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Review

Polymeric particle-mediated molecular therapies to treat spinal cord injury

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ABSTRACT

Spinal cord injury (SCI) is a physically and psychologically debilitating condition that mainly affects young, healthy males who are at the peak of their personal and professional development. SCI damages axons and disrupts myelination, which interrupts sensory and motor neuronal function. Current treatments are mostly palliative, aimed at reducing further damage and pain, but do not provide a cure. Polymeric particles have shown tremendous promise to provide patients with effective treatments that can bring partial or full functional recovery. Their unique properties can facilitate delivery of therapeutic agents to the injury site, provide protection from the host immunity or provide platforms to stimulate the regeneration of damaged axons. This review highlights the current benefits and challenges of the use of polymeric particles to control the release of molecular therapeutics as potential strategies for SCI treatment.

Contents

1. Introduction

Spinal cord injury (SCI) is a debilitating and often irreversible injury to the spinal cord that leads to complete or partial loss of sensation and function below the injury site depending on the severity of the damage (Kan et al., 2010). While SCI could affect people of all ages, it is most prevalent in young, active men between the ages of 16–30; this condition creates physical, emotional, and economic burdens on the individual, as well as on society (Carlson and Gorden, 2002; Cerqueira et al., 2013; Sharma, 2007). A study from the Reeve Foundation estimates that over 1.2 million Americans are living with paralysis resulting from spinal cord injuries (Christopher, 2015). Addressing this major issue will require novel treatment strategies that could reverse the condition and bring functional recovery to patients (Srikanth and Kessler, 2012). Since much progress has been made in basic neuroscience research as well as in the development of novel intervention strategies, the concept of complete SCI repair, while still not achieved, is becoming less elusive (McDonald and Sadowsky, 2002).

Early work has already demonstrated that mature central nervous system (CNS) axons possess an intrinsic ability to

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regenerate when a proper microenvironment is provided at the injury site (Coumans et al., 2001). This discovery has spurred the development of many strategies, such as molecular therapy, cell transplantation, and biomaterial scaffolds, meant to provide a more permissive neural environment to promote axon regeneration and functional recovery after SCI (McCreedy and Sakiyama-Elbert, 2012). In this review, we discuss the barriers to neural regeneration after SCI and highlight recent attempts to overcome them by means of polymeric particles for targeted and localized delivery of molecular therapeutics to the injured spinal cord. Many review articles have previously detailed the chemical and physical properties of polymeric materials (Macaya and Spector, 2012; Perale et al., 2011; Straley et al., 2009). Rather than focusing exclusively on the materials, we provide an overview of polymeric particle systems that deliver growth factors, drugs, and other therapeutic agents, all of which have shown the potential to treat SCI.

2. Pathophysiology of SCI and current treatments

The stages of SCI pathophysiology can be divided into immediate (the injury), acute (seconds to minutes), sub-acute (minutes to weeks), and chronic (months to years) (Hyun and Kim, 2010; Macaya and Spector, 2012). The immediate mechanical injury, such as impact, compression, contusion, or laceration, causes tissue damage and cell death along with an edema and hemorrhaging (Mothe and Tator, 2013). A secondary injury follows due to a local inflammatory response, which leads to further cell death, axonal degeneration, vascular injury and swelling (Mothe and Tator, 2013). The secondary injury typically spreads above and below the lesion site and may continue for days or weeks (Wright et al., 2011). During the sub-acute phase, microglia begin to clear the injured area of debris, leaving behind a fluid-filled cyst cavity (Macaya and Spector, 2012). The cavity becomes enveloped in a dense glial scar acting as a mechanical and chemical barrier to regeneration (Hyun and Kim, 2010; Park et al., 2009). Finally, in the chronic phase, the glial scar stabilizes around the cyst, further encompassing degenerated axons due to secondary injury (Carlson and Gorden, 2002). At this stage, infiltrating fibroblasts could also form a dense fibrous capsule, which acts as a tissue barrier and binds growth inhibitory molecules to further prohibit axonal regeneration (Macaya and Spector, 2012). Weeks, months, or even years after the initial injury, oligodendrocytes continue to undergo apoptosis, leading to demyelination of axons and neuropathic pain as well as further inhibition of axonal growth (Macaya and Spector, 2012). A successful cure for such a complex injury would require multiple therapeutic modalities that can limit secondary damage, enhance residual functions, and promote axonal regeneration (McDonald and Sadowsky, 2002). Currently, there are no treatments that are able to reverse damage to the spinal cord. Surgical interventions are aimed at spinal cord stabilization to alleviate further damage, while drug treatments, such as the anti-inflammatory drug methylprednisolone (MP), are aimed at alleviating pain and swelling (Kan et al., 2010; Straley et al., 2009). Both are associated with severe side effects and are not designed for functional recovery (Silva et al., 2014).

3. Polymeric particle-mediated molecular therapy

As alluded to earlier, SCI pathology is complex. A combination of mechanical and biological factors is responsible for the lack of axonal regeneration and the minimal functional recovery typically observed after the injury. Thus, treating SCI has to take into account the different kinds of damage that occur during and after the injury. Various strategies with the potential to enable neurologic recovery, including molecular therapy, cell transplantation, and scaffold implantation, have been proposed (Cigognini et al., 2011). However, for such therapies to be successful, efficient and controlled delivery of the therapeutics or cells becomes a critical component (Fan et al., 2010). Polymeric particles present the means for such a targeted and controlled delivery approach. Engineered polymeric particles can provide advantages in many aspects of therapeutic delivery: improving the solubility of hydrophobic compounds in aqueous environments, prolonging the half-life of therapeutics in blood circulation, providing an assortment of controlled release profiles, improving bioavailability of drugs, and delivering therapeutics locally to minimize adverse side effects (Singh and Lillard, 2009; Tan et al., 2012). The rate of therapeutics released from polymeric particles can be tailored by several methods: particle properties, such as polymer composition or porosity, polymer molecular weight and arrangement of the polymer chains, particle size and shape, as well as the amount and type of loaded therapeutics (Burdick et al., 2006; Makadia and Siegel, 2011). A number of techniques have already been well-established for the robust production of polymeric particles including emulsification-solvent evaporation (Jiang et al., 2016), nanoprecipitation (Ramanlal Chaudhari et al., 2016), solvent-displacement (Salerno et al., 2010), and emulsification solvent diffusion (Murakami et al., 1999). The choice of synthesizing method depends on the particle application and the type of encapsulated therapeutic agents (Soppimath et al., 2001).

Herein, we review the most recent polymeric particle-mediated therapies, both nano- and microparticles, that have shown promise to promote axonal regeneration and functional recovery after SCI. Note that while various classifications and size cut-offs exist to distinguish between nano- and microparticles (Kohane, 2007), for this review, nanoparticles were typically in size ranges of 20–800 nm and microparticles were typically >1 μm. Another important distinction is that only nanoparticles can be administered systemically and can be internalized by cells; microparticles typically act as a localized therapeutic release depot (Kohane, 2007). Particle-mediated molecular therapies are aimed at protecting neurons from secondary cell death, modulating the inflammatory response, administering growth factors, preventing inhibition of regeneration, and in the case of combination therapies, providing permissive environments for axonal regeneration (Bregman et al., 1997; Li et al., 2007; Thuret et al., 2006).

3.1. Molecular therapy: delivery of neurotropic and other growth factors

Neurotrophins (NTFs) have been extensively studied for their ability to bring functional recovery following SCI due to their role in modulating the survival, axonal growth, and function of neurons. Nerve growth factor (NGF) was the first NTF to be well-characterized after the discovery of its ability to promote neurite outgrowth in dorsal root ganglia (DRG) explants (Levi-Montalcini 1987; Vetter et al., 2010). NGF has since been shown to aid the repair process following SCI (Chen et al., 2013a,b). Another NTF, neurotrophin-3 (NT-3), plays an important role in neural growth by specifically modulating the maintenance, proliferation, and differentiation of neurons that express TrkC receptors (Guo et al., 2006; Hapner et al., 1998). Similarly to NGF, it has also been shown to support axonal regeneration in animal SCI models (Zhou et al., 2003). Another NTF originally isolated from brain, brain-derived neurotrophic factor (BDNF), affects the proliferation, differentiation, and survival of neuronal and non-neuronal cells, while possessing neuroprotective properties similar to NGF and NT-3 (Balaratnasingam and Janca, 2012). BDNF has been shown to promote axonal regeneration in animal models and improve myelination (Han et al., 2015), as well as suppress delayed apoptosis of oligodendrocytes following SCI (Koda et al., 2002).