ACSNANO

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Pleiotropic Microenvironment Remodeling Micelles for Cerebral Ischemia-Reperfusion Injury Therapy by Inhibiting Neuronal Ferroptosis and Glial Overactivation

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Cite This: https://doi.org/10.1021/acsnano.3c05038

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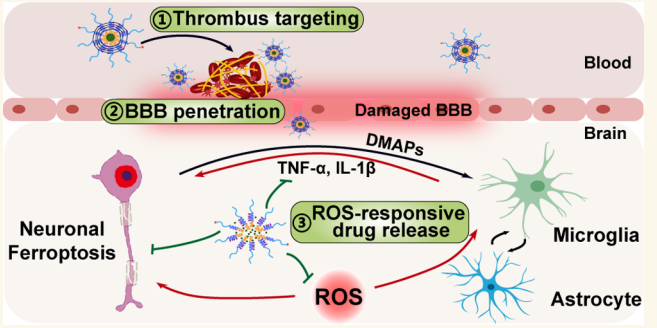
ABSTRACT: Reperfusion injury presents a significant obstacle to neuronal survival following successful recanalization in ischemic stroke, which is characterized by intricate pathophysiological processes comprising numerous interconnected pathways. Oxidative stress-induced neuronal ferroptosis and the overactivation of glial cells play important roles in this phenomenon. In this study, we developed a targeted cross-linked micelle loaded with idebenone to rescue the ischemic penumbra by inhibiting neuronal ferroptosis and glial overactivation. In rat models, the CREKA peptide-modified micelles accumulate in the damaged brain via binding to microthrombi in the ipsilateral microvessels. Upon reactive oxygen species (ROS) stimulation, diselenide bonds within the micelles are transformed to hydrophilic seleninic acids, enabling synchronized ROS consumption and responsive drug release. The released idebenone scavenges ROS, prevents oxidative stress-induced neuronal ferroptosis, attenuates glial overactivation, and suppresses pro-inflammatory factors secretion, thereby modulating the inflammatory microenvironment. Finally, this micelle significantly reinforces neuronal survival, reduces infarct volume, and improves behavioral function compared to the control groups. This pleiotropic therapeutic micelle provides a proof-of-concept of remodeling the lesion microenvironment by inhibiting neuronal ferroptosis and glial overactivation to treat cerebral ischemia-reperfusion injury.



KEYWORDS: *reperfusion injury, microenvironment remodeling, micelles, idebenone, neuronal ferroptosis, glial overactivation*

INTRODUCTION

Acute ischemic stroke, resulting from cerebral artery occlusion, is a dangerous cerebrovascular disease with high risks of disability and mortality.[1] While treatments such as thrombolysis and thrombectomy can effectively restore blood supply to the penumbra, successful reperfusion can also cause serious secondary brain injury.[2,3] Neurons are the most vulnerable cells within the neurovascular unit, and their continuous loss is a primary contributor to neurological impairments.[4] Despite extensive research on neuroprotectants against single molecular mechanisms, their successful clinical application remains challenging, highlighting the urgency to shift from single-target agents to pleiotropic therapeutics for improved treatment outcomes.[5]

Cerebral ischemia-reperfusion injury (CI-RI) is a complex and multifaceted pathophysiological process with several interconnected pathways that evolve over time and affect multiple types of cells.[6,7] Following reperfusion, excessive reactive oxygen species (ROS) cause oxidative damage to DNA, proteins, and lipids, resulting in neuronal cell death.[8,9] While the dominant pathway of cell death after reperfusion remains undetermined, emerging evidence suggests that ferroptosis plays a crucial role in this injury.[10,11] Ferroptosis is a newly identified type of regulated cell death that relies on oxidative stress-mediated production and accumulation of lipid

Received: June 5, 2023
Accepted: September 8, 2023