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REVIEW

Polyethylene glycol as a promising synthetic material for repair of spinal cord injury

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Abstract
Polyethylene glycol is a synthetic, biodegradable, and water-soluble polyether. Owing to its good biological and material properties, polyethylene glycol shows promise in spinal cord tissue engineering applications. Although studies have examined repairing spinal cord injury with polyethylene glycol, these compelling findings have not been recently reviewed or evaluated as a whole. Thus, we herein review and summarize the findings of studies conducted both within and beyond China that have examined the repair of spinal cord injury using polyethylene glycol. The following summarizes the results of studies using polyethylene glycol alone as well as coupled with polymers or hydrogels: (1) polyethylene glycol as an adjustable biomolecule carrier resists nerve fiber degeneration, reduces the inflammatory response, inhibits vacuole and scar formation, and protects nerve membranes in the acute stage of spinal cord injury. (2) Polyethylene glycol-coupled polymers not only promote angiogenesis but also carry drugs or bioactive molecules to the injury site. Because such polymers cross both the blood-spinal cord and blood-brain barriers, they have been widely used as drug carriers. (3) Polyethylene glycol hydrogels have been used as supporting substrates for the growth of stem cells after injury, inducing cell migration, proliferation, and differentiation. Simultaneously, polyethylene glycol hydrogels isolate or reduce local glial scar invasion, promote and guide axonal regeneration, cross the transplanted area, and re-establish synaptic connections with target tissue, thereby promoting spinal cord repair. On the basis of the reviewed studies, we conclude that polyethylene glycol is a promising synthetic material for use in the repair of spinal cord injury.

Key Words: *nerve regeneration; spinal cord injury; polyethylene glycol; nerve tissue engineering; biomaterials; spinal nerve repair; biological drug; blood-spinal cord barrier; neural stem cells; carrier; cell culture; neural regeneration*

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Introduction
After spinal cord injury (SCI), the cavity formed by the necrosis of neurons and glial cells and the glial scar formed by reactive astrocyte hyperplasia are important factors that affect nerve regeneration (Flynnj et al., 2011). Therefore, improving the microenvironment after SCI and filling tissue defects are important strategies for repair of the injured spinal cord (Zhao et al., 2015). Scaffold materials for repairing SCI contain both natural and synthetic materials. Natural materials have good biocompatibility, and the degradation products are easily absorbed without causing inflammatory responses. However, their mechanical properties differ from normal spinal cord tissue, and their quality is difficult to control. Synthetic materials also provide good biocompatibility and tissue degradation, but they offer the additional advantages of high purity, good repeatability, and controllable mechanical and physical properties.

Polyethylene glycol (PEG) is a synthetic material with a wide range of clinical applications, as its functions can be modified by regulating the physical and chemical properties of it or its graft-related materials (Luo, 2004; Cui et al., 2015; Yang et al., 2015). For example, PEG has been approved by the U.S. Food and Drug Administration for use as a preservative additive prior to organ transplantation to limit cold ischemia/reperfusion injury (Pasut et al., 2016). PEG is also used to modify nanoparticles so that they cannot be recognized by the immune system. PEGylated copper oxide nanoparticles selectively reduce the activity of tumor cells and mitigate the inflammatory response (Giannousi et al., 2016). Another clinical use for PEG is to slow the removal of the nanoparticle pharmaceutical drug carrier. For example, the amount of time gold nanoparticles circulate throughout the blood and body is extended when they have been modified with PEG, promoting the accumulation of the nanoparticles at the tumor site (Huo et al., 2017). The application of PEG in SCI has been studied extensively. PEG has been shown to inhibit the inflammatory response, provide neuroprotection, suppress microenvironment changes in SCI, traverse the blood-brain barrier or blood-spinal cord barrier (Liu et al., 2008), and play important roles in cell therapy and tissue regeneration.

This review summarizes previous research findings

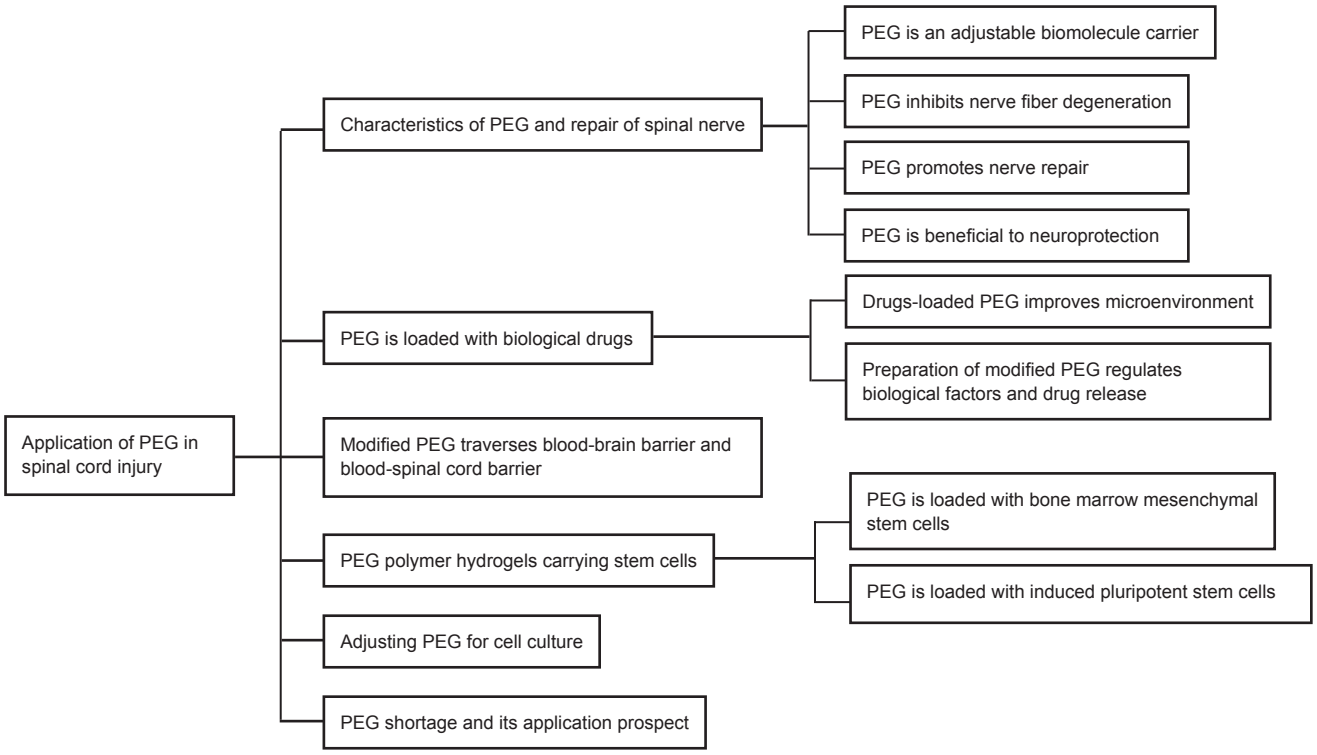

Figure 1 Overview of the topics discussed herein.
This review summarizes current research on polyethylene glycol (PEG) and PEG-coupled polymers and their uses in the field of spinal nerve tissue engineering and their development for use as synthetic scaffolds in the repair of spinal cord injury. These materials have the advantages of good biocompatibility and degradation as well as controllable mechanical and physical properties.

examining the use of PEG in SCI (**Figure 1**) and provides new ideas and solutions for the particularly difficult problems associated with SCI repair. Although PEG is a potentially important material for the repair of SCI, we found some limitations in the use of PEG; thus, we also suggest future research directions for the development of improved PEG materials.

Characteristics of PEG and Repair of Spinal Nerves

PEG, as a biodegradable synthetic scaffold, shows good biocompatibility and low immunogenicity and it is non-toxic. PEG is soluble in both water and many organic solvents. PEG inhibits vacuole and scar formation and will not accumulate in the body (Potter et al., 2008; Krsko et al., 2009). PEG resists nerve fiber degeneration, reduces the inflammatory response, protects the nerve membrane, reduces cell death, protects mitochondria, accelerates improvement of electroneurographic signals, and can be used as a sealant for injured axon membranes (Luo et al., 2002, 2004; Laverty et al. 2004; Phillips et al., 2005; Burdick et al., 2006).

As soft polymers, PEG hydrogels can be used as drug carriers whose size, structure, and property can be controlled to differentially affect biological properties *in vivo*. Electron beam lithography and ultraviolet optical lithography have been used to tightly control the size and shape of hydrogels, successfully generating PEG hydrogels with controllable size and nanostructure (Bae et al., 2010). Fourier transform infrared spectroscopy has been used to verify the formation of a cross-linking network between the polymer chains. A mesoporous silica templating method has also been used to adjust the molecular weight, particle size, and template of PEG hydrogel particles in biomolecular carriers (Cui et al., 2015), thereby reducing its phagocytosis *in vivo*.

PEG has been shown to lessen the inflammatory response and effectively inhibit nerve fiber degeneration in the early stage of SCI. Luo et al. (2004) suggested that PEG applied in the acute phase of SCI inhibits the formation of vacuoles and scars, effectively inhibits nerve fiber degeneration, and creates a good microenvironment for the regeneration of nerve fibers. The role of PEG in blocking nerve fiber degeneration may be related to its ability to protect cell integrity, reduce antigen release, and mitigate the inflammatory response.

PEG hydrogels can rapidly repair nerve conduction after severe SCI, promote the myelination of axons, and improve sensory and motor functions. The implantation of PEG hydrogels into the cavity can provide an attachment or a new pathway for the continuous migration of astrocytes, which will migrate to the empty area, eliminate cell aggregation, and inhibit scar formation (Phillips et al., 2005; Burdick et

al., 2006; Potter et al., 2008; Krsko et al., 2009). Estrada et al. (2014) implanted an immunologically inert PEG600 material into the scar area after resection of a chronic SCI scar; their results showed that long-distance axonal regeneration at the scar area was conducive to the migration of beneficial cells (Schwann cells, endothelial cells, and astrocytes) and elongation (astrocytes), promoting neurological repair.

PEG reduces cell apoptosis by protecting cell membranes and mitochondria and inhibits free radicals and prevents lipid peroxidation. PEG implanted at the injury site markedly reverses the injury-induced changes in cell membrane permeability (Luo et al., 2002, 2004). Shi et al. (1999) showed that PEG implantation at the site of the completely transected spinal cord in pigs promotes reconstruction of the spinal cord and is conducive to the recovery of spinal cord function. Luo et al. (2007) reported that after SCI, PEG significantly reduces caspase-3 activity by repairing damaged cell membranes and decreases programmed cell death. The interaction of PEG with mitochondria enhances mitochondrial function, decreases the release of cytochrome c, and then inhibits cell apoptosis. Laverty et al. (2004) showed that the application of an aqueous solution of PEG in the subarachnoid space reduces the cavity and promotes the recovery of function in dogs, and its local application protects nerve membranes and accelerates improvement of electroneurographic signals.

PEG Loaded with Biological Drugs

The key to successful SCI treatment is to minimize secondary injury, such as the immune inflammatory response, syringomyelia and scar formation, deficiency of neurotrophic factors, and increased neurite growth inhibitors (*e.g.*, Nogo) (Adams, 2007; Walmsley, 2007; Xu et al., 2008). Drugs and biotherapy, such as cyclosporine A and glutathione, are important means of preventing and reducing secondary neuronal apoptosis and improving the local microenvironment. PEG hydrogels have good biocompatibility and certain advantageous compressive properties. *In vitro* and *in vivo* nerve cell co-cultures show that PEG hydrogels are not toxic to nerve cells (Liu et al., 2008; Jiang et al., 2014). PEG-coupled polymers not only promote angiogenesis but also carry drugs or bioactive molecules directly to the SCI site. PEG-coupled polymers can cross both the blood-spinal cord and blood-brain barriers and are thus widely used as drug carriers (Rip et al., 2014).

The polyvinyl alcohol (PVA)/PEG scaffold containing ciprofloxacin inhibits microbial growth, and its application in tissue engineering is promising. The PVA/PEG scaffold is not cytotoxic, promotes cell growth, is strong, and shows good drug release. Zhou et al. (2016) suggested that PEG increases the release efficiency of ciprofloxacin. PEG expands the microchannel and weakens the interaction between PVA chains and ciprofloxacin so that the crystal size of the ciprofloxacin is miniaturized. The introduction of PEG can affect the diffusion and dissolution of the scaffold and increase its release capacity. The layer-by-layer assembly of multilayers of drug or proteins and scaffolding can be customized according to the desired drug or protein release rate. For example, Mehrotra et al. (2010) reduced the speed of protein released from a PEG plus protein plus polyacrylic acid multilayer film to provide sustained, long-term release of brain-derived neurotrophic factor and promote axonal growth. Moreover, Lee et al. (2016) suggested that PEG cross-linking and bridging mechanisms affect protein release efficiency and diffusion coefficients.

PEG-grafted-chitosan (PEG-g-CS) hydrogel is a potential thermal system that is not obviously cytotoxic in the body. An implanted PEG-g-CS hydrogel was maintained *in vivo* for 2 weeks, gradually dissolving at 3 weeks, and resulting in only a mild inflammatory response. Effective drug concentrations were still detected in the blood 5 weeks after implantation (Jiang et al., 2014). Experiments conducted *in vitro* have shown that hydrogels sustain stable release of cyclosporin A for 3 weeks, with no significant burst release. Blood concentration fluctuations have been decreased by regulating PEG-g-CS hydrogel degradation (Jiang et al., 2014; Hou et al., 2016).

Modified PEG Traverses Blood-Brain and Blood-Spinal Cord Barriers

Transactivating-transduction protein (TAT) promotes absorption by human microvascular endothelial cells. TAT-modified PEG material can effectively traverse both the blood-brain barrier and the blood-spinal cord barrier (Liu et al., 2008). Liu et al. (2008) prepared the bioactive polymer TAT-PEG-b-cholesterol as a nanocarrier. Ciprofloxacin was successfully adsorbed on the nanocarrier. Scanning electron microscopy showed that the average diameter of the nanocarrier was less than 200 nm. These TAT-modified nanoparticles are able to traverse the blood-brain barrier and enter the neuronal cytoplasm.

Glutathione PEGylated liposomes were developed to safely enhance drug delivery to the brain. The results of Rip et al. (2014) support the versatility of glutathione-PEG liposomes for enhanced drug delivery to the brain. Wang et al. (2010) suggested that TAT-conjugated PEGylated magnetic polymeric liposomes (TAT-PEG-MPLs) could traverse the blood-spinal cord barrier in rats. They observed low magnetic resonance imaging signals in T2-weighted images and found that TAT-PEG-MPL nanoparticles had significantly accumulated around the injury site as well as inside neurons as determined by their histological analysis as well as by cryo-electron microscopy and flame atomic absorption spectrophotometry (Wang et al., 2010).

Although fibroblast growth factor 2 (FGF2) has excellent potential for treatment of SCI because of its angiogenic and trophic effects, it is unable to penetrate spinal cord tissue when delivered locally (Reuss et al., 2003). However, conjugation to PEG is known to improve penetration of proteins into tissue by reducing clearance and providing immunogenic shielding. Kang et al. (2010) conjugated PEG to FGF2 to nearly double the concentration of FGF2 in the injured spinal cord, indicating that PEGylation of FGF2 enhances tissue penetration.

PEG Polymer Hydrogels as Carriers for Stem Cells

The mechanical properties of the PEG hydrogel scaffold are very similar to those of the spinal cord. There is less immune rejection after implantation with a PEG hydrogel scaffold in the injured spinal cord than with other hydrogel scaffolds in the injured spinal cord (Kumar et al., 2016; Lawrence et al., 2016), thereby promoting the growth of regenerated axons into the scaffold. PEG hydrogels are also used as supporting substrates for the growth of stem cells after injury, inducing cell migration, proliferation, and differentiation (Bakshi et al., 2004; Hardy et al., 2015). Simultaneously, PEG hydrogels isolate or reduce local glial scar invasion, promote and guide axonal regeneration, cross the transplanted area, and re-establish synaptic connections with the target tissue, thereby promoting spinal cord repair (Estrada et al., 2014). At present, the commonly used seed cells include mainly bone marrow mesenchymal stem cells and neural stem cells.

Hardy et al. (2015) showed that oxime cross-linked hydrogels formed by PEG and hyaluronic acid derivatives are conducive to bone marrow mesenchymal stem cell adhesion. Bhutani et al. (2010) chemically fused mouse embryonic stem cells with human fibroblasts under the induction of PEG, and successfully induced human fibroblasts into pluripotent stem cells. Mulyasasmita et al. (2014) developed protein-PEG hybrid hydrogels, called MITCH-PEG, which slowly release encapsulated vascular endothelial growth factor, and provide significant protection from cell damage. MITCH-PEG co-delivery of induced pluripotent stem cells and vascular endothelial growth factor was found to reduce inflammation and promote angiogenesis.

Adjusting PEG for Cell Culture

Gelatin- and PEG-based hydrogels provide a powerful cell culture platform for tissue engineering applications (Li et al., 2016; Truong et al., 2016). Truong et al. (2016) used a rapid cross-linking process to form hydrogels within minutes of mixing the polymer solutions under physiological conditions, showing that hydrogels can be used as injectable materials. Murine embryonic fibroblastic cells cultured in soft gels demonstrate high cell viability.

The addition of silica nanoparticles has been shown not only to improve the mechanical strength and cell adhesion properties of PEG hydrogels but also to control the degree of cell adhesion for use in biomedicine. Gaharwar et al. (2013) found that the addition of silica nanospheres noticeably inhibited the degree of hydration of the PEG hydrogels, which indicated surface interactions between the polymer chains and the silica nanospheres. No obvious change in hydrogel microstructure or average pore size was detected after the addition of the silica nanospheres. Nevertheless, addition of silica nanospheres markedly increased both the mechanical strength and toughness of the hydrogel networks. The biological properties of these nanocomposite hydrogels were assessed by seeding fibroblasts on the hydrogel surface. The addition of silica nanospheres enhanced cell adhesion, promoted cell spreading, and increased the metabolic activity of the cells (Gaharwar et al., 2013).

Kim et al. (2016) believed that the concentration and molecular weight of the PEG cross-linkers could be varied to control the swelling/shrinking behavior and drug release properties as well as lower the critical solution temperature of poly(N-isopropylacrylamide)-PEG hydrogels. This strategy could be applied to various hydrogel systems to control their physical properties for biomedical applications. Akimoto et al. (2016) prepared a poly(N-isopropylacrylamide) hydrogel cross-linked by PEG for three-dimensional cell culture. By altering the temperature, the volume and the storage elastic modulus of the gel were changed. C2C12 cell adhesion was confirmed using RGDS pendants. Such PEG-cross-linked hydrogels are expected to be useful as new material for three-dimensional cell culture to control cell fate and to improve the biocompatibility of cells.

PEG Limitations and Proposed Applications

Rao et al. (2011) suggested that the efficacy of PEG alone is not ideal but that polylysine-modified PEG hydrogel promotes nerve cell adhesion, elevates biocompatibility and stability of neural tissue integration, and contributes to axon regeneration and remyelination. The use of PEG alone cannot completely mimic the three-dimensional porous structure of the spinal cord, and the biocompatibility is relatively insufficient. In addition, its position after transplantation *in vivo* is randomly relative to the structure of the spinal cord, allowing the upper and lower fiber bundles to grow in mismatched or even misplaced channels or pores.

PEG-poly (-L-lactic acid) (PLLA) hydrogels provide biodegradable, porous structures with pore sizes that do not change during degradation. Chiu et al. (2013) found that the pore size was controlled by the particulate size, and they adjusted the polymer concentration, optimized the degradation time, and provided additional guidance for the optimization of material properties to generate three-dimensional, degradable, porous PEG hydrogels. Such coupled hydrogels mitigate the disadvantages of PEG alone. The optimized design of the three-dimensional, porous PEG polymer scaffold along with the biomimetic spinal cord scaffold created by three-dimensional printing technology provided a structural basis for the extension of nerve cell growth across the diseased spinal cord (Namba et al., 2009; Soman et al., 2012). However, because of the limitations imposed by mechanical properties and changes in the microenvironment after SCI, three-dimensional bioprinting of biomimetic porous PEG scaffolds remains a tough challenge and a hot topic in tissue engineering.

PEG has shown good safety and is approved by the U.S. Food and Drug Administration as a preservative additive and in modified nanoparticles for use before organ transplantation to reduce the inflammatory response and slow the *in vivo* clearance rate of nanoparticle drug carriers (Giannousi et al., 2016; Pasut et al., 2016; Huo et al., 2017). However, Romano et al. (2014) found that pegylated liposomal doxorubicin used for treating multiple myeloma was

associated with some adverse events, including thrombocytopenia (9%), peripheral neuropathy (8%), and infections (8%). In addition, low-molecular-weight PEG accelerated the accumulation of platelet derived growth factor and reduced its activity, thereby reducing the differentiation of neural stem/progenitor cells into oligodendrocytes (Elliott Donaghue et al., 2015). Because of the wide use of PEG, the safety of PEG and PEG polymers *in vivo* needs to be further improved.

The drug loading capacity of PEG alone is relatively low, but PEG polymers can improve this. For example, an *in vivo* study demonstrated that PEG-PLA copolymers increase the hydrophobic drug loading capacity as well as enhance slow release, avoid phagocytosis by phagocytes, increase the time drugs spend circulating in the blood, and improve bioavailability (Xiao et al., 2010). PEG-poly(lactic-co-glycolic acid) copolymers have been shown to increase the loading efficiency of poorly soluble drugs (Zhang et al., 2014). The development of new PEG polymers may help optimize the low drug-loading efficiency of PEG alone. The research and development of such PEG polymers and new materials remains a hot research topic.

Although PEG has several shortcomings, it has been used as a component of new materials. Many of its properties may be transferred to these conjugates, giving the material new properties, such as hydrophilicity and flexibility. The end groups of PEG play decisive roles, as the various end groups offer different advantages. Functional groups, such as toluenesulfonate, amino, carboxyl and aldehyde, can be introduced into both ends of the PEG chain to further expand the useful applications of PEG. Thus, PEG has broad application prospects in organic synthesis, peptide synthesis, the slow or controlled release of drugs, targeted drug delivery, and stem cell transplantation.

Conclusions

Multiple disciplines are involved in the repair of SCI. Engineered materials, such as PEG, are important components of research in spinal cord tissue engineering. Research has shown that in addition to being stable, nontoxic, and biocompatible, PEG does not accumulate in the body, can be used as a sealant for injured axon membranes, inhibits the formation of vacuoles and scars, protects against nerve fiber degeneration, reduces inflammation, protects nerve membranes, decreases cell death, protects mitochondria, suppresses cell apoptosis, and improves electroneurographic signals. Such advantages of PEG offer promise for its use coupled with bioactive molecules and drugs as tissue-engineered scaffolds in the repair of the injured spinal cord.

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