International Journal of Nanomedicine

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REVIEW

Bioactive Materials Facilitate the Restoration of Neurological Function Post Cerebral Ischemic Stroke

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Abstract: The recovery process following ischemic stroke is a complex undertaking involving intricate cellular and molecular interactions. Cellular dysfunction or aberrant pathways can lead to complications such as brain edema, hemorrhagic transformation, and glial scar hyperplasia, hindering angiogenesis and nerve regeneration. These abnormalities may contribute to long-term disability post-stroke, imposing significant burdens on both families and society. Current clinical interventions primarily focus on endovascular therapy, overlooking the protection of brain cells themselves. However, the use of bioactive materials in stroke management has shown notable safety and efficacy. By precisely targeting the ischemic site at a cellular and molecular level, this therapeutic approach mitigates ischemia-induced brain tissue damage and promotes site repair. This review examines the protective benefits of bioactive materials in reducing cell damage and facilitating nerve restoration in accordance with the pathophysiological basis of ischemic stroke. Enhanced understanding of ischemic stroke mechanisms has the potential to advance the targeted and efficient clinical use of bioactive materials.

Keywords: angiogenesis, bioactive materials, inflammation, ischemic stroke, nerve regeneration, oxidative stress

Introduction

Ischemic stroke denotes a clinical syndrome resulting from the interruption of cerebral blood flow, leading to ischemic and hypoxic necrosis of localized brain tissue, thereby causing corresponding neurological deficits.[1,2] The increasing prevalence and incidence of stroke are closely associated with the rise in common risk factors, for instance, diabetes, hypertension, obesity, hyperlipidemia, substance abuse, and smoking.[3,4] Globally, the number of ischemic stroke cases rose from 4.07 million in 1990 to 7.86 million in 2020, projected to reach 9.62 million by 2030.[5] The subsequent cognitive and motor impairments impose a significant burden on families and society, with the estimated global cost of stroke exceeding $891 billion, constituting 1.12% of global Gross Domestic Product.[6] Therefore, an urgent need exists to innovate viable therapeutic approaches for ischemic stroke.

Conventional therapeutic modalities primarily include intravascular intervention (intravenous thrombolysis and thrombectomy) and pharmacotherapy. Recombinant tissue plasminogen activator (rt-PA), an endogenous or exogenous plasminogen activator, catalyzes the conversion of plasminogen to plasmin, leading to the degradation of fibrin in thrombi and their subsequent dissolution. Since the Food and Drug Administration approved rt-PA in 1996, intravenous thrombolysis has become the standard intervention for acute ischemic stroke.[7] However, stringent temporal constraints and exclusion criteria limit its efficacy for most patients. A national stroke registry analysis showed that only 12.6% of 11,675 documented stroke patients qualified for thrombolytic therapy, with just 1.6% receiving intravenous rt-PA.[8] In addition, among those who underwent intravenous thrombolysis, 34% experienced early reocclusion after initial recanalization, leading to neurological deterioration and increased in-hospital mortality.[9] Moreover, bleeding

Received: 31 August 2024
Accepted: 10 December 2024
Published: 31 December 2024

complications constitute a substantial limitation of intravenous thrombolysis using rt-PA in ischemic stroke patients.[10–12] The underlying mechanisms may be linked to immune response,[10] inflammation[11] and disruption of the blood-brain barrier (BBB).[12,13]

In 2015, several seminal trials demonstrated the superiority of endovascular thrombectomy over conservative medical management for anterior circulation macrovascular occlusive stroke.[14] Nevertheless, endovascular thrombectomy requires rigorous prerequisites concerning patients' physiological status, institutional capabilities, and healthcare professionals' proficiency.[15] Another limitation of thrombectomy arises in patients with severe vascular occlusion.[10] Both intravenous thrombolysis and endovascular thrombectomy face challenges in achieving effective recanalization. Over 50% of ischemic stroke patients treated with rt-PA thrombolysis do not show clinical improvement, a condition known as 'ineffective recanalization.[16,17] Notably, despite successful reperfusion, the infarct often expands, exacerbating neurological deficits due to ischemia-reperfusion injury, excessive brain edema, and hemorrhagic transformation.[17,18]

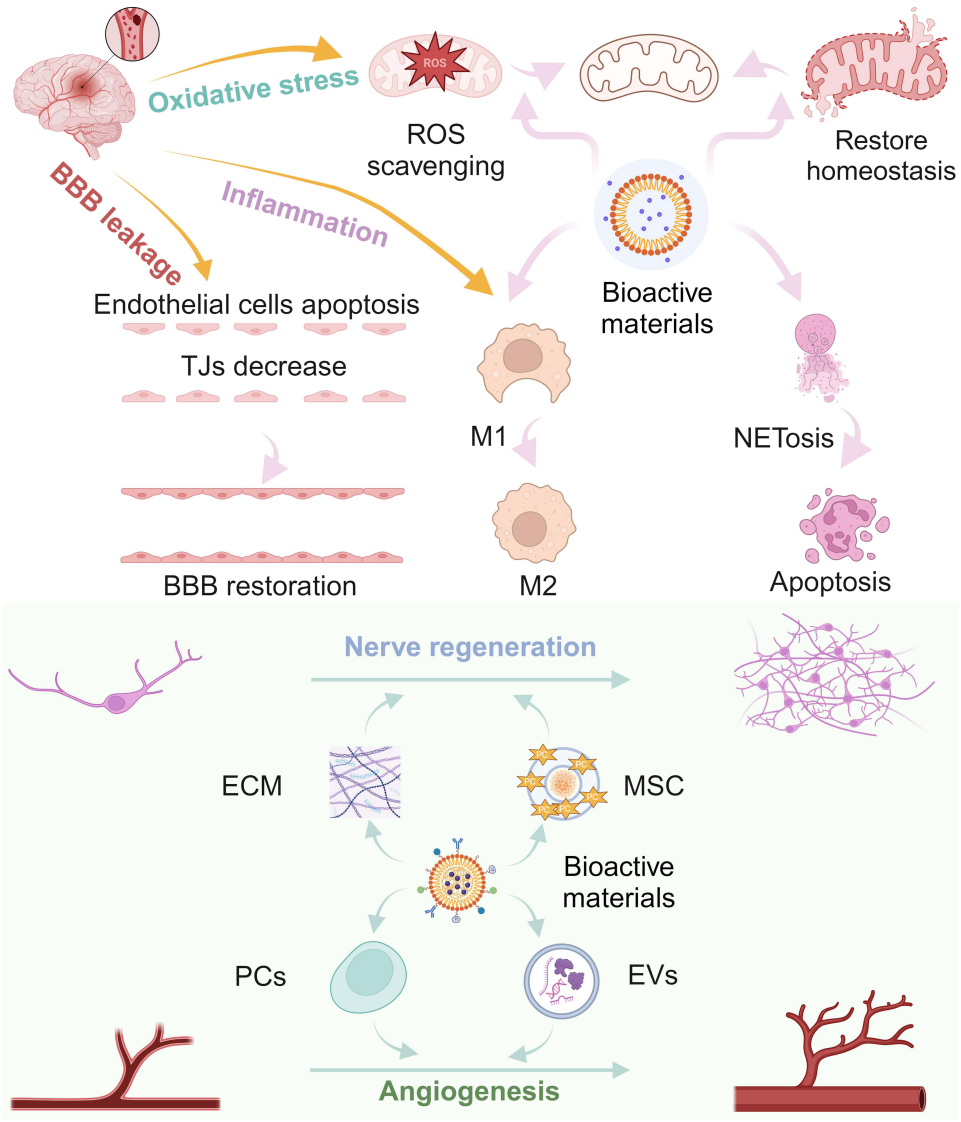
Initially, pharmacotherapy for ischemic stroke concentrated on neuronal protection. Following the introduction of the neurovascular unit paradigm by the National Institute of Neurological Disorders and Stroke in 2001, the scope of pharmacotherapy was broadened to encompass the protection of various neuronal subtypes, including astrocytes, pericytes, and endothelial cells.[19,20] Macromolecules endowed with anti-inflammatory and antioxidant attributes encounter challenges in traversing the BBB, demonstrating insufficient dissemination within the infarct core. Additionally, numerous small molecule drugs encounter diverse challenges in efficient absorption, including the BBB obstruction and abbreviated half-life. Furthermore, constrained antioxidant and anti-inflammatory efficacy, in conjunction with a lack of precise targeting capabilities, have also contributed to the inefficacy of certain clinical trials involving neuroprotective agents.[18]

A fundamental tenet in the clinical management of ischemic stroke is the timely restoration of blood perfusion to the ischemic penumbra to salvage compromised neurons. Nevertheless, survivors remain vulnerable to significant risks of disability, neurological deficits, and other complications post ischemia-reperfusion.[21] Regrettably, conventional treatment methods have been inadequate in mitigating the risk of these complications and in the long-term management of patients. Considering the significant constraints of conventional therapies, bioactive substances such as hydrogels,[22–24] polymer nanoparticles,[25,26] liposomes,[27] and micelles[28,29] offer innovative and promising solutions due to their inherent biochemical and biophysical attributes, encompassing biocompatibility, biodegradability and targeting capabilities.[30,31] Additionally, bioactive materials address the challenges of short plasma half-life and insufficient BBB permeability of drugs through various technologies, such as polyethylene glycol functionalization and targeted ligand binding on nanomedicine surfaces. Concurrently, these materials induce specific responses in microenvironment to accelerate ischemic tissue repair, facilitating effective drug distribution to ischemic brain tissue and improving stroke prognosis.[32]

Hence, this review elucidates the pivotal role of bioactive materials in mitigating cellular damage and promoting blood vessel and nerve regeneration by engaging with the cellular and molecular mechanisms of cerebral ischemia and hypoxia.[33–36] Scheme 1 provides a graphical representation to enhance understanding of these interrelated processes. Notably, it is crucial to recognize and address existing constraints and challenges to fully exploit the potential of bioactive materials in the treatment of ischemic stroke. By thoroughly examining these aspects, our objective is to enrich the current discourse and facilitate future progress in this field.

Bioactive Materials Inhibit Neuronal Necrosis by Regulating Mitochondrial Homeostasis and Cellular Behavior

Following cerebral ischemia, a cascade of events ensues, encompassing mitochondrial impairment, rapid elevation of reactive oxygen species (ROS), inflammatory cascade activation, augmented BBB permeability, culminating in neuronal demise.[2] ROS instigate cellular damage, disrupting cytoplasmic membrane integrity, inducing ion dysregulation and precipitating mitochondrial dysfunction. Furthermore, Cellular debris and necrotic remnants can initiate the inflammatory cascade, stimulating microglia to secrete a plethora of pro-inflammatory cytokines, chemokines and upregulate the expression of cellular adhesion molecules. Subsequently, neutrophils adhere to endothelial cells in response to inflammatory cytokines, migratory cues from chemokines prompt their excessive infiltration into the ischemic locus, exacerbating cerebral injury. Following this, endothelial cell apoptosis ensues and the expression of tight junction proteins



Scheme 1 Treatment of ischemic stroke mediated by bioactive materials. The Scheme was created in BioRender. Wang, C. (2025) https://BioRender.com/t09f458.

(TJPs) between endothelial cells decreases. This compromises the integrity of the BBB, contributing to local brain edema and hemorrhage, exacerbating functional decline. Hence, imperative strategies in ischemic stroke management entail mitigating the aforementioned pathological cascade to enhance neurological recovery.

Regulating Oxidative Stress and Homeostasis in Mitochondria

Mitochondrial dysfunction stands prominently as a pivotal mechanism in ischemic stroke, marked by mitochondrial oxidative stress and disruption of mitochondrial quality control.[37] Upon mitochondrial damage, they undergo membrane encapsulation, forming autophagosomes to eliminate dysfunctional mitochondria.[38,39] Oxygen depletion constrains mitochondrial oxidative phosphorylation, diminishing adenosine 5'-triphosphate (ATP) synthesis and yielding a large amount of ROS such as superoxide anion, hydroxyl radical, and hydrogen peroxide. The equilibrium between ROS generation and scavenging upholds redox homeostasis. Post-cerebral ischemia, this equilibrium falters, precipitating oxidative stress. The repercussions of oxidative stress hinge upon the magnitude of fluctuations in ROS and their derivatives. Physiological levels of mitochondrial ROS serve as redox mediators in intracellular signaling, while excessive ROS disrupt cellular equilibrium, culminating in mitochondrial dysfunction.[40,41] This steady-state dynamic fluctuation may be countered by the endogenous antioxidant system, yet profound oxidative stress can induce irreversible

harm to the organism.[42] Hence, the elimination of surplus ROS to reinstate redox homeostasis and the facilitation of mitochondrial function recovery are imperative for enhancing the neurological function of ischemic brain tissue.

Concerning the regulation of ROS levels, Dl-3-n-butylphthalide (NBP), a compound derived from celery seeds, has been authorized by the National Medical Products Administration for the clinical management of ischemic stroke since 2002.[43] NBP directly stimulates cytochrome C oxidase 7c (Cox7c) within endothelial cell mitochondria, augmenting ATP synthesis, diminishing ROS emission, and aiding in the stabilization of mitochondrial membrane potential. Furthermore, NBP potentially enhances the expression of Zonula occludens and occludin in endothelial cells through Cox7c upregulation, thereby preserving the integrity of the BBB.[44] NBP may additionally foster mitochondrial fusion and ultimately ameliorate cerebral ischemia/reperfusion symptoms by modulating the Adenosine 5'-monophosphate-activated protein kinase -mediated mitofusin 1 pathway.[43] A study assessing the efficacy and safety of NBP in patients experiencing acute cerebral infarction undergoing revascularization demonstrated that NBP substantially enhanced short-term outcomes at 90 days.[45] Moreover, the precise administration of NBP via Ceria nanoparticles as conveyors eradicates ROS in brain endothelium and hippocampal neurons (Figure 1), thereby restoring mitochondrial membrane potential, morphology, and functionality. Consequently, in vitro BBB impairment and neuronal apoptosis were mitigated.[46] To enhance blood concentration at the ischemic site, biomaterials have undeniably assumed an indispensable role. Yang et al devised a ROS-responsive, transformable, and triple-targeted NBP nanotherapy, which notably augmented cellular NBP uptake and elevated plasma NBP concentration at ischemic sites.[47]

Following cerebral ischemia, alterations occur in mitochondrial membrane permeability. To adapt to ischemia-induced changes, mitochondria selectively eliminate dysfunctional counterparts via autophagy, a pivotal process for sustaining mitochondrial homeostasis.[48] Wang et al engineered an inhalable nanotherapeutic agent, denoted as P/D @ Mn/Co_3O_4, synthesized from an artificial platelet membrane and Mn/Co_3O_4 encapsulated in 2.3-(dioxy propyl)-trimethylammonium chloride. This bioactive material depolarizes mitochondrial membrane potential by depleting the H^+ surrounding the mitochondria, prompts mitochondrial autophagy, removes aberrant mitochondria.[49]

As previously documented, specific bioactive substances can mitigate ROS levels and facilitate mitochondrial function restoration. These bioactive materials comprise polyphenol nanoparticles,[50] recombinant human heavy chain ferritin nanoparticles[51] and Cyclosporine A nanoparticles.[52] Additionally, a cutting-edge two-dimensional (2D) nanomaterial, namely layered transition metal carbon/nitrogen compound (MXene), has garnered significant attention owing to its exceptional antioxidant attributes. Fan et al devised a nanotherapeutic agent, 2D MXene-loaded isoquercetin, demonstrating its capability to further ameliorate ROS-induced cellular activity decline by scavenging surplus ROS.[53]

These findings reaffirm the viability of mitigating surplus ROS and fostering mitochondrial homeostasis through the utilization of bioactive substances. Hence, this strategy holds significant promise for the advancement and clinical translation of ischemic stroke therapy.

Regulating the Activation and Polarization of Microglia

Microglia, as resident macrophages within central nervous system (CNS), are pivotal in neuroinflammation and the pathological progression of ischemic tissue.[54,55] Following cerebral ischemia, cellular demise releases damage-associated molecular patterns, activating inflammatory pathways and triggering an inflammatory storm. Upon ischemic insult, microglia undergo activation, exerting a dual effect of neurotoxicity and neuroprotection, with the balance of these two effects dictating neuronal fate.[56] Post-cerebral ischemia, microglia swiftly transition from a surveilling state to an "activated" state within minutes, manifesting phenotypic changes encompassing morphological transformation, proliferation, and polarization.[57] These activated microglia migrate to injury sites, engaging in phagocytosis.[58] Remarkably, microglia and macrophages exhibit dynamic responses to ischemic injury. Local microglia and newly recruited macrophages display an M2 phenotype during the early phases of ischemic stroke, transitioning gradually to an M1 phenotype within the peri-infarct region. [59] M1 microglia secrete proinflammatory cytokines and chemokines, including tumor necrosis factor, Interleukin 6 (IL-6), IL-1β, IL-12, and C-C motif chemokine ligand 2, exacerbating ischemia-induced nerve inflammation. Conversely, M2 microglia activation fosters the release of anti-inflammatory cytokines like IL-10 and transforming growth factor β, aiding neural function recovery.[60] Therefore, manipulating microglia activation and polarization emerges as a promising strategy against cerebral ischemia.

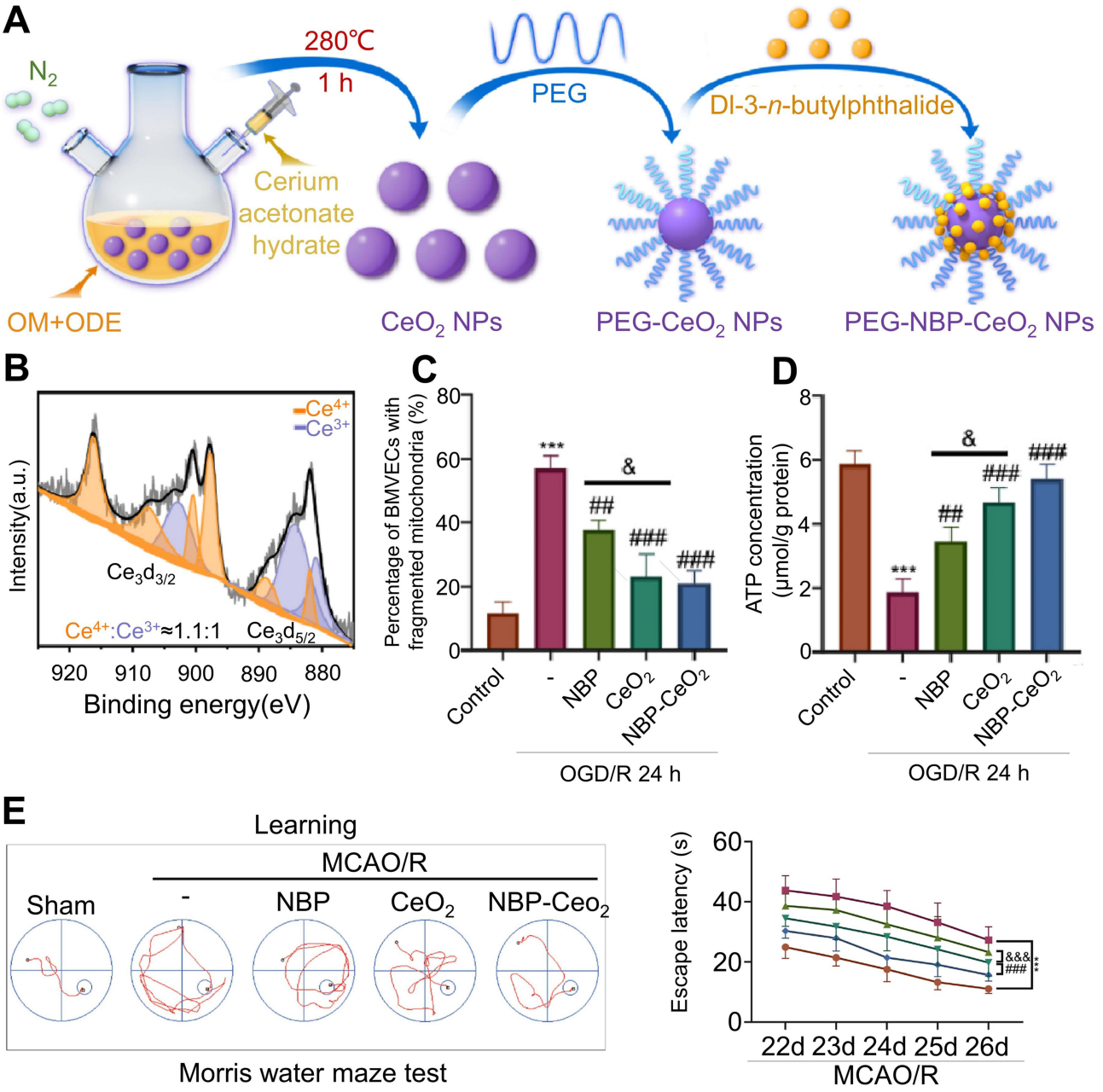


Figure 1 Cerium oxide nanoparticles are utilized for targeted drug delivery to ischemic regions in stroke therapy. (**A**) The synthesis protocol for NBP-CeO_2 NPs. (**B**) XPS analysis of Ce 3 d showed the binding energy level of Ce (III) in NBP-CeO_2 NPs. (**C**) Quantitative representation of the proportion of BMVECs containing mitochondrial fragments (n = 3; $^{***}P < 0.001$, $^{\&}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$). (**D**) Assess the ATP content in BMVECs to elucidate mitochondrial function (n = 3; $^{***}P < 0.001$, $^{\&}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$). (**E**) Representative swim trajectories in the spatial learning evaluation segment of Morris water maze test. Mice locate the underwater platform as the escape latency period 22–26 days after MCAO/R (n = 12; $^{***}P < 0.001$, $^{\#\#\#}P < 0.001$, $^{\&\&\&}P < 0.001$). Reprinted from Biomaterials, Li X, Han Z, Wang T, et al. Cerium oxide nanoparticles with antioxidative neurorestoration for ischemic stroke. Biomaterials. 2022;291:121904. doi:10.1016/j.biomaterials.2022.121904. Copyright 2022, with permission from Elsevier.[46]

Abbreviations: ATP, Adenosine 5'-triphosphate; BMVECs, brain microvascular endothelial cells; MCAO/R, middle cerebral artery occlusion/reperfusion; NBP-CeO_2 NPs, DI-3-n-butylphthalide-cerium oxide nanoparticles; XPS, X-ray photoelectron spectroscopy.

Inhibiting microglial activation is a crucial neuroprotective strategy that can salvage neurons in the ischemic penumbra.[26,61] Rapamycin (RAPA), an established inhibitor of mechanistic target of rapamycin complex 1 (mTORC1), attenuates microglial activation by suppressing the phosphatidylinositol-3-kinase (PI3K)/protein kinase (AKT)/mTORC1 pathway, thereby ameliorating the neuroinflammatory response following ischemia.[62,63] Due to its hydrophobic characteristics, the amalgamation of bioactive substances with RAPA emerges as a favorable option.[64,65] Gao et al formulated

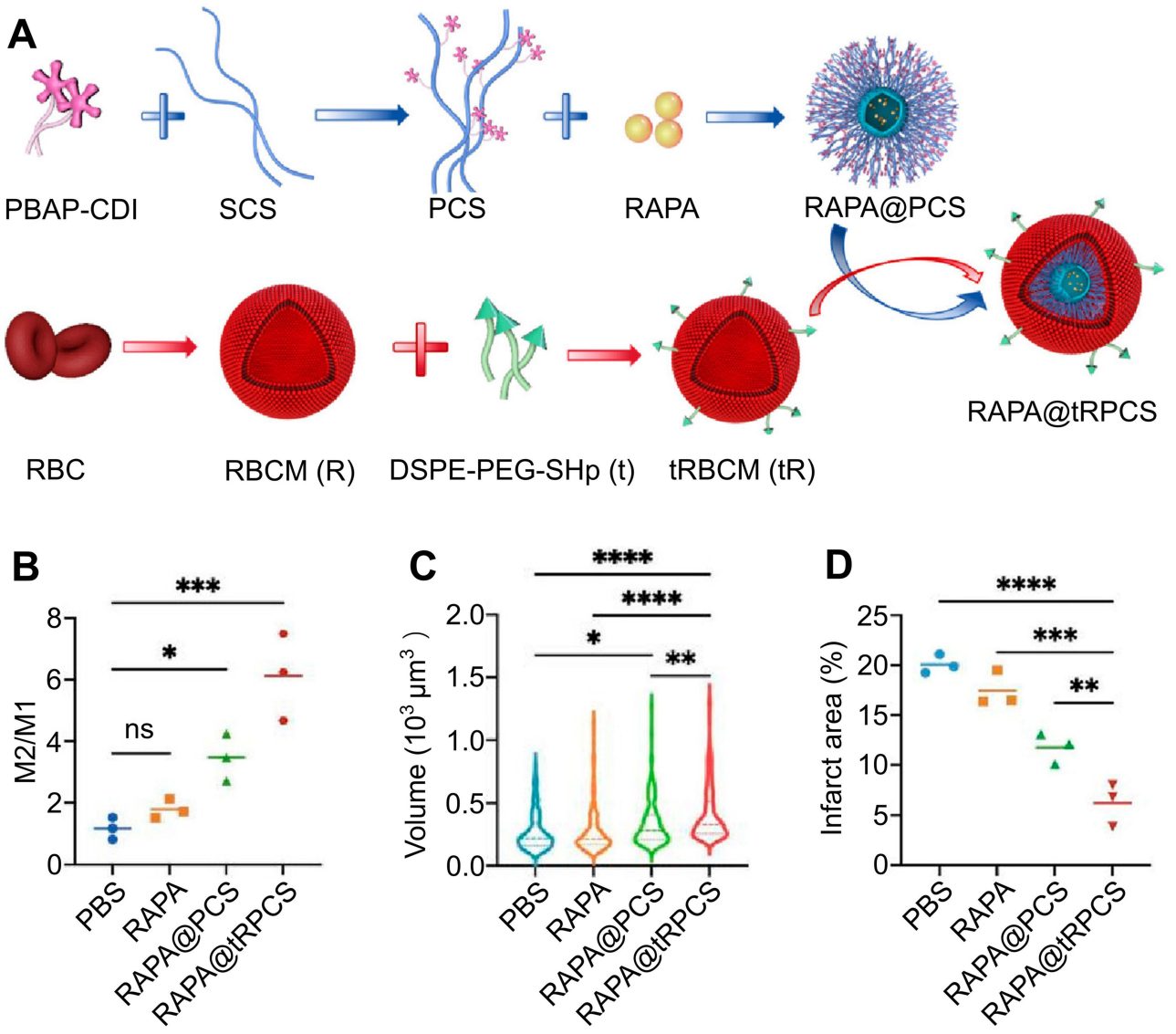


Figure 2 Polysaccharide sulfate-based nanocarriers deliver targeted neuroprotective agent rapamycin in the management of cerebral infarction. (**A**) The schematic design of RAPA @ tRPCS. (**B**) Phenotypic changes in microglia upon exposure to various nanoparticles (n = 3; *P < 0.05, ***P < 0.005). (**C**) The effect of different nanoparticles on microglia size (n = 3; *P < 0.05, **P < 0.01, ****P < 0.001). (**D**) The infarct volumes at 7 days after tMCAO were measured with ImageJ in different groups (n = 3; **P < 0.01, ***P < 0.005, ****P < 0.001). Reprinted with permission from Cao Y, Yu Y, Pan L, et al. Sulfated polysaccharide-based nanocarrier drives microenvironment-mediated cerebral neurovascular remodeling for ischemic stroke treatment. Nano Lett. 2024;24(17):5214–5223. Copyright 2024, American Chemical Society.[65]
Abbreviations: ns, not significant; tMCAO, transient middle cerebral artery occlusion.

a nanocarrier for the specific transport of RAPA (Figure 2). The nanocarrier comprised a sulfated chitosan (SCS) polymer core, functionalized with a ROS-responsive boronic ester, encased in a red blood cell membrane shell incorporating a stroke-targeting peptide. Upon exposure to elevated intracellular ROS levels in ischemic brain tissue, the nanocarrier promotes the release of SCS and RAPA, thereby aiding in the restoration of cerebral function.[65]

Microglia exert a pivotal role in the evolution of injury and tissue reorganization post-ischemic stroke.[66] Given the deleterious impact of M1 microglia on ischemic brain tissue, modulating microglial polarization holds considerable significance.[67–69] Edaravone dexborneol (Eda-Dex) is a neuroprotective agent sanctioned for ischemic stroke therapy in China as of 2020. It mitigates the synthesis of pro-inflammatory cytokines and chemokines by impeding the polarization of microglia/macrophages and astrocytes towards the M1 phenotype.[55,70] Additionally, it prompts the transformation of lipopolysaccharide-stimulated microglia from the M1 to M2 phenotype by negatively regulating the Toll-like receptor 4/myeloid differentiation marker 88 /nuclear factor kappa B (NF-κB) signaling cascade.[71] The TASTE-SL randomized clinical trial demonstrated that among patients experiencing acute ischemic stroke within 48 hours, sublingual administration of Eda-

Dex yields superior short-term prognosis compared to placebo.[72] The clinical application of this substance is constrained due to its abbreviated biological half-life and inadequate water solubility.[73] As previously stated, Yin et al reported an engineered nanoerythrocytes modified with MG1 peptide and RVG29 peptide, which has the ability to effectively penetrate the BBB and accurately recognize M1 microglia. The platform reprograms microglia from classical M1 to alternative M2 by activating heme oxygenase-1 within microglia, stimulating the signaling pathway of Notch1/Hes1/ transcription 3, and further inhibiting NF- κB p65 translocation.[74]

Furthermore, High mobility group box 1 (HMGB1) serves as a potent pro-inflammatory mediator that promotes M1 polarization in microglia. Eighteen β-Glycyrrhetinic acid acts as a potent intracellular inhibitor of HMGB1. Jin et al developed a ROS-responsive 18 β-Glycyrrhetinic acid-conjugated polymer nanoparticle system to modulate microglial polarization by inhibiting the translocation of nuclear HMGB1.[75]

Regulating the Activation and Infiltration of Neutrophils

Neutrophils, integral constituents of the innate immune system and regulators of the adaptive immune response, wield significant influence within ischemic brain tissue.[76] The neutrophil extracellular trap (NET) is a reticular DNA structure comprising double-stranded DNA, histones, and granular proteins released by activated neutrophils, tightly regulated for production and clearance. NETosis represents a distinctive form of neutrophil demise, concomitant with the liberation of NETs. NETs compromise the integrity of the BBB, instigate thrombosis, and subsequently exacerbate neuronal injury and neurological impairment following ischemia.[21,77] Increased plasma NET biomarkers are linked to poorer stroke outcomes.[78] Following cerebral ischemia, neutrophils undergo rapid activation and transmigrate across the endothelium towards the ischemic region. Upon reaching the site, they adhere to endothelial cells via integrin β2 on neutrophils and intercellular adhesion molecule-1 expressed on endothelial cells. Subsequently, the count of rolling or adherent white blood cells escalates, with excessive neutrophil infiltration leading to cerebral tissue damage.[79,80] In summary, neutrophils exacerbate ischemic cerebral injury through diverse mechanisms, such as inducing capillary congestion, secreting inflammatory mediators, and augmenting thrombosis via the formation of neutrophil-platelet aggregates and NETs.[81,82] Hence, regulating the activation and infiltration of neutrophils represents a promising therapeutic avenue for ischemic stroke management.

Neutrophil activation generates a substantial quantity of NETs. Hence, the primary approach to controlling neutrophil activation involves averting the release of NETs. Yin et al studied and designed a neutrophil hijacking/reprogramming nanoplatform, termed APTS (Figure 3). This platform was synthesized by modifying polydopamine-coated A151/PEI nanoparticles with a targeted peptide (TP peptide) and sialic acid. TP peptide facilitates the recognition of neutrophils adhering to inflammatory endothelial cells, thereby inducing the uptake of APTS by neutrophils and reprogramming them from NETosis to apoptosis via ROS-mediated citrulline histone inhibition pathway, significantly reducing the formation of NETs.[83] Notably, Cl-amidine, an inhibitor of peptidylarginine deiminase 4, is encapsulated within self-assembled liposomal nanocarriers, which are modified with ROS-responsive polymers and fibrin-binding peptide. This formulation aims to suppress the NETs release process to enhance the reduction in mortality associated with cerebral infarction.[21]

The aggregation and clearance of neutrophils are pivotal determinants influencing neuroinflammation in acute ischemic stroke. Resolvin D2 (RvD2), a lipid-lowering hormone, has the ability to reprogram energy metabolism from glycolysis to oxidative phosphorylation. This, in turn, facilitates the phagocytic clearance of neutrophils by microglia, diminishing local neutrophil accumulation and mitigating neuroinflammation in the ischemic brain.[84,85] Given that RvD2 easily binds to proteins, Dong et al elucidated a drug delivery framework comprising neutrophil membrane-derived RvD2-loaded nanovesicles.[86] Mechanistically, RvD2 instigates nitric oxide production in the endothelium, consequently attenuating neutrophil-endothelium interactions.[87] RvD2 additionally interacts with the G protein-coupled receptor on neutrophils to impede neutrophil infiltration and provoke neutrophil apoptosis, thus expediting inflammation resolution.[88] Furthermore, specific biomaterials, such as platelet-mimicking nanoparticles, possess the capacity to diminish neutrophil infiltration.[89]

Furthermore, the swift and efficient migration of neutrophils into the brain following cerebral ischemia has garnered significant interest. Their inflammatory homing characteristics render them an appealing conduit for targeted drug administration.[90,91] Additionally, neutrophils play an indispensable role in penetrating the BBB to facilitate drug delivery to the brain.[92]

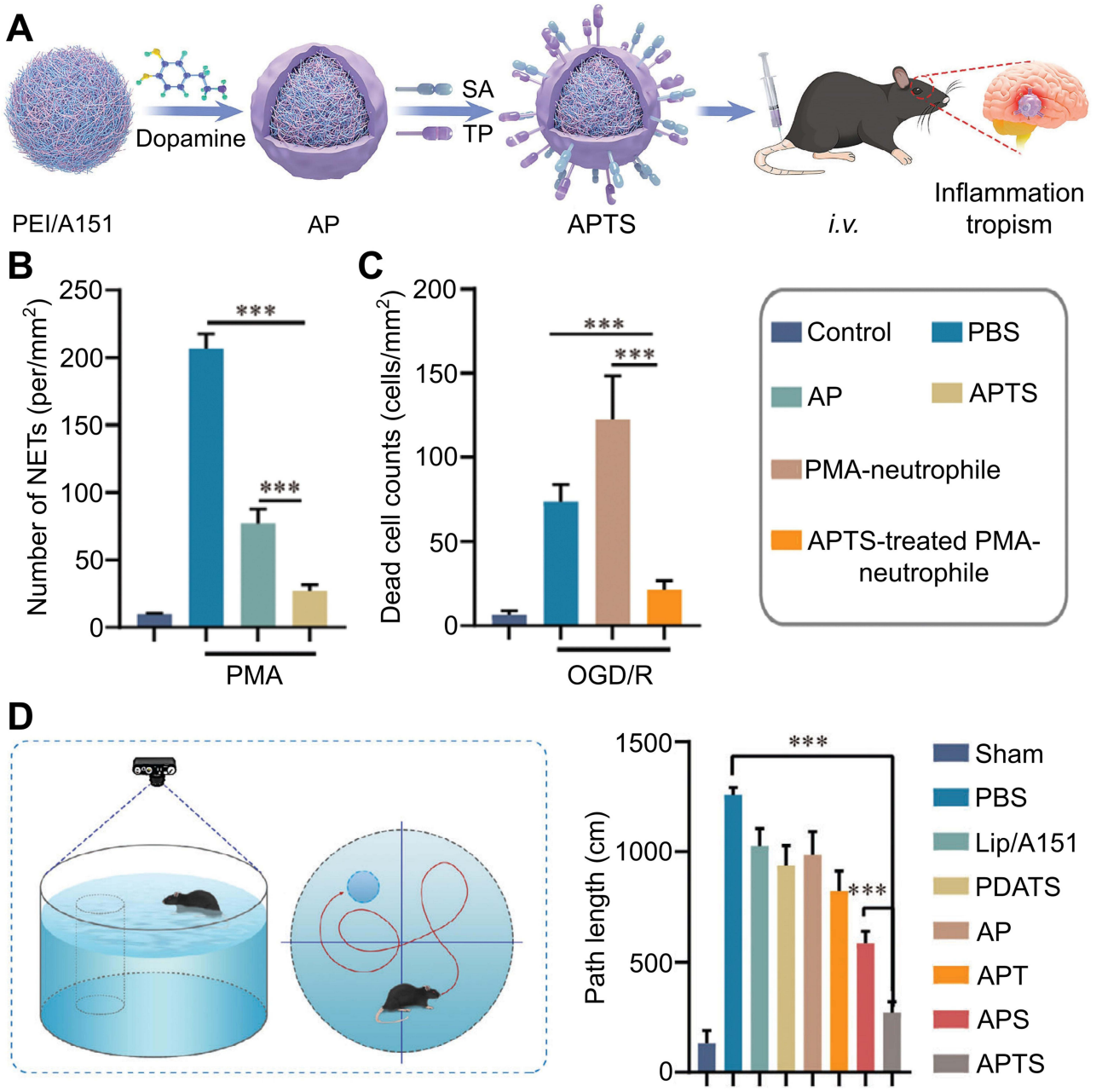


Figure 3 A APTS significantly reduces the formation of NETs by reprogramming neutrophil NETosis to cell apoptosis. (**A**) Preparation process of APTS. (**B**) The number of NETs after different treatments (n = 6; ***$P < 0.001$). (**C**) Quantitative analysis of dead cell counts in different treatments (n = 6; ***$P < 0.001$). (**D**) Schematic diagram of Morris water maze test. Path length in different processing (n = 8; ***$P < 0.001$). Reproduced from Yin N, Wang W, Pei F, et al. A neutrophil hijacking nanoplatform reprograming NETosis for targeted microglia polarizing mediated ischemic stroke treatment. Adv Sci. 2024;5:e2305877. http://creativecommons.org/licenses/by/4.0/.[83] Copyright 2024, The Authors. Advanced Science published by Wiley-VCH GmbH.
Abbreviations: APTS, neutrophil hijacking nanoplatform; NETs, neutrophil extracellular traps.

Regulating Apoptosis and Connectivity of Endothelial Cells

BBB represents a distinctive and dynamic regulatory interface comprising capillaries, pericytes, basement membranes and astrocytes.[93] Endothelial cells, along with their tight junctions (TJs), constitute the primary barrier to permeability, while pericytes and astrocytes assume significant regulatory functions.[94] In physiological homeostasis, BBB serves as a pivotal "Gatekeeper", orchestrating essential roles in the regulation of paracellular permeability, ion balance, nutrient trafficking, and cerebral blood flow.[95]

Endothelial cells, pivotal constituents of BBB, envelop the entire microvasculature. Following a stroke, these cells experience oxygen deprivation, leading to BBB dysfunction and increased permeability. EPALRESTAT, an Aldose reductase (AR) inhibitor, mitigates endothelial cell apoptosis by modulating mTOR phosphorylation via the AR/AKT/mTOR signaling pathway. It also sustains the expression levels of TJPs in endothelial cells, thus safeguarding BBB.[96]

TJs govern solute flux between contiguous endothelial cells, establishing a seamless and impermeable barrier termed paracellular diffusion, quantifiable by high transendothelial resistance.[97] The modulation of TJPs expression is governed by various intrinsic signaling cascades, encompassing phosphorylation, matrix metalloproteinases, and microRNAs.[98] Following cerebral ischemia, the TJs among endothelial cells deteriorate, culminating in heightened paracellular permeability. This phenomenon contributes to angiogenic edema, hemorrhagic transformation, and elevated mortality rates.[99] Consequently, preventing TJPs degradation and enhancing its expression emerge as promising strategies to mitigate BBB permeability. These bioactive materials include c(RGDyK) peptide modified, caffeic acid phenethyl ester (a NF-κB inhibitor)-loaded and reactive nitrogen species stimuli-responsive liposomal nanocarrier,[100] neutrophil membrane-fused nanoliposomal leonurine[92] and Dietary Fe_3O_4 nanozymes.[101]

It is noteworthy that Liu et al devised a cerium-doped myricetin oligomer nanostructure, which modulates TJPs expression through the activation of protective autophagy, thus showcasing its capability in BBB restoration.[102] Moreover, Gao et al devised an M2 microglia-targeting lipid nanoparticle (Figure 4). This nanoparticle was observed to stimulate IL-10 production and amplify the anti-inflammatory response through the Janus kinase-STAT pathway, thus augmenting the integrity of the BBB.[103]

Bioactive Materials Promote Nerve Tissue Repair by Regulating Angiogenesis and Nerve Regeneration

The cerebrovascular system not only delivers glucose and oxygen to brain tissue but also shields the brain from neurotoxin harm.[104] Following cerebral ischemia, the brain initiates a cascade of endogenous reparative mechanisms to accommodate to this perturbation, primarily involving angiogenesis and neurogenesis. Following cerebral ischemia, nerve cells migrate to regions where early vascular remodeling and increased vascular density persist.[105] Nonetheless, this innate self-repair mechanism is notably limited.[106] Hence, breaching limitations and advocating for restoration are imperative in enhancing the prognosis of ischemic stroke patients. Stem cell therapy demonstrates distinctive therapeutic potential for ischemic stroke, with the cellular homing, differentiation, and paracrine capabilities of stem cells instilling optimism for neuroprotection.[15,107] Recently, the utilization of bioactive materials has augmented the capacity of stem cells to stimulate vascular and nerve regeneration in ischemic locales. Hence, a thorough comprehension of bioactive material-mediated mechanisms underlying vascular and nerve regeneration is imperative for ischemic stroke therapy.

Regulating the Recruitment and Paracrine Secretion of Progenitor Cells

Angiogenesis represents a pivotal stage in brain tissue regeneration post-stroke. Endothelial progenitor cells (EPCs) serve as precursors to vascular endothelial cells, possessing the ability to differentiate into endothelial cells and adhere to active angiogenic loci, thus fostering the genesis of new blood vessels subsequent to tissue ischemia.[108] Concurrently, through the secretion of extracellular vesicles (EVs) and diverse pro-angiogenic factors in a paracrine manner, EPCs expedites the maturation of endothelial cells and the proliferation, differentiation, and migration of peripheral EPCs, thus facilitating the restoration of impaired vascular endothelium.[109] Elevated levels of circulating EPCs post-acute ischemic stroke correlate with enhanced functional outcomes and diminished infarct volume.[110] The diminished quantity of EPCs constitutes an independent risk determinant for unfavorable prognosis among individuals afflicted by acute ischemic stroke.[111,112] Increasing the abundance and viability of progenitor cells (PCs) and EVs at the site of localized infarction emerges as a novel objective for fostering angiogenesis.

Intrinsic EPCs engage in neovascularization through the C-X-C chemokine receptor 4 / stromal cell-derived factor (SDF-1) axis subsequent to cerebral ischemia.[113] SDF-1, recognized as Chemokine C-X-C motif chemokine ligand 12, represents a chemotactic cytokine delineated by two variants, α and β, with SDF-1α being the predominant variant. Given its capacity to attract EPCs, neural PCs, and mesenchymal stem cells to the infarcted region, SDF-1α has garnered

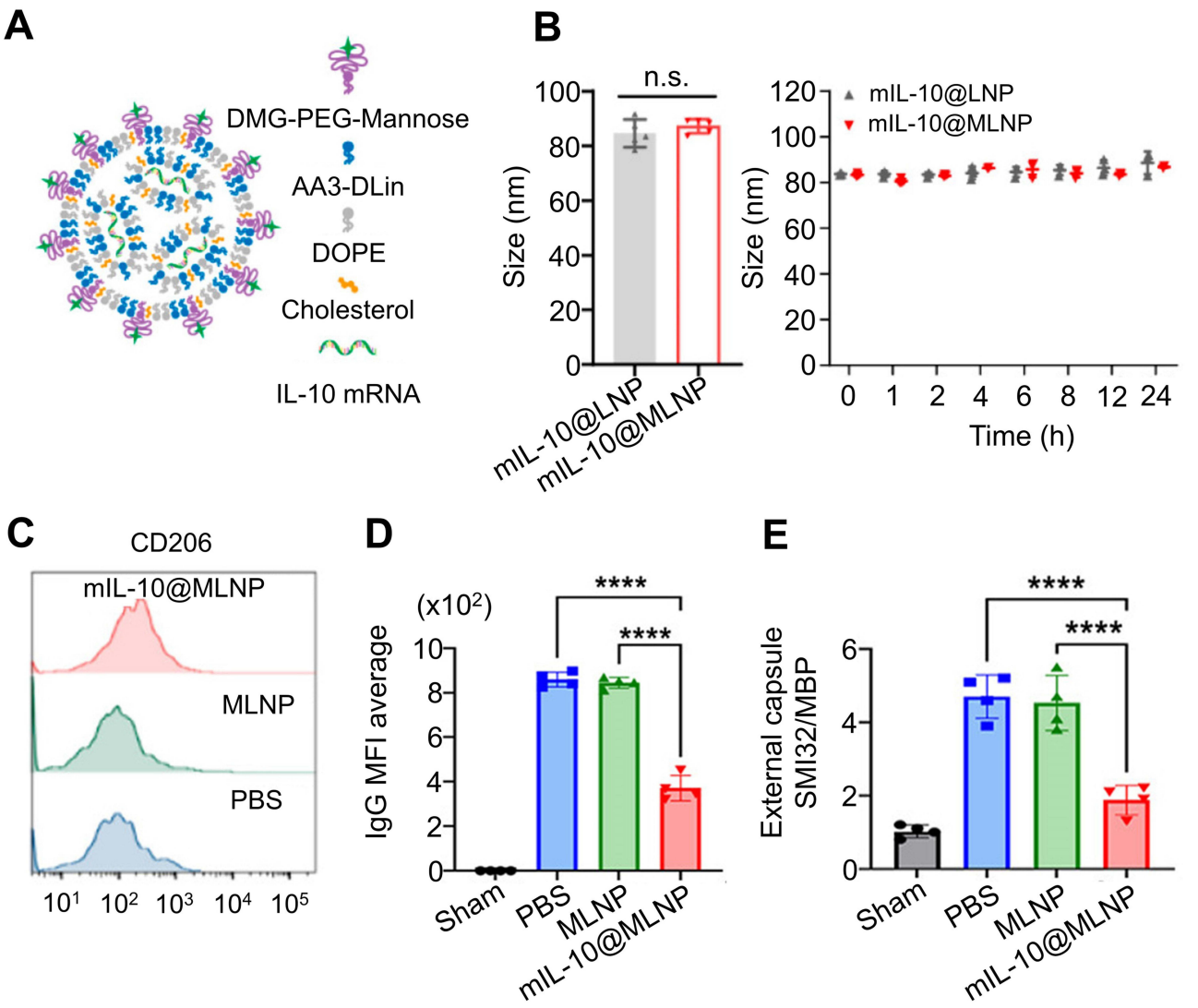


Figure 4 Targeting mRNA nanoparticles to improve BBB damage after ischemic stroke. (**A**) Schematic diagram of targeting mIL-10@MLNPs. (**B**) The average particle size of mIL-10@LNPs and mIL-10@MLNPs (left). Size of mIL-10@LNPs in 10% serum condition at 37 °C for up to 24 h (right). (**C**) Representative histograms of $CD206^+$microglia isolated from the ischemic hemisphere of the designated treatment group. (**D**) Quantitative analysis of IgG leakage MFI in each group (n = 4; ****$P < 0.0001$). (**E**) Quantitative assessment of SMI32/MBP MFI ratio in the outer capsule of the indicator group (n = 4; ****$P < 0.0001$). Reprinted with permission Gao M, Li Y, Ho W, et al. Targeted mRNA nanoparticles ameliorate blood-brain barrier disruption postischemic stroke by modulating microglia polarization. ACS Nano. 2024;18(4):3260–3275. Copyright 2024, American Chemical Society.[103]

Abbreviations: BBB, blood−brain barrier; MFI, mean fluorescence intensity; mIL-10@MLNPs, mIL-10-loaded M2 microglia-targeting lipid nanoparticle; n.s., not significant; SMI32/MBP, non-phosphorylated neurofilament H/myelin basic protein.

significant interest in ischemic stroke therapy in recent years (Figure 5). [114] In vitro studies have demonstrated that SDF-1α mitigates EPC apoptosis under ischemic conditions through the PI3K/AKT/ endothelial nitric oxide synthase (eNOS) pathway.[115] The localized administration of SDF-1 augments angiogenesis by bolstering EPC recruitment in ischemic tissues.[116] Nevertheless, the therapeutic efficacy of chemokines is significantly compromised by adverse BBB permeability and systemic side effects.[117] Thus, targeted administration of SDF-1α employing bioactive materials presents a promising approach. Kim et al devised and synthesized a dual ionic pH-responsive copolymer poly (urethane amino sulfamethazine). Their findings demonstrate that targeted delivery of SDF-1α can efficiently modulate the microenvironment and augment angiogenesis.[117] Furthermore, Wilson et al formulated SDF-1 bound Heparin Nanoparticles. The findings indicated a significant increase in perfusion vessels within 10 days post-stroke.[114]

EVs are diminutive phospholipid bilayer structures secreted via paracrine action by cells, encapsulating essential proteins, lipids, and genetic material for intercellular communication. EPC-derived EVs (EPC-EVs) express α4 integrins and CD29 (β1 integrin), facilitating their internalization into human microvascular endothelial cells and human umbilical vein endothelial

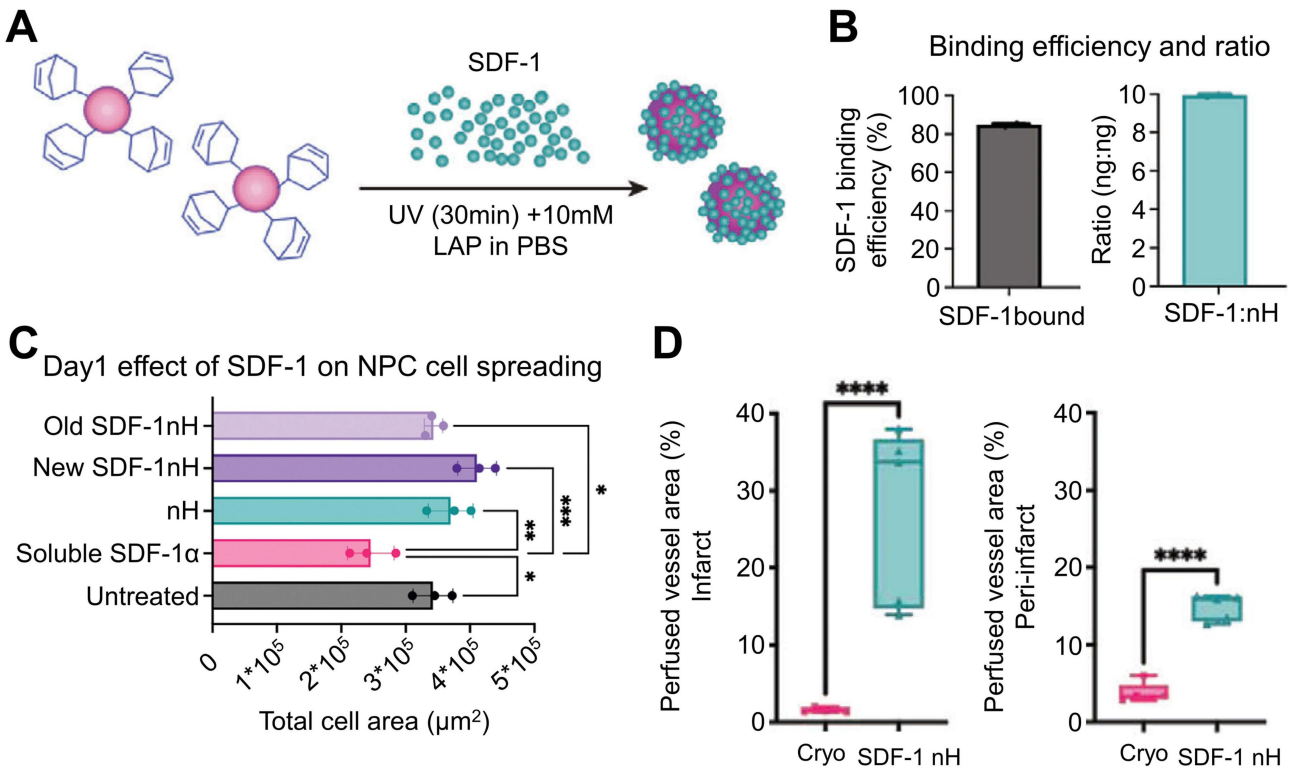


Figure 5 SDF-1 bound nH promote angiogenesis after stroke by recruiting progenitor cells for differentiation. (**A**) Covalent binding of SDF-1 soluble growth factor with nH. (**B**) ELISA data combining SDF-1 and nH measurements and the ratio of SDF-1 to nH. (**C**) Quantification of NPC dissemination following 24 hours of exposure to nH, soluble SDF-1, bound and unbound SDF-1 nH at 200 ng SDF-1 (n = 3; *$P < 0.05$, ** $P < 0.01$, ***$P < 0.005$). (**D**) The perfusion vascular area in the infarcted area (left). The perfusion vascular area around the peri-infarct area (right) (n = 5; ****$P < 0.001$). Reproduced with permission from Wilson KL, Joseph NI, Onweller LA, et al. SDF-1 bound heparin nanoparticles recruit progenitor cells for their differentiation and promotion of angiogenesis after stroke. Adv Healthc Mater. 2023;27:e2302081. © 2023 Wiley-VCH GmbH.[114]
Abbreviations: nH, heparin nanoparticles; NPC, neural progenitor cell; SDF-1, Stromal cell-derived factor 1.

cells (HUVECs). EPC-EVs transport mRNA to endothelial cells, activate the PI3K/Akt/eNOS signaling pathway, and induce angiogenesis. Simultaneously, EVs upregulate the expression of the anti-apoptotic protein Bcl-xL in endothelial cells, exerting an anti-apoptotic effect. Additionally, EVs harbor polymerase genes responsible for mRNA synthesis in eukaryotes.[118] Hu et al discovered that miR-21-5p is abundantly enriched in EPC- EVs and selectively suppresses the expression of the angiogenesis inhibitor thrombospondin-1 in recipient endothelial cells, thereby promoting endothelial repair.

Furthermore, exogenous EPC-EV uptake enhances the proliferation and migration capacities of HUVECs.[119] A study elucidating the regenerative efficacy of cord blood (CB) EPC-EVs on CB-EPCs in vitro demonstrated that EPC-EVs augmented the regenerative capacity of EPCs without altering their endothelial characteristics even at elevated concentrations.[120] And a comparative investigation contrasting stem cell therapy with stem cell-derived EV therapy revealed both modalities enhancing angiogenesis in ischemic stroke, with no discernible disparity between the two.[121,122] These findings suggest that EVs possess therapeutic potential as a substitute for stem cells. Thus, EV-based treatment is poised to emerge as an ideal approach for promoting post-stroke brain repair.

Nevertheless, EVs-based therapy encounters challenges including low production, variable biological efficacy, and reduced tissue retention.[123] Hence, it is crucial to engineer novel EVs using bioactive materials to generate high-yield EVs with enhanced biological activity for clinical implementation.[124,125] Jiang et al developed a dual-responsive hydrogel sensitive to glucose and ROS. These hydrogels exhibit responsiveness to the cerebral microenvironment post-stroke in type 2 diabetes mice, enabling controlled release. Intracerebral injection of these hydrogels in ischemic mice enhances EVs retention and facilitates sustained release, thereby promoting angiogenesis and enhancing neural recovery. These findings underscore the safety and efficacy of this microenvironment-responsive, sustained-release EVs hydrogel system as a therapeutic approach for diabetic stroke.[126] In the future, biomaterials enhanced EVs-based therapy is poised to make a substantial impact in ischemic stroke.

https://doi.org/10.2147/IJN.S493987

Regulating the Local Ecological Microenvironment of Stem Cells

The microenvironment refers to the physical and chemical milieu that surrounds cells, comprising the extracellular matrix (ECM), oxygen concentration, growth factors, and other components. It exerts influence on the proliferation, differentiation, migration, and homing behavior of cells. ECM is a sophisticated three-dimensional network produced by cells, akin to soil, that enmeshes cells within tissues and organs throughout the body. It is pivotal in neural development and regeneration, including the maintenance of the stem cell niche, neural cell migration, and axonal growth.[127] During ischemic stroke, the autophagy of damaged tissues and the degradation of the ECM by metalloproteinases lead to the gradual formation of a stroke cavity in locally affected brain tissue. This cavity lacks physical support structures necessary for cell infiltration and tissue regeneration, consequently leading to impaired angiogenesis and neurogenesis.[128] The grafting of neural stem cells (NSCs) enhances functional recovery following an ischemic stroke. Nevertheless, following cerebral ischemia, the local microenvironment is disrupted, characterized by ECM degradation, elevated levels of inflammatory factors, and excessive ROS, all of which diminish NSC survival and differentiation rates, thus limiting the therapeutic efficacy of NSC transplantation.[129] Hence, orchestrating the microenvironment encompassing the niche of stem cells assumes a pivotal role in fostering neural regeneration.

The natural ECM furnishes essential biomechanical and biochemical cues within the extracellular milieu, rendering it a promising candidate for bioactive material development.[130–132] Bioactive materials mimicking the ECM can be categorized as follows:[130] 1) decellularized matrix sourced from tissues/organs, 2) matrix derived from cells, and 3) materials comprising purified ECM constituents. ECM mimics biomaterials, particularly decellularized matrix, which can mend tissue defects and stimulate in situ tissue regeneration. It has been effectively employed to facilitate constructive remodeling of neural tissue.[133–135] An essential strategy for CNS regeneration involves fabricating an artificial scaffold that mimics the physiological ECM, guiding nerve regeneration spatially.[136]

Notably, Álvarez et al devised an ECM emulation platform utilizing supramolecular nanoscale fibril scaffolds derived from peptide amphiphile (PA) molecules.[137] They observe that nanofibers displaying enhanced intensity of internal supramolecular motion demonstrate heightened bioactivity toward motor and cortical neurons derived from human induced pluripotent stem cells. Highly mobile PA scaffolds were shown to elicit augmented activation of the β1-integrin pathway and enhance the matured electrophysiological activity of neurons. Furthermore, Moshayedi et al formulated a self-polymerizing hydrogel utilizing hyaluronic acid as its base.[138] This hydrogel serves as a platform for structural motif adhesion and for the storage and controlled release of growth factors, thereby fostering the survival and differentiation of transplanted stem cells.

Following cerebral infarction, the local microenvironment harbors elevated levels deleterious substances, exacerbating the viability of transplanted stem cells within the stroke-inflicted region. In light of this, Xu et al developed a dual-buffered arm mesenchymal stem cell bioengineering system to manipulate the local microenvironment (Figure 6), enhance the biological activity of mesenchymal stromal cells, and facilitate neuronal regeneration.[139] Similar bioactive materials also encompass surface-bound ROS-responsive micellar carriers[140] and Polylactic-co-glycolic acid-polyethylene glycol micelle biomaterials enriched with Reelin and embryonic NSC.[28]

Conclusion and Perspectives

At present, the clinical management of ischemic stroke mainly depends on endovascular treatment and the use of neuroprotective drugs. Nevertheless, the increasing incidence and prevalence of stroke pose significant challenges to its treatment. As medical technology advances, novel neuroprotective medications continue to emerge. A thorough assessment of the merits and drawbacks of these medications is imperative to foster the development of more efficacious bioactive compounds. Hence, we undertook a comprehensive review of diverse drugs employed in ischemic stroke treatment and delineated their individual mechanisms of action, detailed in Table 1.

Reestablishing mitochondrial homeostasis, exerting anti-inflammatory effects, reducing BBB permeability, and fostering brain tissue regeneration represent prevalent pharmacological approaches in the treatment of ischemic stroke. These methodologies seek to impede ischemic cell apoptosis, regulate the ischemic microenvironment, mobilize stem cells, and enhance their viability and differentiation, thereby ameliorating neurological function post-cerebral ischemia.

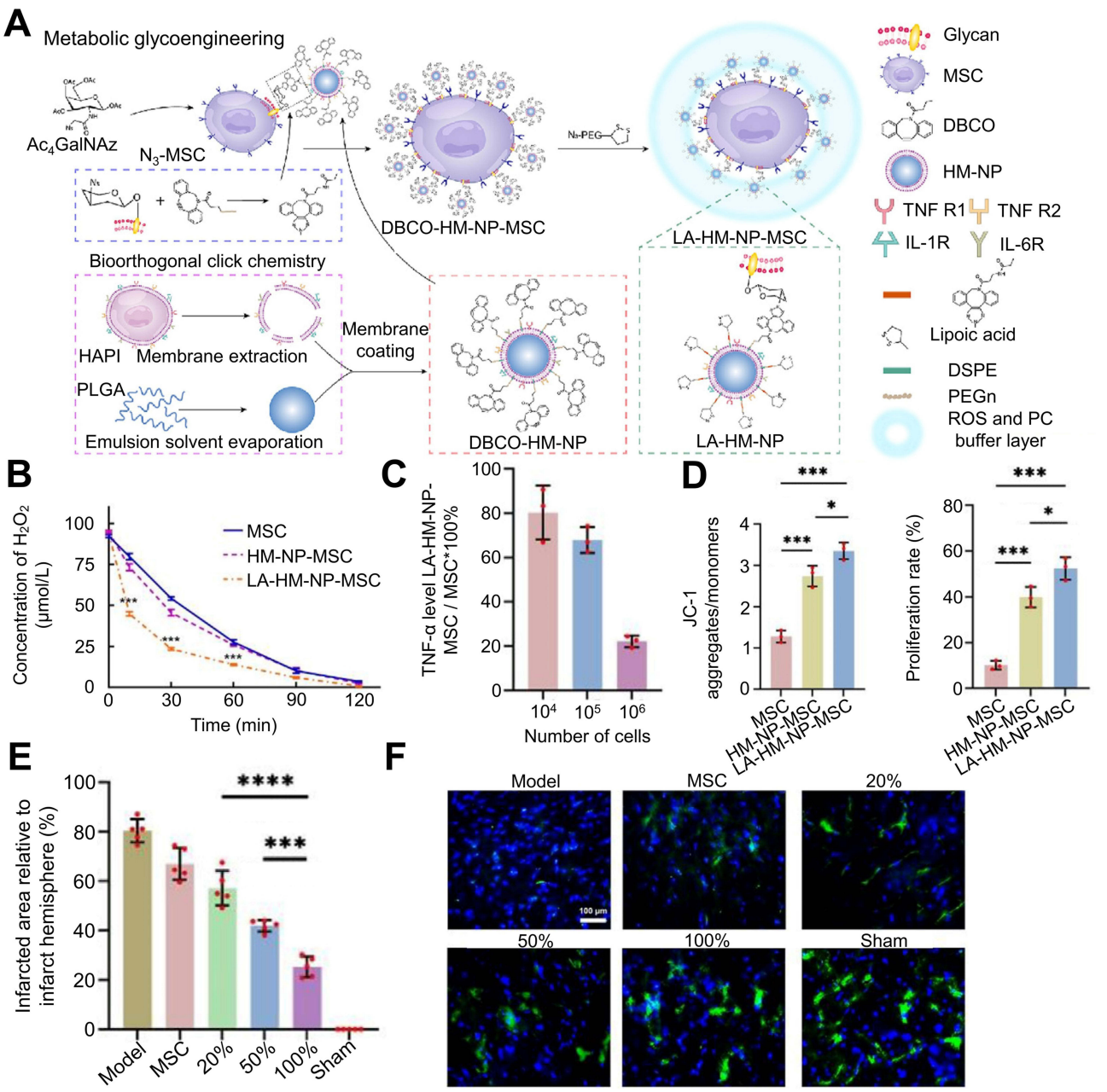


Figure 6 The bioorthogonal MSC bioengineering system promotes neuronal regeneration after ischemic stroke through hormone effects. (**A**) Schematic diagram for preparing LA-HM-NP-MSC. (**B**) The ability of LA-HM-NP-MSC to remove ROS. (**C**) The PC absorption capacity of LA-HM-NP-MSC relative to natural MSC. (**D**) Quantitative evaluation of mitochondrial membrane potential (left) (n = 3; *$P < 0.05$, ***$P < 0.001$). Quantitative analysis of cell proliferation (right) (n = 3; *$P < 0.05$, ***$P < 0.001$). (**E**) Infarct size in stroke rats 28 days after MSC treatment (n = 5; ***$P < 0.001$, ****$P < 0.0001$). (**F**) Representative NeuN immunofluorescence images of the infarcted region following 2 months of MSC therapy (scale bar = 100 μm). Reproduced from Xu J, Sun Y, You Y, et al. Bioorthogonal microglia-inspired mesenchymal stem cell bioengineering system creates livable niches for enhancing ischemic stroke recovery via the hormesis. Acta Pharm Sin B. 2024;14(3):1412–1427. (http://creativecommons.org/licenses/by-nc-nd/4.0/).[139] Copyright 2024, The Authors. Published by Elsevier B.V. on behalf of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

Abbreviations: LA-HM-NP-MSC, lipoic acid- activated HAPI microglia derived membrane-nanoparticle-mesenchymal stem cell; MSC, mesenchymal stem cell; PC, proinflammatory cytokines; ROS, reactive oxygen species.

Maintaining moderate ROS levels and mitochondrial equilibrium are pivotal for cell viability. Following cerebral ischemia, this equilibrium is disrupted. Bioactive materials can alleviate brain tissue damage by scavenging excessive ROS and reinstating mitochondrial dynamics equilibrium. Moderate inflammation and repair are crucial for maintaining homeostasis. The inflammatory response in the local microenvironment following cerebral ischemia is heterogeneous. Early microglia exacerbate inflammation by releasing pro-inflammatory cytokines and chemokines, whereas late microglia facilitate tissue repair by altering their phenotype and secreting anti-inflammatory cytokines. Concurrently, neutrophils exacerbate the

Table 1 Conspectus of Anti-Ischemia Tactics and Repair Mechanisms in Management of Ischemic Stroke

Anti-ischemia strategy	Component	Mechanism	Specific example	Ischemic model	Reference
Oxidative stress	Mitochondria	Stimulates Cox7c within endothelial cell mitochondria	NBP	MCAO/R mouse model	[43,44]
		Eliminate ROS and save mitochondrial membrane potential, morphology, and function	NBP-CeO_2 NPs	Middle cerebral artery embolization/ recanalization mouse model	[46]
		Enhancing NBP delivery	ROS-responsive, transformable, and triple-targeting NBP nanotherapy	MCAO mouse model	[47]
		Scavenging ROS and damaged mitochondria	P/D @ Mn/Co_3O_4	MCAO/R mouse model	[49]
		Enhancing the activity of antioxidant enzymes	Polyphenolic nanoparticles	Transient BCCAO model	[50]
		Eliminate excessive ROS in nerve cells	Recombinant human heavy chain ferritin nanoparticles	Transient MCAO mice model	[51]
		Inhibiting the opening of mPTP and ROS production	Cyclosporine A nanoparticles	MCAO ischemic/ reperfusion injury model in mice	[52]
		Scavenge of ROS	2D MXene-loaded isoquercetin	Rat model of MCAO	[53]
Inflammation	Microglial	Suppressing the PI3K/ AKT/ mTORC1 pathway	RAPA	Thromboembolic stroke murine model	[62]
		Targeted delivery of RAPA	Ph-sensitive RAPA-loaded theranostic system	Rats with transient MCAO	[64]
		Targeted delivery of RAPA	Sulfate polysaccharide nanocarrier loaded with RAPA	Murine model of transient MCAO	[65]
		Inhibiting the proinflammatory activation of microglia	Edaravone dexborneol	Mouse transient MCAO model	[70]
		Negatively regulating the TLR4/ MyD88/NF-κB signaling pathway	Edaravone dexborneol	BV-2 microglial cells	[71]
		Inducing heme oxygenase-1, stimulating Notch1/Hes1/Stat3 signaling	MG1 peptide and RVG29 peptide engineered nanoerythrocyte	Mouse model of MCAO	[74]
		Suppressing the translocation of nuclear HMGB1	ROS-responsive 18β-glycyrrhetic acid-conjugated polymeric nanoparticles	Photothrombotic stroke model of mouse	[75]
	Neutrophils	Suppress the NETs release process	C-Lipo/CA	Mouse model of MCAO/R	[21]
		Facilitated neutrophil reprogramming from NETosis to apoptosis	APTS	MCAO/R mouse model	[83]
		Inhibiting neutrophil infiltration	RvD2-loaded nanovesicles	MCAO/R mouse model	[86]

(*Continued*)

Table 1 (Continued).

Anti-ischemia strategy	Component	Mechanism	Specific example	Ischemic model	Reference
BBB leakage	Endothelial cell	Suppressed the degradation of TJPs	Leo@NM-Lipo	Transient MCAO mouse model	[92]
		Reducing AR activation, and upregulating AKT/mTOR signaling pathway	Epalrestat	Permanent MCAO mouse model	[96]
		Restored expression of the claudin-5	R-Lipo-CAPE	Transient MCAO/R model mice	[100]
		Ameliorating local redox state and elevating ZO-1 and Claudin-5 in the hippocampus	Fe_3O_4 Nanozymes	Mice model of MCAO	[101]
		Activation of protective autophagy	Myricetin oligomer-derived nanostructure doped with Ce	Ischemia reperfusion BCCAO mouse model	[102]
		Elevated expression of ZO-1	mIL-10@MLNPs	Transient MCAO mouse model	[103]
Regeneration of brain tissue	Angiogenesis	Recruitment of PCs	SDF-1 bound Heparin nanoparticles	Photo-Thrombotic stroke mouse model	[114]
		Targeted delivery of SDF-1α	SDF-1α-loaded pH-sensitive polymeric micelles	Rat model of permanent MCAO	[117]
		Increase the migration and tube formation of human umbilical vein endothelial cells	Extracellular vesicles-hydrogels	Distal MCAO ischemia model	[126]
	Neuroregeneration	Provide a desirable microenvironment	Reelin-loaded PLGA/PEG micelles	Photothrombotic stroke mouse model	[28]
		Enhanced β1-integrin pathway activation	Supramolecular peptide amphiphile nanofibers	hiPSC-derived motor and cortical neurons	[137]
		Promoted survival of human neural progenitor cells	Hyaluronic acid-based self-polymerizing hydrogel	Mouse cortical model of photothrombotic stroke	[138]
		Establish viable niches through the hormesis effect	LA-HM-NP-MSC	MSCs	[139]
		Protect MSCs from excessive oxidative damage	MSC-TK-M/Lu	Transient MCAO mouse model	[140]

Abbreviations: AKT/mTOR, protein kinase/ mechanistic target of rapamycin; AR, aldose reductase; ATP, Adenosine triphosphate; BBB, blood-brain barrier; BCCAO, bilateral common carotid artery occlusion; BMVECs, brain microvascular endothelial cells; cGAS-STING, the cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes; Cox7c, cytochrome C oxidase 7c; hiPSC, Human induced pluripotent stem cell; HMGB1, high mobility group box 1; MCAO, middle cerebral artery occlusion; MCAO/R, middle cerebral artery occlusion/reperfusion; mPTP, mitochondrial permeability transition pore; MSC, mesenchymal stromal/stem cells; NBP, Dl-3-n-butylphthalide; NETs, neutrophil extracellular traps; NPs, nanoparticles; NSCs, neural stem cells; OGD/R, oxygen-glucose deprivation/reoxygenation; PCs: progenitor cells; PI3K/AKT/mTORC1, phosphatidylinositol-3-kinase/ protein kinase/ mechanistic target of rapamycin complex 1; RAPA, rapamycin; R-Lipo-CAPE, reactive nitrogen species stimuli-responsive liposomal nanocarrier-caffeic acid phenethyl ester; ROS, reactive oxygen species; SDF-1, stromal cell-derived factor-1; TLR4/MyD88/NF-KB, toll-like receptor 4/ myeloid differentiation marker 88/ nuclear factor-kappaB; TJs, tight junctions; ZO-1, zonula occludens-1.

inflammatory cascade through the release of NETs and local infiltration. Excessive inflammation and inadequate repair during ischemia can disrupt homeostasis. Bioactive materials can mitigate brain tissue damage by suppressing microglia and neutrophil activation, promoting microglial polarization towards the M2 phenotype and inhibiting the infiltration of neutrophil. The integrity of the BBB is compromised by Ischemic microenvironment, while the bioactive material enhances neural function by mitigating endothelial cell apoptosis and reinstating TJPs expression between endothelial cells.

Hence, modulation of the aforementioned cellular behaviors represents a pivotal therapeutic strategy. Lastly, bioactive materials are instrumental in advancing neural function repair by modulating progenitor cells and their corresponding

EVs and enhancing the local microenvironment for stem cells. These modalities constitute a crucial facet of contemporary pharmacotherapy for ischemic stroke.

Despite the plethora of available medications, effective clinical management of ischemic stroke remains elusive. Following cerebral ischemia, the pathophysiological cascade is intricate, defying remediation through mono-modal pharmacotherapy. Moreover, neuronal regeneration post-cerebral ischemia is severely constrained. Thus, mere antioxidative or anti-inflammatory interventions are unlikely to yield favorable outcomes in ischemic stroke management. Employing multi-modal bioactive materials with targeted delivery mechanisms, holds promise in elevating local drug concentrations, mitigating systemic adverse effects and enhancing prognostic outcomes. Concurrently, such interventions may complement endovascular therapies, fostering enhanced cerebral tissue recovery. Furthermore, harnessing bioactive materials to augment stem cell recruitment, viability, and differentiation represents a focal point and a formidable challenge in advancing stroke therapeutics.

Abbreviations

AKT, protein kinase; ATP, adenosine 5'-triphosphate; BBB, blood-brain barrier; CNS, central nervous system; Cox7c, cytochrome C oxidase 7c; 2D, two-dimensional; Eda-Dex, edaravone dexborneol; IL-6, Interleukin 6; mTORC1, mechanistic target of rapamycin complex 1; MXene, layered transition metal carbon/nitrogen compound; NBP, dl-3-n-butylphthalide; PI3K, phosphatidylinositol-3-kinase; RAPA, Rapamycin; ROS, reactive oxygen species; rt-PA, recombinant tissue plasminogen activator; SCS, Sulfated chitosan; TJs, tight junctions; TJPs, tight junction proteins.

Data Sharing Statement

Data available on request from the corresponding author.

Disclosure

The authors report no conflicts of interest in this work.

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