Acta Pharmaceutica Sinica B 2026;16(7):4746−4747

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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COMMENTARY

Reprogramming the spleen−brain axis: Splenic monocyte/macrophage-mediated nanotherapy for ischemic stroke

KEY WORDS

Macrophage reprogramming;
Nanomedicine;
Magnolol;
Oxidative stress;
PPARγ;
CCR2/CCL2

Ischemic stroke remains one of the leading causes of mortality and long-term neurological disability worldwide[1]. Although rapid reperfusion therapies, including thrombolysis and endovascular thrombectomy, have significantly improved acute stroke management, cerebral ischemia−reperfusion (I/R) injury continues to represent a major unresolved clinical challenge. Reperfusion itself can amplify oxidative stress, neuroinflammation, and neuronal apoptosis, thereby limiting the therapeutic benefit of vascular recanalization. Increasing evidence suggests that post-ischemic injury is not solely a neuron-centered process, but rather a highly coordinated systemic inflammatory response involving extensive communication between the injured brain and peripheral immune organs[2]. Among these, the spleen has emerged as a critical immunological hub in stroke pathology through the so-called spleen−brain axis[2]. Following cerebral I/R injury, the spleen undergoes contraction and releases monocytes/macrophages (Mo/Mϕ) into the circulation, where they subsequently infiltrate ischemic brain lesions primarily through the CCL2/CCR2 chemotactic pathway and contribute to inflammatory amplification and oxidative injury. Pioneer work has demonstrated that spleen-targeted nanoparticles can regulate Mo/Mϕ polarization in cerebral I/R injury, highlighting the therapeutic potential of this immune reservoir[2]. Consequently, while conventional strategies such as splenectomy and macrophage depletion have provided mechanistic insights in preclinical models, their significant drawbacks highlight an unmet need for targeted approaches that can precisely reprogram splenic Mo/Mϕ polarization without compromising systemic immune homeostasis.

In a recent study published in *Acta Pharmaceutica Sinica B*, the groups of Hui Cai, Mingzhen Zhang, and Shaoying Lu[3] developed an innovative spleen-targeted nanomedicine strategy that harnesses the endogenous migratory behavior of splenic monocytes/macrophages as "living vehicles" for targeted drug delivery to ischemic brain lesions. Rather than directly attempting to overcome the blood−brain barrier (BBB), the authors leveraged the natural trafficking properties of splenic immune cells through the spleen−brain axis to achieve targeted therapeutic delivery, representing a conceptual shift in neuroinflammatory nanomedicine. The study utilized magnolol, a bioactive natural product derived from *Magnolia officinalis* with known antioxidant and anti-inflammatory activities. However, free magnolol suffers from poor aqueous solubility, limited stability, and suboptimal tissue accumulation. To address these limitations, the authors engineered a series of PEGylated magnolol liposomes and identified Mag-PEG_{5K} as the optimal formulation for spleen-targeted delivery. Through systematic optimization of PEG chain length, Mag-PEG_{5K} achieved favorable particle stability, sustained drug release, enhanced splenic accumulation, and efficient uptake by splenic Mo/Mϕ—a formulation design principle that may inform future development of spleen-targeted nanomedicines beyond the stroke context.

Importantly, the study demonstrated that Mag-PEG_{5K}-loaded splenic Mo/Mϕ actively migrated to ischemic brain tissue through the CCR2/CCL2 axis following cerebral I/R injury. This finding establishes a biologically integrated delivery strategy in which endogenous immune-cell trafficking serves as the transport

Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2026.06.027

mechanism for nanotherapeutics. Compared with conventional brain-targeting nanomedicine approaches that primarily focus on BBB penetration, this immune-cell-mediated delivery paradigm provides an alternative route for achieving lesion-specific drug accumulation. Indeed, the broader potential of immune-assisted CNS drug delivery has been further demonstrated by recent work showing that calvarial immune cells can be hijacked *in situ* by drug-loaded nanoparticles, leveraging skull-meninges microchannels as an alternative BBB-bypassing route for stroke therapy[4]. Mechanistically, the therapeutic effects of Mag-PEG_{5K} involved dual regulation of oxidative stress and macrophage polarization. The authors showed that Mag-PEG_{5K} efficiently localized to mitochondria and significantly reduced intracellular reactive oxygen species (ROS) accumulation, thereby suppressing pro-inflammatory M1 macrophage activation. Simultaneously, magnolol-mediated activation of peroxisome proliferator-activated receptor gamma (PPARγ) promoted macrophage reprogramming away from the M1 phenotype. The coordinated reduction of TNF-α and IL-1β secretion subsequently attenuated downstream neuronal inflammatory cascades and reduced neuronal apoptosis. This integration of mitochondrial ROS regulation with immunomodulatory macrophage reprogramming is particularly noteworthy, as neuroinflammation following stroke involves highly interconnected oxidative, metabolic, and immune signaling networks that are often inadequately addressed by single-pathway interventions.

The study further demonstrated significant *in vivo* therapeutic efficacy, including reduced infarct volume, improved histopathological recovery, and enhanced long-term neurological function in tMCAO mice. Notably, Mag-PEG_{5K} outperformed free magnolol, highlighting the importance of the spleen-targeted delivery strategy rather than the pharmacological activity of magnolol alone. Conceptually, this work contributes to the growing recognition that peripheral immune modulation may represent an effective therapeutic strategy for neurological disorders. Rather than viewing infiltrating macrophages solely as pathological contributors, the study reframes these immune cells as programmable therapeutic intermediates. This perspective is further supported by recent single-cell transcriptomic studies identifying a distinct repair-associated macrophage subset derived from $CCR2^{+}$ monocytes that actively promotes remyelination and angiogenesis after ischemic stroke[5]. Such a strategy may have broader implications not only for ischemic stroke, but also for other neuroinflammatory diseases involving peripheral immune recruitment, including traumatic brain injury, multiple sclerosis, and neurodegenerative disorders.

Despite these advances, several challenges remain. The therapeutic strategy relies heavily on CCR2-dependent immune-cell migration, which may vary across disease stages and patient populations. The inflammatory heterogeneity observed in human stroke could influence splenic immune activation and therapeutic responsiveness. Furthermore, while the murine tMCAO model provides important mechanistic insight, the translational relevance of spleen—brain immune trafficking in humans remains incompletely understood. Additional studies in clinically relevant systems, large animal models, long-term biosafety evaluation, and translational manufacturing optimization will therefore be important for future development.

In summary, the work by Cai, Zhang, Lu and colleagues[3] presents a compelling spleen—brain axis-directed nanotherapeutic strategy for ischemic stroke by transforming splenic monocytes/macrophages into endogenous drug delivery carriers. Through coordinated regulation of oxidative stress and macrophage polarization, the study establishes a biologically integrated platform for immune microenvironment remodeling following cerebral ischemia—reperfusion injury. Beyond advancing peripheral immunity-oriented stroke nanomedicine, this work also expands the conceptual framework for immune-cell-guided therapeutic delivery in neuroinflammatory diseases.

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