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Injury to the Spinal Cord is helped by a Reactive Oxygen Species-Responsive Hydrogel that Contains Bone Marrow-Derived Stem Cells

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Abstract

The disabling and overwhelming condition known as spinal cord injury (SCI) is accompanied by intricate inflammation-related pathological processes like the release of excessive reactive oxygen species (ROS) into the extracellular microenvironment and widespread apoptosis of neuron, glial, and oligodendroctyl cells by infiltrating inflammatory immune cells. For the purpose of encapsulating bone marrow derived mesenchymal stem cells (BMSCs), a thioketal-containing and ROS-scavenging hydrogel was made in this study. This hydrogel promoted neurogenesis and axon regeneration by scavenging the overproduced ROS and re-building a regenerative microenvironment. By reducing 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 tumor necrosis factor-alpha (TNF-), the hydrogel was able to effectively encapsulate BMSCs and played a remarkable role in vivo as a neuroprotective agent. The motor functional recovery of SCI rats was significantly enhanced by the ROS-scavenging hydrogel that was encapsulated in BMSCs. It also reduced the formation of scars and enhanced the neurogenesis of the spinal cord tissue. A combinational strategy against ROS-mediated oxidative stress is provided by our work, which has the potential to be utilized not only in SCI but also in other diseases of the central nervous system that share similar pathological conditions.

Keywords: Spinal cord injury (SCI) • ROS scavenging • BMSCs • Axon regeneration • Anti-oxidation

Introduction

Traumatic spinal cord injury (SCI) is a catastrophic event that can result in impairment or dysfunction of the locomotor and sensory systems, resulting in life-altering paralysis, severe complications, and even death for patients. There have been 27 million SCI cases worldwide up to this point, with 93.8 thousand new cases occurring annually. However, the current clinical treatments for SCI are unable to restore motor function or axon regeneration with sufficient efficacy. Numerous severe secondary injuries occur around the lesion site after trauma-caused primary injuries, including uncontrolled oxidative stress and inflammation, tissue remodeling, and cytotoxic neural excitement caused by a rapid and large influx of calcium ions and glutamate, which causes the necrosis and apoptosis of neurons and glial cells, both of which contribute to the loss of neurons. The application of biocompatible polymers to reduce secondary inflammation, the creation of patterned hydrogels or oriented scaffolds to guide the regenerated axons, immune cells polarization-regulating nanoparticles or hydrogels, and cell transplantation have all played major roles in the treatment of SCI to this point. In a rat SCI model, for instance, a hyaluronic acid (HA) and poly(ethylene glycol) diacrylate (PEGDA)-modified polycaprolactone (PCL) nanofiber-modified hydrogel promotes macrophage polarization, resulting in an increase in the number of immature neurons and axons. SCI therapy also utilizes other types of scaffolds, such as chitosan micro-hydrogels and an imidazole-conjugated poly(organophosphazenes) hydrogel for macrophage targeting. However, the efficacy of these biomaterials on motor recovery is still insufficient without the specific addition or encapsulation of neurogenesis-promoting biomolecules or stem cells. However, despite the fact that damaged neurons can be replaced with stem cells like mesenchymal stem cells (MSCs), their application is still limited by their low bioavailability in the lesion site and insufficient behavior restoration efficacy in cases of severe paraplegia. However, a promising treatment for SCI is stem cell transplantation using hydrogels, which provide an artificial extracellular matrix (ECM) for the implanted cells, serve as a physical barrier to prevent unfavorable diffusion, and reduce secondary inflammation caused by mechanical mismatch. However, the majority of implanted cells may not survive in the cytotoxic and inhibitory microenvironment, so the therapeutic effect of non-stimuli responsive hydrogels is insufficient. Because they cause oxidative stress, cytotoxic neuro-excitement, and a new round of severe inflammatory response, the overproduction of reactive oxygen species (ROS) is thought to be one of the main causes. Coenzyme Q10 has been shown to regulate apoptosis and oxidative stress, protect transplanted BMSCs, and increase the effectiveness of SCI treatment. However, its chemically unstable nature and relative slow adsorption may result in low bioavailability and, consequently, low protection in vivo [1-4].

Biomaterials can successfully regulate the hostile environment, protect transplanted cells, and significantly promote neurogenesis by scavenging overproduced ROS. Kim and co. Administered the optimal amount of cerium oxide nanoparticles (CONPs) to the site of the lesion, which decreased the size of the cavity and the number of inflammatory cells, as well as the mRNA expression of inflammatory cytokines and apoptotic proteins. In a similar vein, in the treatment of SCI, selenium nanoparticles (Se NPs), iron oxide NPs, and Mn (III) tetrakis (4-benzoic acid) porphyrin NPs can reduce ROS. In addition, the polymer-based ROS scavenging biomaterials have unique advantages like adjustable degradability and harmless degradable products and are effective in SCI treatment. For the purpose of scavenging ROS in SCI, tetramethylpiperidine 1-oxyl (Tempol)-grafted hydrogel and high-density thioether-containing lipid-polymer nanoparticles have been shown to be effective. Transplanted bone-derived MSCs (BMSCs) into a MnO2 NPs-dotted HA hydrogel and

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demonstrated that the MnO2 NPs significantly shield the BMSCs from an ROS-rich microenvironment, whereas the BMSCs encapsulated in the undotted hydrogel suffer a significant loss. For SCI treatment, however, the combination of stem cells and ROS-scavenging hydrogels has received little attention. This combination has numerous advantages; including modulating the inflammatory microenvironment and protecting encapsulated stem cells from apoptosis, resulting in a superior in vivo SCI therapy [5].

A thioketal-containing hyperbranched polymer (HBPAK) is crosslinked with methacrylate hyaluronic acid (HA-MA) to create a ROS-responsive and scavenging hydrogel in this study. Within this hydrogel, neural-specific CQAASIKVAV peptides (IKVAV for short) are covalently grafted, and rat-derived epidermal growth factor (EGF) and rat-derived basic When transplanted for SCI treatment in vivo, this hydrogel is able to scavenge excess ROS, promote the polarization of M2 macrophages, reduce inflammation, and protect the encapsulated BMSCs from oxidative stress. In vitro, the obtained hydrogel's fundamental physiochemical properties, including its anti-oxidation, anti-inflammatory, and biocompatibility, are characterized. The in vivo therapeutic effect, particularly anti-oxidation and axon regeneration, is evaluated using a rat transection spinal cord injury model at the T10 level (two millimeters) [6].

Materials and Methods

Hyaluronic acid (HA, Mw=100 kDa, Haihua, Jiangsu, China), methacrylic anhydride (MA), cysteine hydrochloride (Aladdin, Shanghai, China), poly(ethylene glycol) diacrylate (PEGDA575), thiol-containing IKVAV peptide (CQAASIKVAV, GL Biochem., Shanghai, China), bFGF (PeproTech, USA), and EGF (PeproTech, USA) were utilized straight from the package without any further purification. Methanol tert-butyl ether, dimethyl sulfoxide, and N,N-dimethylformamide (DMF) were all obtained from China National Pharmaceutical Group Corporation. Beyotime Biotechnology in Shanghai, China, supplied the Live/Dead staining kit. Nanjing Jiancheng Bioengineering Institute in Nanjing, China, supplied the inhibition and production superoxide anion assay kit. Abcam (Shanghai, China) supplied the antibodies against smooth muscle actin (-SMA), CD31, CD86, CD163, MAP2, and anti-8-hydroxy-2 deoxyguanosine (anti-8-OHdG). 7Sea Biotech Co. Ltd., based in Shanghai, China, supplied the Cell Counting Kit-8 (CCK-8). Cell Signaling Technology (CST, Boston, USA) supplied the antibodies of anti-neurofilament 200 (anti-NF200), anti-class III beta tubulin (anti-Tuj-1) and anti-platelet derived growth factor subunit (anti-PDGFR-). Boster (Wuhan, China) supplied the rat tumor necrosis factor- (TNF-), interleukin-1 (IL-1) and IL-6 enzyme-linked immunosorbent assay (ELISA) Research Reagent as well as anti-glial fibrillary acidic protein (anti-GFAP). Dihydroethidium (DHE) pack was bought from Yeason (Shanghai, China). Gibco (New York, USA) supplied the alpha-minimum essential medium (-MEM), high glucose Dulbecco's modified Eagle medium (DMEM), fetal bovine serum (FBS), and an antibiotic mixture containing penicillin and penicillin. The Milli-Q cycle purification system (Millipore, USA) was used to produce the ultra-purified water used in this study [7,8].

Combination and portrayal of HBPAK and HA-Mama

The ROS-responsive hyperbranched polymers (HBPAK) were combined through a Michael expansion response between the PEGDA with end-covered twofold bonds and ROS-cleavable thioketal diamine (TK) as indicated by a strategy detailed beforehand. Deuterated dimethyl sulfoxide (DMSO-D6) or deuterated chloroform (CDCl3) was used to fully dissolve 10 mg of TK and HBPAK, respectively, and 500 MHz 1H nuclear magnetic resonance (H NMR) was used to characterize them to confirm their structures. After the HBPAK was dissolved in N, N-dimethylformamide (DMF) to a concentration of 5 mg/mL, the weight-average molecular weight (Mw) and polydispersity (PDI) were measured by hydrogel permeation chromatography (GPC, Waters 1515). The ROS-scavenging abilities were confirmed by assays using hydrogen peroxide (H_2O_2) and 1′-diphenyl-2-picrylhydra. Hydrogels' anti-oxidative and protective effects in vitro. It is widely acknowledged that transplanting stem cells aids in axon regeneration in CNS-related diseases. Thus, exemplification of undifferentiated organisms was proposed in the plan of our SCI-treatment framework. In addition, BMSC renewal can be maintained by EGF without inducing differentiation in vitro. However, a number of studies demonstrate that in the presence of bFGF and EGF, BMSCs would transform into neural progenitor-like cells. In addition, ependymal cells in the central canal are significantly more proliferative when EGF and bFGF are administered simultaneously in vivo. These cells migrate to the rostral and caudal sites and grow axons. To make the THIEF hydrogel, EGF and bFGF were added to the THI hydrogel [7].

Culture of Schwann cells revealed the TH, PH, THI, and PHI hydrogels' cytotoxicity as well as BMSCs S6b) with their extracts, and the CCK-8 assay came next. When compared to the control, the cell viability of all hydrogel groups was nearly 100%, indicating that there was no cytotoxicity. The measurement of PicroGreen DNA proliferation provided additional support for these findings, excluding the possibility of redox substances interfering with the CCK-8 assay as well. Additionally, the relative viability of BMSCs co-cultured with the extracts of various hydrogels collected on days 3 and 7 was greater than 90 percent, proposing neglectable cytotoxicity of the corruption items. In addition, the BMSCs were cultured for 1–5 days, respectively, in the TH, PH, THI, PHI, THIEF, and PHIEF hydrogels, and Live/Dead staining was performed. At day 1 and day 3, all groups had live cell percentages greater than 70% without significant differences or changes over time. PEG- and HA-based hydrogels typically have good biocompatibility, it is known. As a result, UV exposure during gelation, insufficient cell-matrix interactions, and difficulties in introducing nutrition and oxygen into the cell membrane are probably to blame for the damage or death of encapsulated cells [8].

Reduced formation of fibrotic and glial scars currently, it is unclear whether scars are beneficial or detrimental to neural repair and axon regeneration. In point of fact, the scars that appear at various points on an injured spinal cord have two primary components. In most cases, the inflammatory immunocytes and fibroblasts that make up fibrotic scars are found in the core of the lesion, while activated astrocytes interact with fibromeningeal cells and other gliocytes to form the scar border known as a penumbra or a glial scar. Although scarring can prevent an injury or wound from expanding further, it would prevent axon regeneration. In addition, the axon growth inhibitory ligands, such as chondroitin sulfate proteoglycans, semaphorins, and ephrins, that are released from the incipient scar can either mediate axon growth cone collapse or restrict axonal plasticity. The glial scar, on the other hand, is also thought to be a result of regeneration failure, though it hasn't been proven to be the cause recently. However, excessive early scar formation is detrimental to neurogenesis and function restoration. The inflammation results in the formation of the fibrotic scar, rendering the microenvironment unsuitable for repair and regeneration. Specific to the lesion site, activated macrophages and microglia would express a significant amount of integrin 5-1, the canonical fibronectin receptor, to mediate the assembly of the fibronectin matrix, which in turn would contribute to the accumulation of fibroblasts and the deposition of fibronectin that result in the formation of the fibrotic scar [9].

Discussion

Therefore, successful SCI treatment relies heavily on the regulation of scar formation. On day 7, the traumatic spinal cord tissue was stained with Masson stain after surgery. The less aniline blue positive area on day 7 indicates that the THIEF-Cell group had less collagen deposition and scarring. Both the THIEF-Cell and THI hydrogel groups showed fewer aniline blue-positive areas on day 56 and more purple-colored areas at the site of the lesion, indicating that fewer scars had formed and that more neural fibers had survived. Day 7 saw the appearance of these two distinct scars was then investigated by immunofluorescence staining. GFAP-labeled activated astrocytes play a role in the glial scars that enter the lesion gap and create a harmful cavity. In this case, the fibrotic scar marker PDGFR- was chosen. PDGFR-/GFAP double staining were therefore performed. The seven-day quantitative analysis demonstrates that, in comparison to the PHIEF-cell (14.8 2.1%) and SCI groups, the percentage of PDGFR-+ areas in the THIEF-Cell (10.0 1.2%) and THI hydrogel (10.0 1.5%) groups was significantly lower. Similar to the other two groups, the THIEF-Cell group had a lower percentage of GFAP+ areas (1.8 0.8%) and the THI hydrogel group had a lower percentage of GFAP+ areas

(1.9 0.9%). Whether or not BMSCs are encapsulated, the ROS-scavenging hydrogel can significantly reduce the formation of fibrotic and glial scars in the lesion site, which is crucial for axon regeneration [10].

Conclusion

One-pot synthesis of thioketal-containing hyperbranched polymer (HBPAK), biocompatible HA-MA and IKVAV peptides encapsulated with cell growth factors, and BMSCs produced a BMSC-encapsulated ROS-scavenging hydrogel. This hydrogel could significantly reduce the oxidative microenvironment both in vitro and in vivo and was highly biocompatible. In a rat spinal cord transection model, the BMSC-encapsulated ROS-scavenging hydrogel was applied to the lesion site, significantly reducing oxidation, inflammation, and cell apoptosis. This improved motor recovery and reduced scar formation in vivo. In contrast, transplanting BMSCs into a hydrogel that did not respond to ROS had a performance that was comparable to that of the SCI control but was worse than transplanting them into a hydrogel that did respond to ROS. Through comprehensive regulation of the hostile pathological microenvironment, our ROS-scavenging hydrogel represents a promising strategy for stem-cell-based therapies for CNS diseases.

Acknowledgement

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Conflict of Interest

None.

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