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A Perspective on Reactive Oxygen is Beneficial for Spinal Cord Injury

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Introduction

The hydrogel was able to successfully encapsulate BMSCs and performed a remarkable role in vivo as a neuroprotective agent by lowering the production of endogenous reactive oxygen species (ROS), attenuating ROS-mediated oxidative damage, and downregulating inflammatory cytokines like interleukin-1 beta (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-). The ROS-scavenging hydrogel that was encapsulated in BMSCs dramatically accelerated the recovery of motor function in SCI rats. Also, it improved the spinal cord tissue's neurogenesis and decreased the creation of scarring. Our study provides a combinatorial approach against ROS-mediated oxidative stress, which has the potential to be used not just to SCI but also to other central nervous system illnesses that share comparable clinical characteristics.

Description

Until now, the treatment of SCI has largely relied on the use of biocompatible polymers to reduce secondary inflammation, the development of patterned hydrogels or oriented scaffolds to direct the regenerated axons, the use of immunocell polarization-regulating nanoparticles or hydrogels, and cell transplantation. A hyaluronic acid (HA) and poly(ethylene glycol) diacrylate (PEGDA)-modified polycaprolactone (PCL) nanofiber-modified hydrogel, for instance, encourages macrophage polarisation and increases the quantity of immature neurons and axons in a rat SCI model. Several types of scaffolds are also used in SCI therapy, including chitosan micro-hydrogels and an imidazole-conjugated poly(organophosphazenes) hydrogel for targeting macrophages. However, without the precise inclusion or encapsulation of neurogenesis-promoting macromolecules or stem cells, the effectiveness of these biomaterials on motor rehabilitation is still insufficient [1].

But even though stem cells like mesenchymal stem cells (MSCs) can replace injured neurons, their application is still constrained by their low bioavailability in the lesion site and insufficient behaviour restoration efficiency in severe paraplegia cases. Yet stem cell transplantation utilising hydrogels, which give transplanted cells an artificial extracellular matrix (ECM), act as a physical barrier to stop undesirable diffusion, and lessen secondary inflammation brought on by mechanical mismatch, is a promising treatment for SCI. The therapeutic efficacy of non-stimuli responsive hydrogels is insufficient since the majority of implanted cells might not survive in the cytotoxic and inhibitive milieu. The overproduction of reactive oxygen species (ROS) is regarded to be one of the major culprits because they lead to oxidative stress, cytotoxic neuro-excitation, and a new round of severe inflammatory response. It has been demonstrated that coenzyme Q10 controls apoptosis and oxidative stress, safeguards transplanted BMSCs, and improves the efficacy of SCI treatment. Yet, due to its chemical instability and relative delayed adsorption, it may have low bioavailability and, as a result, provide insufficient protection in vivo [2,3].

Traumatic spinal cord injury (SCI) is a catastrophic occurrence that can cause the locomotor and sensory systems to be impaired or dysfunctional, leading to life-altering disability, serious complications, and even patient death. Up to this time, there have been 27 million SCI instances reported worldwide, with 93.8 thousand new cases reported each year. Unfortunately, motor function or axon regeneration cannot be sufficiently restored with the existing clinical treatments for SCI. Following trauma-induced primary injuries, a number of severe secondary injuries, including uncontrolled oxidative stress and inflammation, tissue remodelling, and cytotoxic neural excitement brought on by a large and sudden influx of calcium ions and glutamate, which results in the necrosis and apoptosis of neurons and glial cells, both of which contribute to the lesion, occur around the lesion site.

By scavenging excess ROS, biomaterials can ably control the hostile environment, safeguard newly transplanted cells, and considerably enhance neurogenesis. Cerium oxide nanoparticles (CONPs) were administered in the right quantity to the site of the lesion by Kim and colleagues, who saw a reduction in the cavity's size, the number of inflammatory cells present, and the mRNA expression of inflammatory cytokines and proteins associated with apoptosis. In a similar line, Mn (III) tetrakis (4-benzoic acid) porphyrin nanoparticles, iron oxide nanoparticles, and selenium nanoparticles (Se NPs) can all lower ROS in the therapy of SCI. Additionally, the polymer-based ROS scavenging biomaterials are efficient in treating SCI and offer special benefits including customizable degradability and harmless degradable products.

Tetramethylpiperidine 1-oxyl (Tempol)-grafted hydrogel and high-density thioether-containing lipid-polymer nanoparticles have both been demonstrated to be efficient at scavenging ROS in SCI. The MnO2 NPs considerably shelter the bone-derived MSCs (BMSCs) from a ROS-rich milieu, whereas the BMSCs enclosed in the undotted hydrogel suffer a significant loss, according to research that transplanted BMSCs into a HA hydrogel with MnO2 NPs. However, the combination of stem cells and ROS-scavenging hydrogels for the therapy of SCI has garnered little attention. The modulation of the inflammatory milieu and the protection of encapsulated stem cells from apoptosis are just two of the many benefits of this combination [4,5].

In this study, a ROS-responsive and scavenging hydrogel is produced by crosslinking a thioketal-containing hyperbranched polymer (HBPAK) with methacrylate hyaluronic acid (HA-MA). Covalently grafting neural-specific CQAASIKVAV peptides (abbreviated IKVAV) and rat-derived basic fibroblast growth factor (EGF) and basic fibroblast growth factor (RBFGF) into this hydrogel This hydrogel can scavenge excess ROS, encourage the polarisation of M2 macrophages, lessen inflammation, and shield the encapsulated BMSCs from oxidative stress when it is implanted for SCI treatment in vivo. The basic physiochemical characteristics of the produced hydrogel, such as its anti-oxidation, anti-inflammatory, and biocompatibility, are described in vitro. The in vivo therapeutic efficacy is assessed using a rat transection spinal cord injury model at the T10 level (two millimetres), with a focus on anti-oxidation and axon regeneration [1].

Hence, controlling scar development is crucial for effective SCI treatment.

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After surgery, the injured spinal cord tissue was Masson stained on day 7. The THIEF-Cell group saw less collagen deposition and scarring, as seen by the smaller aniline blue positive area on day 7. On day 56, both the THIEF-Cell and THI hydrogel groups displayed less aniline blue-positive regions and more purple-hued regions at the lesion site, demonstrating that fewer scars had developed and that more neural fibres had survived. The two separate scars that appeared on Day 7 were then examined using immunofluorescence staining. The glial scars that enter the lesion gap and form a dangerous cavity are largely composed of activated astrocytes that have been GFAP-labeled.

The fibrotic scar marker PDGFR- was selected in this instance. Thus, PDGFR-/GFAP double staining was carried out. The seven-day quantitative analysis shows that the percentage of PDGFR-+ regions in the THIEF-Cell (10.0 1.2%) and THI hydrogel (10.0 1.5%) groups was considerably lower than that in the PHIEF-cell (14.8 2.1%) and SCI groups. The percentage of GFAP+ regions in the THIEF-Cell group (1.8 0.8%) and the THI hydrogel group (1.9 0.9%) were both lower than in the other two groups. The ROS-scavenging hydrogel can greatly lessen the development of fibrotic and glial scarring in the lesion site, which is essential for axon regeneration whether or not BMSCs are encapsulated.

Conclusion

A BMSC-encapsulated ROS-scavenging hydrogel was created by combining a thioketal-containing hyperbranched polymer (HBPAK), biocompatible HA-MA and IKVAV peptides, and cell growth factors in a single pot. This hydrogel was very biocompatible and had the ability to drastically lower the oxidative microenvironment both in vitro and in vivo. The BMSC-encapsulated ROS-scavenging hydrogel was applied to the lesion site in a rat spinal cord transection model, dramatically lowering oxidation, inflammation, and cell death.

Conflict of Interest

No conflict of interest by the author.

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