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ARTICLE

Carrier-Free Nanodrug Based on Co-Assembly of Methylprednisolone Dimer and Rutin for Combined Treatment of Spinal Cord Injury

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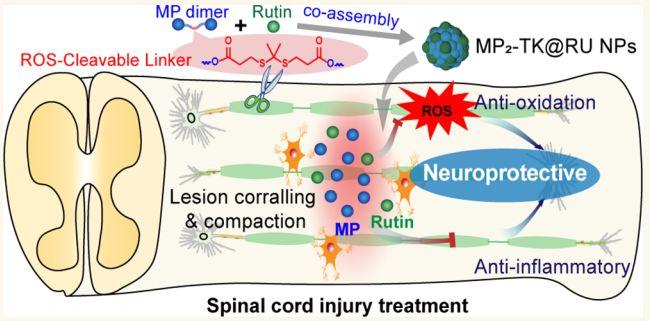
ABSTRACT: Spinal cord injury (SCI), which is characterized by excessive inflammatory cell infiltration and accumulation of oxidative substance, would severely impede neurological functional recovery and lead to permanent and profound neurologic deficits and even disability. Methylprednisolone (MP) is the most commonly used clinical anti-inflammatory drug for SCI treatment, but high doses are typically required that can cause severe side effects. Here, we developed a carrier-free thioketal linked MP dimer@rutin nanoparticles (MP_2-TK@RU NPs) which can achieve combined SCI treatment by coassembling reactive oxygen species (ROS) cleavable MP dimers and rutin. This proposed nanodrug possesses the following favorable advantages: (1) the carrier-free system is easily accessible and has a high drug-loading capacity, which is preferred by the pharmaceutical industry; (2) The ROS-cleavable linker increases the efficiency of targeted drug delivery to the injury site; (3) Rutin, a type of plant-derived natural flavonoid with good biocompatibility, anti-inflammatory, and antioxidant properties, is codelivered to enhance the therapy outcomes. The obtained MP_2-TK@RU NPs exhibited potent anti-inflammatory and antioxidative properties both *in vitro* and *in vivo*, demonstrating superior locomotor function recovery and neuroprotective efficacy in rats with SCI. This carrier-free nanodrug is anticipated to provide a promising therapeutic strategy for clinical SCI treatment.



KEYWORDS: *spinal cord injury, carrier-free nanodrugs, anti-inflammation, antioxidative, neuroprotection*

INTRODUCTION

Spinal cord injury (SCI) frequently results in permanent disability, including the loss of sensory and motor innervation of the limbs and body, which leads to severe autonomic functional impairment.[1,2] According to current estimates, there are more than 25 million SCI patients in the world, and the number of new cases continues to rise by approximately 1 million per year, resulting in a significant social impact and a colossal economic cost.[3] Traumatic events, cancer, osteoarthritis, and infections, among others, can cause the primary injury of spinal cord. Subsequently, as a delayed and progressive process, a sustained secondary injury ensues, resulting in the death of neurons and glial cells, which worsens the prognosis.[4,5] The secondary injury is strongly related to oxidative stress and inflammation.[6,7] The initial trauma to the spinal cord induces microvascular damage, and the subsequent ischemia causes ongoing edema, vessel thrombosis, and vasospasms, resulting in a hypoxic microenvironment at the lesion site. Subsequently, the ischemia and hypoxic microenvironment disrupt the equilibrium of oxidative and antioxidant cell pathways, resulting in the accumulation of aberrant free radicals, such as reactive oxygen species (ROS) and reactive nitrogen, which ultimately results in oxidative stress in the spinal cord.[8,9] Inflammatory cells, such as neutrophils, monocytes, and macrophages, infiltrate the injury sites alongside the breakdown of the blood-spinal cord barrier and release various inflammatory cytokines, chemokines, oxygen-free radicals, proteolytic enzymes, and nitric oxide. All of these inflammatory mediators are able to further amplify inflammation and exacerbate neuronal dysfunction or loss, ultimately leading to neuronal death in the spinal cord and tissue disintegration.[10,11] Consequently, modulating the micro-

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