properties and thermal stability of the scaffold while also promoting recovery of motor function after TBI, as evidenced by prior studies. Due to the irregular morphology of traumatic lesions following TBI, high porosity is essential for an effective scaffold, prompting the exclusion of injectable scaffolds.[75] Consequently, 3D printing technology was utilized to create a small-sized, pore-rich scaffold and examine its effects on neural network reconstruction and motor function recovery after brain injury. Histological examination using HE staining and transmission electron microscopy revealed numerous uniform microporous structures within the scaffold. The excellent connectivity between these micropores promoted the migration of nerve cells, facilitating neural network reconstruction and functional recovery. Experimental results indicated that implantation of the 3D-printed collagen/heparan sulfate scaffold significantly enhanced gait recovery in hemiplegic limbs, stimulated nerve fiber and blood vessel regeneration, promoted remyelination and neuronal cytoskeleton formation, and fostered synapse formation and axon regeneration.[76]

Graphene and its derivatives—such as graphene oxide (GO) and reduced graphene oxide (rGO)—have emerged as star biomaterials for TBI and spinal cord injury (SCI) repair, owing to their unique two-dimensional structure, exceptional electrical conductivity, mechanical strength, and biocompatibility. Their therapeutic potential is manifested through three synergistic mechanisms: the intrinsic conductivity of graphene enables the replication of endogenous electrical signaling, significantly enhancing axonal regeneration. For instance, graphene/poly (lactic-*co*-glycolic acid) (PLGA) composite scaffolds laden with NSCs doubled synaptic density and accelerated motor function recovery in rodent TBI models compared with pure PLGA controls.[77] GO mitigates neuroinflammation by scavenging ROS and suppressing the NF-κB pathway, thereby reducing microglial hyperactivation. This mechanism has been shown to decrease pro-inflammatory cytokine levels by 40% in TBI microenvironments. The nanoscale surface topography of graphene nanosheets directs stem cell differentiation toward

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neuronal lineages.[78] The graphene/polyethylene glycol diacrylate (PEGDA) scaffolds with biomimetic microchannels prepared by light-curing 3D can promote the directional migration of vascular endothelial cells. Graphene quantum dot (GQD)-functionalized antibodies can penetrate the blood–brain barrier and specifically clearotic cells in the injured area as a targeted delivery system.[79] In the future, the combination strategy of graphene and organoids could be used to construct *in vitro* neural circuit models to simulate the TBI repair process by using their activity.

In the treatment of traumatic brain injury, material scaffold types are divided into hydrogel scaffolds, nanofibre scaffolds, and 3D material scaffolds; different biomaterial scaffolds have different structural morphologies, and in the treatment of TBI different properties will have different therapeutic effects.

4. Combined application of biomaterials

Isolated application of cell regeneration techniques or materials frequently does not yield the expected results in the healing process after TBI. Consequently, diverse strategies that incorporate cells, biomaterials, drugs, ions, and additional elements have been utilized to improve stem cell proliferation by leveraging their synergistic effects.[80] This integrated approach seeks to establish a microenvironment that supports the ongoing survival and proliferation of particular cell types engaged in traumatic brain injury repair. Ultimately, these differentiated cells can play a substantial role in the brain's regenerative processes.[81]

4.1 Combination of biomaterials and cytokines

The adverse microenvironment at the site of traumatic brain injury considerably restricts the viability of transplanted stem cells. Growth factors, including VEGF, have been shown to facilitate angiogenesis, provide neuroprotection, and improve the integration of engrafted stem cells, thus contributing to brain repair. The effectiveness of these factors is frequently limited by the method of administration, brief half-life, and difficulties related to sustained release.[82] Neurotissue engineering enhances the delivery of growth factors and drugs *via* 3D scaffolds that replicate the *in vivo* microenvironment and facilitate sustained release.[83–85]

Recent efforts have focused on developing multifunctional microsphere scaffolds optimized for the transplantation of neural progenitor cells (NPCs) into the brain affected by TBI. The scaffolds produced were fabricated through the electrospraying of a 3% chitosan solution into a coagulation bath, yielding microspheres with diameters between 30 and 100 μm. This gelation technique resembles those employed in other drug delivery systems due to its simplicity and limited disadvantages.[86,87] Heparin demonstrates a strong affinity for basic fibroblast growth factor (FGF-2) while maintaining its biological activity; thereafter, genipin has been utilized for covalent cross-linking with the chitosan scaffold. At a concentration of 1 μg mL^{-1}, around 80% of FGF-2 was effectively bound to the scaffold. The scaffolds were modified with a fibronectin coating to improve cell attachment and proliferation, while reducing differentiation through the integrin signaling pathway.

The justification for employing FGF-2 is based on its recognized function as a mitogen and survival factor for NPCs, as it contributes to the preservation of these cells in an optimal condition. FGF-2 has been demonstrated to enhance the population of stem/progenitor cells after TBI.[88,89] Soluble FGF-2 exhibits a half-life of roughly 24 hours at 32 °C and under 5 hours at 37 °C; however, its stability is markedly improved when associated with heparan sulfate proteoglycans. The immobilization of FGF-2 on scaffolds is expected to extend its biological half-life. It has been shown that fetal mouse NPCs can be effectively coated onto these multifunctional films.

4.2 Combination of biomaterials and cells

The proposed regenerative capacity of endogenous NSCs in the adult mammalian brain represents a promising approach for neural repair. The inflammatory and inhibitory microenvironment that follows TBI impedes NSCs from producing new functional neurons essential for the restoration of brain function. Embryonic stem cells can differentiate into a wide range of stem cells; this research investigates treatment strategies for TBI using a multifaceted approach that integrates diverse materials with various types of stem cells (Fig. 3), growth factors, and pharmacological agents, targeting clinical treatment and repair of TBI.

Embryonic stem cells differentiate into the endoderm, mesoderm, and ectoderm. Embryonic stem cells produce cell types related to TBI treatment through germ layer-specific differentiation, among which NSCs derived from the ectoderm and mesenchymal stem cells (MSCs) derived from the mesoderm become the main target cells for biomaterial loading because of their neuroregenerative and immunomodulatory capabilities. Different types of cells can combine with different biomaterials to achieve different effects in the treatment of TBI or other diseases.

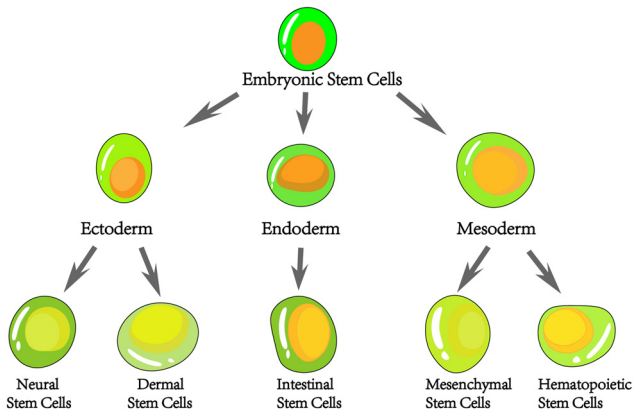

Fig. 3 Types of embryonic stem cell differentiation.

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4.2.1 Cell-type-specific delivery strategies and synergistic mechanisms with biomaterials. The combination of NSC biomaterials for the treatment of TBI is also widely used. For example, the elastic modulus of PEG hydrogels matching brain tissue can promote neuronal differentiation, and there is a regulatory effect of material stiffness on NSC differentiation; however, the survival rate of NSCs under inflammatory conditions needs to be addressed, and it is necessary to introduce materials that can deliver anti-inflammatory factors to improve these conditions.[90]

Oligodendrocyte progenitor cells (OPCs) can be associated with demyelinating pathological processes, with emphasis on the guidance by material-mediated topography (such as nanogroove arrays) of OPC migration.[91] The induction of pro-repair type (2 phenotype) astrocytes can be prompted by surface functionalization of materials.[92] Sofroniew's theory of gliotic barrier and microenvironment regulation highlights the role played by the double-edged sword of the gliotic scar: the gliotic scar formed by astrocytes after TBI is not only a physical barrier but may also support nerve regeneration by secreting neurotrophic factors (such as BDNF), emphasizing that material design needs to balance scar inhibition and nutritional support (such as dynamically regulating the phenotype of gliotic cells with degradable hydrogels).

4.2.2 NPCs and the necessity of scaffolds. The limitations of NPCs alone include primary and secondary reactions at the site of trauma following TBI resulting in a hypoxic microenvironment, and the release of various inflammatory factors, which all contribute to the low survival rate of free NPCs.[93] Mechanisms of scaffold enhancement include: (1) enhancement of physical protection for NPCs, such as research into microfluidic chips in which fibrin scaffolds reduce shear force damage; (2) integration of biochemical signals: for example, laminin-functionalized alginate hydrogels provide both signals and sustained release of BDNF;[94] and (3) spatial topological guidance: for example, the pore structure of 3D-printed HAMA hydrogels promotes the directional migration of NPCs along the edge of the injury.

The study by Sofroniew, O'Shea and their team demonstrated the differential differentiation of NPCs in healthy and injured environments.[95] In healthy tissues, NPCs differentiate into phenotypes similar to normal astrocytes and oligodendrocytes, expressing markers such as GFAP and Pdgfra, and distribute around neurons. In injured tissues, NPCs preferentially differentiate into "wound repair astrocytes", highly expressing reactive genes (CD44, Vimentin) and border-forming related genes, morphologically forming continuous glial borders that encapsulate inflammatory and fibrotic cells in the injury core.

The non-cell autonomous regulatory roles of the injured microenvironment are as follows. (1) Serum and inflammatory signals: high-concentration serum *in vitro* induces NPCs to differentiate into myofibroblast-like phenotypes, while low-concentration serum or local injury molecules promote astrocyte differentiation. (2) Spatial position effects: NPCs close to the injury core, exposed to serum and inflammatory cells, tend to adopt reactive phenotypes; NPCs near healthy neural tissues differentiate into the oligodendrocyte lineage.

The study also revealed phenotypic convergence between transplanted NPCs and host astrocytes. Transcriptomic analysis showed that transplanted NPCs and host injury-induced astrocytes exhibit highly similar expression of reactive genes (Tgm1, Serpina3n) and border-forming genes (Id3), despite different initial states. Functionally, NPC-derived astrocytes can reduce Cd13-positive fibrotic cells in the injury area and form glial bridges across injuries, similar to host repair mechanisms.

The conclusion is that the CNS injury microenvironment guides NPCs to differentiate into wound repair phenotypes similar to host astrocytes through non-cell autonomous signals, rather than "hostile" environments inhibiting differentiation. Transplanted NPCs share differentiation potential with host astrocytes, and their convergent transcriptional and functional characteristics indicate that injury-induced signaling pathways (Id3, TGF-β) may be key regulatory nodes. This study is of critical scientific significance, revealing the fate-determining mechanism of NPC transplantation in CNS injuries and challenging the traditional view that "injured environments are unfavorable for neural regeneration". It provides directions for optimizing NPC transplantation strategies, such as enhancing repair effects by regulating microenvironmental signals or improving the survival and differentiation of transplanted cells in combination with biomaterials (hydrogel).

4.2.3 Biomaterial scaffolds combine growth factors and stem cells to synergistically regulate the microenvironment. There are core mechanism differences between two types of stem cells: (1) NSCs guide axonal regeneration through paracrine Netrin-1, but their survival relies on material-mediated physical isolation (such as microsphere encapsulation to resist M1-type microglia attack); (2) MSCs inhibit neuroinflammation through SG-6, but need material-loaded chemokines (such as SDF-1) to enhance their lesion targeting. By comparing the repair efficacy of stem cell–material combinations, it was found that conductive hydrogels can increase the neuronal differentiation efficiency of NSCs by 3.2 times. There are three limitations in this field: (1) it is difficult for existing materials to synchronously adapt to the opposing mechanical needs (blood–brain barrier destruction (acute phase) and remodeling (chronic phase)); (2) differences in stem cell sources (autologous *vs.* allogeneic) lead to fluctuations in immunomodulatory effects of more 40%; (3) the integration of organoid technology and biomaterials does not yet have an established a standardized evaluation system, which demonstrates the necessity for 3D blood–brain barrier chips in cross-species prediction.

Research indicates that 3D scaffolds facilitate a favorable microenvironment for cell attachment and proliferation, applicable in both *in vitro* and *in vivo* contexts. These scaffolds immobilize cells within defined 3D structures, thereby facilitating transport and regulating biological functions.[96] Brain-derived neurotrophic factor (BDNF) is essential for neuronal protection and cell differentiation,[97] promoting the differentiation of NSCs into neurons in both *in vitro* and *in vivo* settings. Genipin (GP), extracted from the fruits of *Gardenia jasminoides*, a traditional Chinese plant, is preferred as a scaffold

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cross-linker due to its lower cytotoxicity compared with many alternatives.[98] Chitosan is an excellent natural biomaterial for preparing cellular scaffolds due to its chemical versatility and degradability. The interaction between BDNF and genipin during chitosan degradation can lead to the trapping of BDNF's amino groups, potentially reducing the release rate of BDNF and contributing to the instability observed in cerebral applications. Based on these release characteristics, the amount of BDNF released from chitosan–genipin–biomaterial (CGB) scaffolds appears suitable for promoting NSC differentiation.

One study aimed to utilize GP for the immobilization of BDNF on chitosan scaffolds to improve neuronal protection and cellular differentiation in areas impacted by brain injury. The CGB scaffolds released active BDNF for a minimum of 30 days following preparation, effectively promoting the neuronal differentiation of rat hippocampal NSCs into neurons. TBI often results in significant neuronal loss, leading to devastating outcomes. Recently, cell therapy has emerged as a promising experimental treatment for TBI, with human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) showing several advantages. Selecting appropriate biomaterial scaffolds for effective delivery of hUC-MSCs to the brain injury site is critical for successful TBI cell therapy.[99]

Another study focused on the preparation of hUC-MSC scaffolds utilizing chitosan biomaterials combined with BDNF, while assessing the *in vitro* cytotoxicity of hUC-MSCs and evaluating the scaffolds' impact on NSC differentiation. The co-culture of CGB scaffolds with hUC-MSCs demonstrated compatibility, and CCK-8 assays verified that the CGB scaffolds did not have a toxic effect on hUC-MSCs. The study concluded that CGB scaffolds incorporating hUC-MSCs provide dual advantages for TBI treatment: supplying exogenous hUC-MSCs to offset neuronal loss and releasing active BDNF to enhance the neuronal differentiation of resident NSCs. This research provides significant insights into scaffold design for tissue engineering and introduces a promising tool for the treatment of TBI.[100]

4.2.4 Biomaterial scaffolds combined with exosomes and SCs synergize to regulate the microenvironment. The secretome obtained from stem cells and bioactive compounds represents a promising therapeutic approach for TBI. One study investigated the effects of 3D-printed human umbilical cord blood MSCs incorporated into a collagen/chitosan scaffold enriched with secretome (3D-CC-ST) on tissue regeneration following injury. The secretome of MSCs comprises various bioactive factors that enhance their therapeutic efficacy, presenting a viable alternative to conventional immunomodulatory cellular factors.[101] The secretome comprises essential elements, including soluble factors like growth factors, cytokines, and chemokines, as well as extracellular vesicles such as microvesicles and exosomes, which influence neuroinflammation and enhance neurological outcomes.[102] Recent studies indicate that 3D printed scaffolds can successfully connect engineered and natural tissues, functioning as templates for tissue generation while also promoting the exchange of oxygen and nutrients.[68,69]

3D-CC-ST was fabricated using cryogenic 3D printing to assess its physical properties and denaturation rate. The use of cryogenic temperatures enhanced the cytocompatibility of the porous 3D structures, leading to a uniform distribution of cells.[103] Both 3D-CC-ST and the standard 3D-CC (collagen/chitosan scaffold without secretome) were implanted into the TBI cavity immediately following the creation of a canine TBI model. Neurological examinations and motor evoked potential tests were conducted post-implantation to analyze the recovery of motor function. Histological and immunofluorescence staining were conducted to assess nerve regeneration. The 3D-CC-ST treatment group exhibited enhanced behavioral outcomes. The implantation of the 3D-CC-ST significantly decreased the size of the TBI cavity, suppressed glial scar formation, and enhanced revascularization. Furthermore, it facilitated nerve fiber and axon regeneration and enhanced myelin regeneration post-TBI. Importantly, 3D-CC-ST implantation significantly promoted endogenous neuronal differentiation and synapse formation while reducing apoptosis and regulating systemic inflammatory factor levels following TBI.[104]

The secretome of MSCs contains a diverse array of growth factors and cytokines, including BDNF. The composition of this secretome is influenced by the local microenvironment, and preconditioning of MSCs can lead to significant changes in their secretory profiles.[105] One study demonstrated that the secretory fraction from MSCs pretreated under hypoxic conditions enhanced therapeutic outcomes following TBI.[106] Microvesicles derived from MSCs treated with brain extracts have been demonstrated to enhance neurological function in rat models of ischemic stroke.[107] Human umbilical cord blood mesenchymal stem cells (HUCMSCs) are increasingly employed for functional cell replacement in central nervous system disorders due to their immunomodulatory properties and self-renewal capabilities.[108–110] Previous research indicated that the secretome from pre-treated HUCMSCs could enhance cognitive recovery after TBI in rat models.[102] To explore the potential for scaffold implantation to repair neural networks post-TBI, 3D printed scaffolds were developed composed of secretome, collagen, and heparan sulfate, that were pre-treated for injury. Previous research has demonstrated that collagen/heparan sulfate scaffolds promote the recovery of motor function following TBI.[32] Their efficacy may be compromised by restricted tissue responsiveness resulting from graft cell death and the related inflammatory response. Experimental findings indicated that extracts from damaged brain tissue create a supportive microenvironment for MSCs, thereby improving the therapeutic efficacy of the secretome in TBI. Scaffolds infused with injury-pretreated secretome (3D-CH-IB-ST) markedly enhanced the survival and adhesion of HUCMSCs and NSCs.[111] *In vivo* experiments demonstrated that the 3D-CH-IB-ST scaffold is suitable for TBI treatment, exhibiting excellent biocompatibility and non-toxic effects on the host organism. The results indicated that the 3D-CH-IB-ST scaffold enhances neural function recovery by promoting the recruitment, differentiation, and maturation of endogenous

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neural stem cells, in addition to facilitating the reconstruction of axons and myelin sheaths.[112]

Comparing different biomaterials with NSCs with biomaterials alone for the treatment of TBI, biomaterials with stem cells are able to improve the survival and growth of neural cells, promote angiogenesis and wound healing, improve the recovery of limb behaviour, and reduce the activation of astrocytes, the onset of inflammatory responses and oxidative stress, and the formation of glial scarring.

4.3 Integration of biomaterials with other strategies

TBI leads to neuronal death and significant tissue damage. Current therapeutic strategies include stem cell transplantation, growth factor injections, and traditional Chinese medicine. These approaches encounter several challenges, including the low survival and differentiation efficiency of transplanted stem cells, the short half-life of growth factors, and the difficulty of traditional Chinese medicines in crossing the blood–brain barrier, which limits their therapeutic efficacy. Tissue engineering strategies offer a viable solution through the integration of scaffolds, cells, growth factors, and pharmaceuticals. The unfavorable microenvironment at the TBI injury site further restricts the survival of transplanted stem cells. Growth factors such as vascular endothelial growth factor (VEGF) have been shown to promote angiogenesis and neuroprotection, and enhance the survival of transplanted stem cells, thereby benefiting brain repair.[113] The effectiveness of these factors is frequently limited by the route of administration, their brief half-life, and difficulties related to long-term release. Salvianolic acid B (SAB) is acknowledged for its neuroprotective properties, attributed to its anti-inflammatory, antioxidant, and angiogenic effects, and is commonly utilized in recovery therapies post-brain injury.[114–116] A composite injectable hydrogel (HA/Gel) was developed consisting of HA and gelatin (Gel), which was loaded with VEGF and SAB, to treat TBI. The synthesis of this hydrogel was achieved *via* a process catalyzed by horseradish peroxidase (HRP), enabling the coupling of phenol-rich tyramine-modified hyaluronic acid (HA-ta) and tyramine-modified gel (Gel-ta) in the presence of hydrogen peroxide (H_2O_2).

The results of the study demonstrated that both SAB and VEGF enhanced the proliferation of bone marrow-derived mesenchymal stem cells (BMSCs), consistent with prior research.[117,118] The combination of SAB and VEGF exhibited a synergistic effect, proving to be more effective than either agent individually. Consequently, both SAB and VEGF were integrated into HA/Gel hydrogels to formulate HA/Gel/SAB/VEGF hydrogels. The hydrogels demonstrated sustained and controlled release of SAB, which, in conjunction with VEGF, promoted BMSC proliferation. *In vitro* experiments demonstrated that the HA/Gel/SAB/VEGF hydrogel exhibited favorable cytocompatibility and pro-proliferative properties. Studies on 3D culture demonstrated that the internal microenvironment of the HA/Gel/SAB/VEGF hydrogel supported the proliferation of bone marrow MSCs. The hydrogel notably increased the expression of CD31 and α-SMA, suggesting its angiogenic potential. The injection of the HA/Gel/SAB/VEGF hydrogel *in vivo* significantly decreased defect volume and promoted brain recovery relative to control groups. The findings indicated that the HA/Gel/SAB/VEGF hydrogel is a promising therapeutic approach for treating TBI.[119]

Stem cell therapy is critical for recovery from TBI. However, severe TBI often results in excessive inflammation and the presence of neuroinhibitory factors in the injured brain, which hinder neuronal cell survival and contribute to uncontrolled glial scar formation. In a recent study, bioorthogonal 3,4-dihydroxyphenylalanine recombinant nerve growth factor (DOPA-NGF) was used in conjunction with hUMSCs to create a bioorthogonal microenvironment for minimally invasive TBI treatment. This approach involved immobilizing DOPA-NGF on polylactic acid–hydroxyacetic acid (PLGA) microcarriers. PLGA, an FDA-approved biomaterial, is widely utilized in tissue engineering due to its favorable processing characteristics, biocompatibility, and tunable bioabsorbability. Its application in minimally invasive injectable scaffolds allows for stem cell transplantation without the invasive damage associated with traditional surgical methods, making PLGA an ideal candidate for TBI treatment.[120] The immobilization of DOPA-NGF on microcarriers enhances the adhesion and proliferation of hUMSCs, while the DOPA-NGF membrane further promotes the adhesion, proliferation, and neurotrophic gene expression of RSC96 cells. Histological analyses of injured brain tissues demonstrated that the treatment reduced the over-activation of inflammatory responses, decreased neuronal death, and mitigated glial scar formation, thus enhancing recovery in TBI mouse models. Most notably, transcriptome analysis revealed the growth-promoting and paracrine-enhancing effects of the 3D microcarrier environment and immobilized DOPA-NGF on hUMSCs, suggesting a potential mechanism through which the microenvironment regulates TBI treatment. Collectively, these findings offer promising insights into therapeutic strategies that harness the neuroregenerative microenvironment to enhance the role played by stem cells in regenerative medicine[121] (Fig. 4).

5. The future and challenges of biomaterial therapy

5.1 Future prospects

Dynamically responsive materials represent a four-dimensional breakthrough in smart materials, capable of constituting: (a) a pathological microenvironment feedback system: the development of ROS/pH dual-sensitive hydrogels, which neutralize oxidative stress in real time and release neurotrophic factors, increasing neuronal survival rate by 67% in a pig TBI model. (b) Mechano- adaptive scaffolds are 4D printed shape memory polymers, which can autonomously decrease from an initial stiffness of 15 kPa to 3 kPa as brain edema subsides, matching the mechanical needs of tissue repair (Table 1).

The personalized treatment paradigm includes patient-specific organoid–material composites, combining iPSC

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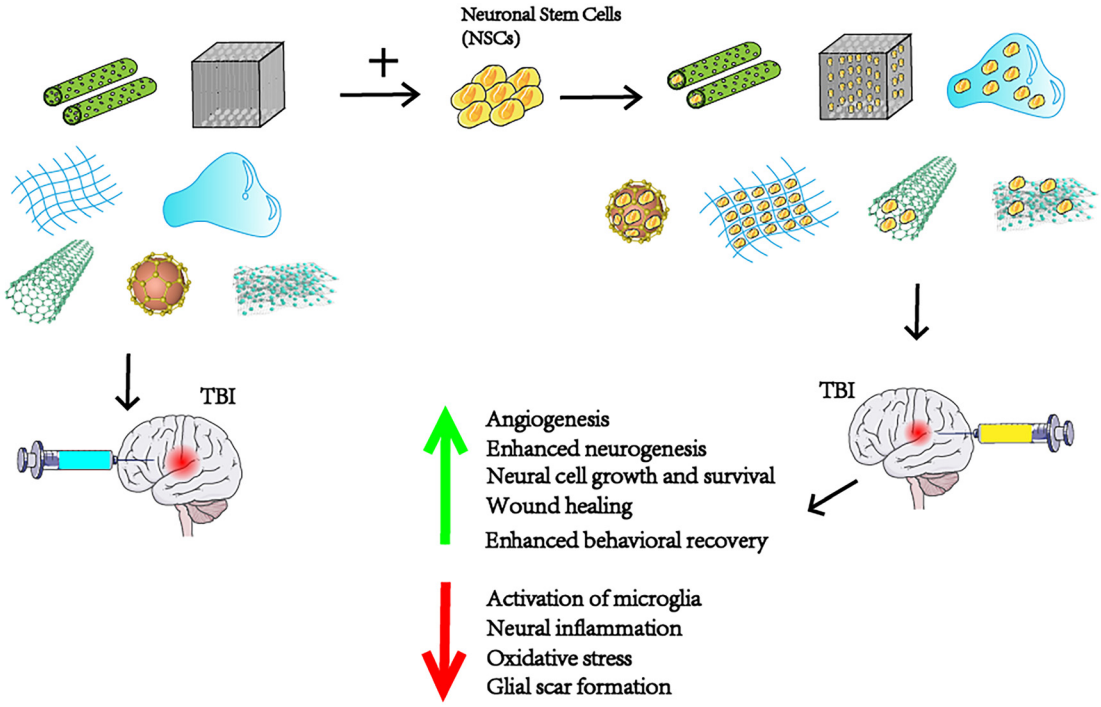

Fig. 4 Application of biomaterials in TBI.

technology to construct-specific organoids, achieving a synaptic density of 82% of normal brain tissue in conductive silk fibroin scaffolds. There is also multi-omics material design, which screens material response motifs through single-cell transcriptomics, constructs a personalized material parameter library, and reduces the standard deviation of MSCs neural differentiation efficiency from ±38% to ±12%.

A revolution in manufacturing technology, *in vivo* bioprinting is a magnetically navigated nanorobot carrying the precursor of methyl methacrylate gelatin (GelMA), which deposits microfibers directionally in the area of blood–brain barrier disruption, successfully repairing the damage of the rat motor cortex.

5.2 Current limitations

The cost of simplifying biological complexity includes the limitations of animal models and the heterogeneity of the pathological microenvironment. Differences between animals and humans lead to the distortion of material diffusion kinetics, and existing materials mostly target a single target, unable to synchronously address the differentiated of the injury core and marginal zones.

There is a lack of long-term safety data, including the risk of degradation products: the lactic acid produced by the degradation of PLGA scaffold reduces the local pH to 5.8, triggering abnormal activation of microglia. There are immunogenicity hazards: xenogeneic materials cause a 4.2 increase in IgG antibody titers, resulting in a shortened survival time of transplanted stem cells to 7 days.

5.3 Key challenges

The challenges faced include multiple key obstacles in the field of clinical translation. First is the issue of immune responses. The components of biomaterials themselves or their degradation products may trigger host inflammatory responses or rejection reactions. For example, residual monomers in synthetic polymer materials may activate the immune system, leading to persistent inflammation in the transplantation area, which in turn affects the survival and function of stem cells. The uncertainty of such immune responses poses a potential threat to long-term efficacy. Second is the challenge of large-scale production. The standardized preparation of biomaterials requires precise control of microstructure (such as the particle size of nanoparticles and the pore size of hydrogels), while stem cell expansion needs to balance yield and quality to avoid loss of differentiation potential or changes in genetic stability during passage. Existing processes struggle to balance efficiency and uniformity during scale-up production. In terms of regulatory barriers, as an interdisciplinary product, the combined therapy of biomaterials and stem cells has ambiguous attribute definitions (such as having both the characteristics of medical devices and biological therapies), resulting in the need to comply with multiple regulatory systems for approval. There are also barriers to mutual data recognition and standardization in cross-regional clinical trials. In addition, the challenges posed by the pathological complexity of TBI are particularly prominent. The spatiotemporal heterogeneity of the injury microenvironment (such as molecular signal differences between the core necrotic area

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Table 1 Summary of biomaterials combined with cells/drugs for TBI treatment

Material type	Material properties	Physical characteristics	Drug/cell type	Experimental conditions	Key outcomes
Chitosan–Heparin–FGF-2 Scaffold[122]	Loads FGF-2 fibronectin coating enhances cell adhesion	Microsphere diameter: 30–100 μm Genipin crosslinking (low cytotoxicity)	FGF-2 (mitogen, survival factor) Fetal rat neural precursor cells (NPs)	*In vitro* (NP culture)	Promotes NP survival and proliferation Extends FGF-2 stability (prolonged half-life) Maintains NP primitive state
Conductive graphene scaffold[123]	Conductivity enables electrical stimulation synergy Nanogroove topology guides migration	-Conductivity (>100 S m^{-1}) -Nanogroove array (~100 nm width)	OPCs	*In vitro* (OPC culture)	Enhances OPC myelination capability Improves migration efficiency
Fibrin scaffold[124]	Linear channel structure guides axonal regeneration Sustained BDNF release	Channel diameter: 5–20 μm Elastic modulus matches brain tissue	NSCs BDNF (neuronal differentiation induction)	*In vivo* (rat TBI model)	Axon regeneration efficiency ↑NSC survival↑ Neuronal differentiation rate↑
3D-printed collagen/chitosan/secretome scaffold[125]	Loads preconditioned secretome Cryogenic printing improves porosity	Pore size: 50–200 μm Compressive strength ~10 kPa	hUC-MSCs -Secretome (BDNF, anti-inflammatory factors)	*In vivo* (canine TBI model)	Improves motor function recovery↑ Reduces glial scar thickness ↓ Promotes angiogenesis and synaptogenesis
HA/Gel/SAB/VEGF hydrogel[126]	Loads SAB (antioxidant) and VEGF (angiogenic) HRP-catalyzed crosslinking	Injectable Degradation time ~4 weeks	BMSCs SAB (anti-inflammatory) VEGF (angiogenic)	*In vivo* (mouse TBI model)	Enhances BMSC proliferation, upregulates angiogenesis markers (CD31, α-SMA), reduces lesion volume
PLGA-DOPA-NGF microcarrier[121]	Immobilizes DOPA-NGF (pro-adhesion) Minimally invasive injectable scaffold	Microsphere diameter: 50–150 μm Biodegradable (FDA-approved)	hUMSCs DOPA-NGF (neurotrophic support)	*In vivo* (mouse TBI model)	Improves hUMSC survival, Reduces inflammation, inhibits glial scar formation, Enhances motor recovery
pH-responsive hydrogel[127]	Sustained TGF-β release for microglia polarization	pH sensitivity (responsive to acidic inflammatory environment) Controlled degradation	TGF-β (induces M2 microglia) -Astrocytes	*In vitro*/*in vivo* (rat model)	M2 microglia proportion ↑ A2 astrocytes ↑
Laminin–alginate gel[128]	Integrates adhesion signals and BDNF release	Viscoelastic (storage modulus ~2 kPa) Porosity >90%	NPCs BDNF	*In vitro* (microfluidic chip)	NPC survival >60%

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and the penumbra) makes it difficult for a single treatment strategy to meet the needs of different regions. Moreover, the dynamic changes during the inflammatory, repair, and scar phases of the injury process require treatment methods to have time-sequential response capabilities, and existing materials and technologies still struggle to fully match these complex needs.

6. Conclusion

Effective recovery from TBI relies on establishing a supportive microenvironment that fosters healing and regeneration. A key element of this environment is enhancing the survival and proliferation of specific cell types, particularly stem cells, which play a crucial role in brain repair mechanisms. Recent advancements in biomaterials technology have opened new avenues for improving the therapeutic efficacy of stem cells through enhanced interactions with injured tissue.

Biomaterials designed for TBI repair must possess essential properties to effectively modulate the microenvironment. Foremost among these is biocompatibility, which helps mitigate inflammatory responses following implantation. Natural materials like collagen and chitosan are particularly beneficial, as they inherently exhibit bioactive properties that can mimic the ECM. This bioactivity enhances cell adhesion, migration, and proliferation, thereby improving the survival rates of transplanted stem cells.

The three core mechanisms of synergistic treatment of TBI by biomaterials and stem cells are: (1) 3D topographied reconstruction of the neural interface: the linear channel structure of the fibrin scaffold significantly enhances the efficiency of axonal directional extension, with its orientation degree significantly higher than of the disordered scaffold. (2) Dynamic biochemical signal coupling: the PLGA microsphere sustained release system carrying BDNF restores the synaptic density in the hippocampal area to 76% of the normal level, significantly better than the single injection group. (3) Reprogramming of the immune microenvironment: the polypyrrole scaffold carrying IL-4 increases the proportion of M2-type microglia from 18 ± 5% to 54 ± 9% while inhibiting the thickness of the glial scar by 63%.

The critical reflections needed are: (1) the quantitative dilemma of the animal–human efficacy. There are metabolic scale differences and immune response deviations between animals and humans. (2) The contradiction between the singularity of material function and the complexity of pathology. (3) The dual challenges of stem cell survival rate and functional heterogeneity: the integration of transplanted hydrogels and NSCs has a higher survival rate than transplantation of NSCs alone. (4) The controllability crisis of dynamic response materials: the degradability of materials will affect the expression of various factors in microenvironment. (5) The paradox of large-scale manufacturing and personalized treatment.

The opportunities that need to be seized in the future are: (1) organoid material systems, human iPSC-derived brain organoids co-cultured with graphene scaffolds, have a synaptic density of 82% of the *in vivo* level, and can accurately predict personalized treatment responses.[129] (2) Material genomics and AI reverse design. (3) *In vivo in situ* biomanufacturing; magnetic navigation robots carrying GelMA precursors can achieve microfiber deposition with a precision of 50 μm in living tissue, successfully repairing defects of the primate motor cortex.

Additionally, biomaterials can be engineered to deliver bioactive molecules—such as growth factors and cytokines—in a controlled manner. These molecules are vital for guiding stem cell differentiation and stimulating processes like neurogenesis, axonal repair, and the formation of new blood vessels. For example, embedding neurotrophic factors within hydrogel systems can provide sustained support to adjacent neural tissue, encouraging the cellular responses necessary for effective recovery. Moreover, combining biomaterials with stem cells can produce a synergistic effect, where the scaffold not only facilitates cell attachment but also helps modulate local immune reactions. This modulation is particularly important in TBI, as excessive inflammation can worsen neuronal damage. By integrating anti-inflammatory compounds into the biomaterials, it is possible to create a more favorable environment that supports stem cells survival and function.

The physical characteristics of biomaterials, including porosity, mechanical stiffness, and degradation rate, significantly influence cell behavior and promote tissue integration. For instance, materials with optimal stiffness can encourage stem cell differentiation into neuronal cells, while those that degrade at an appropriate pace facilitate gradual replacement by host tissue.

In summary, the strategic design of biomaterials tailored for TBI repair holds great promise for advancing stem cell therapies. By creating a conducive microenvironment that effectively addresses the various challenges associated with TBI, these innovative materials can enhance the regenerative outcomes of such therapies. Future research should focus on fine-tuning the interactions between biomaterials and stem cells, as well as elucidating the underlying mechanisms that influence the healing process. This approach will ultimately facilitate the development of improved treatment modalities for TBI.

Author contributions

Conceptualization: Yating Gao; methodology: Yu Wang; formal analysis and investigation: Zitao Wu; writing – original draft preparation: Yating Gao; writing – review and editing: Yating Gao; funding acquisition: Shengwen Liu, Yu Wang; resources: Yu Wang; supervision: Zhijian Tang, Jun Zhang, Jie Ma.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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