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Review

Combination therapies in the CNS: Engineering the environment

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ABSTRACT

The inhibitory extracellular environment that develops in response to traumatic brain injury and spinal cord injury hinders axon growth thereby limiting restoration of function. Several strategies have been developed to engineer a more permissive central nervous system (CNS) environment to promote regeneration and functional recovery. The multi-faced inhibitory nature of the CNS lesion suggests that therapies used in combination may be more effective. In this mini-review we summarize the most recent attempts to engineer the CNS extracellular environment after injury using combinatorial strategies. The advantages and limits of various combination therapies utilizing neurotrophin delivery, cell transplantation, and biomaterial scaffolds are discussed. Treatments that reduce the inhibition by chondroitin sulfate proteoglycans, myelin-associated inhibitors, and other barriers to axon regeneration are also reviewed. Based on the current state of the field, future directions are suggested for research on combination therapies in the CNS.

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Abbreviations: BMSCs, bone marrow stem cells; CNS, central nervous system; chABC, chondroitinase ABC; cAMP, cyclic adenosine monophosphate; dbcAMP, dibutyryl cAMP; ESNPCs, embryonic stem cell-derived neural progenitor cells; ECs, endothelial cells; ECM, extracellular matrices; IT, intrathecal; LMTs, lipid microtubes; MC, methylcellulose; MAIs, myelin-associated inhibitors; MAG, myelin-associated glycoprotein; NSCs, neural stem cells; NT-3, neurotrophin-3; NgR, Nogo-receptor; Ompg, oligodendrocyte myelin glycoprotein; OPCs, oligodendrocyte precursor cells; OPF, oligo (ethylene glycol) fumarate; PDGF, platelet-derived growth factor; PAN/PVC, poly (acrylonitrile)/poly(vinyl chloride); PLGA, poly-lactic-co-glycolic acid; SCs, Schwann cells; SCI, spinal cord injuries; TBI, traumatic brain injuries.

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1. Introduction

Over 1.4 million traumatic brain injuries (TBI) and 12,000 spinal cord injuries (SCI) occur annually in the United States [1,44]. Causes of TBI and SCI include combat, sports-related injuries, falls, violence and motor vehicle accidents. Individuals with TBI or SCI experience disabilities that range from cognitive impairment to loss of sensation and partial to complete paralysis. Current therapies for improving clinical outcomes include limiting inflammation, preventing secondary cell death and enhancing the plasticity of spared circuits. These strategies, however, do not promote repair of neural tissue or restoration of severed axonal connections. The limited regenerative capacity of the CNS is in part due to the inhibitory extracellular environment. New therapies focused on engineering a permissive environment for regrowth of axons and restoration of neural populations are needed to improve functional recovery following TBI and SCI.

Early work on SCI has demonstrated that CNS axons maintain an intrinsic ability to regenerate in a permissive environment [15]. In the peripheral nervous system, where regeneration is more successful, these permissive environmental cues include neurotrophic factors and growth-supporting extracellular matrices (ECM) [48]. Cell transplantation and biomaterial scaffolds have been investigated to replace damaged tissue and provide soluble or mechanical cues for regeneration. However, the multi-faceted inhibitory nature of the adult CNS has limited the efficacy of such treatments. A combinatorial approach, therefore, may be more effective. In this mini-review we discuss the barriers to neural regeneration in the CNS and highlight recent attempts to overcome these barriers using combination therapies to engineer a permissive environment for axon growth.

2. CNS inhibitory environment

Initial trauma after a CNS injury leads to immediate disruption of neural tissue by shearing axons, rupturing blood vessels, and causing necrotic cell death [35]. Ischemic injury and inflammation, marked by infiltration of macrophages, neutrophils, and leukocytes releasing pro-inflammatory cytokines and reaction oxygen species, initiate a secondary phase of cell death accompanied by demyelination of spared axon tracts [10,14,18]. Fluid-filled cystic cavities commonly form at the injury site surrounded by a glial scar composed of reactive astrocytes, glial progenitors, microglia and macrophages, fibroblasts and Schwann cells (SCs) [66]. Chondroitin sulfate proteoglycans (CSPGs) present in the scar tissue contain glycosaminoglycans (GAGs) that inhibit extending axons and prevent re-growth into the injury zone [5]. Myelin-associated inhibitors (MAIs), such as Nogo, myelin-associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (Ompg), signal through a common receptor, the Nogo-receptor (NgR), to induce growth cone collapse and prevent axon regeneration through white matter [49].

This cascade of events following CNS trauma establishes a formidable barrier to regeneration and restoration of function. Replacing neuronal populations, along with promoting axonal sprouting and formation of new circuitry, are desired for repair following injury. In SCI, bridging the injury site to reconnect severed axonal pathways with their distal targets and remyelination of regenerating axons are necessary to restore function. The physical and molecular barriers of the CNS lesion, however, limit endogenous repair and remodeling. Engineering an environment suitable for regeneration is therefore crucial to enhance recovery following TBI and SCI.

3. Combination therapies

Many strategies have been developed to address the individual aspects of CNS trauma including limiting inflammation and secondary injury, remodeling injured tissue, neutralizing inhibitory molecules, increasing trophic support and replacing neural cell populations. Functional recovery in studies targeting a single component, however, is often modest. Combining therapies may help overcome multiple barriers to regeneration and provide synergistic effects on functional recovery. Here we review the most common and recent combination therapies that include the use of two or more individual strategies to promote regeneration. While the majority of the work has been performed in SCI, successful therapies can be extrapolated to other types of CNS trauma.

3.1. Neurotrophin release

In the developing CNS, neurotrophic factors promote the directed growth and survival of many types of neurons. The introduction of neurotrophins to the injured spinal cord can promote neuronal survival and enhance regeneration of specific ascending and descending axonal pathways. Notably, BDNF promotes growth of rubrospinal, raphespinal, cerulospinal and reticulospinal pathways while neurotrophin-3 (NT-3) elicits sprouting and growth of corticospinal and dorsal column sensory axons (for a complete review see [48]) [6,22,50,77]. NGF and GDNF also support growth of regenerating axons, however, their potential for promoting aberrant growth of pain-associated nociceptive spinal axons may reduce their desirability for SCI [4,58,69]. Combining neurotrophic factor delivery with cell transplantation or biomaterial scaffolds may provide synergistic effects to improve functional recovery.

3.1.1. Cell transplantation and neurotrophin release

Coupling cell transplantation with neurotrophic factor delivery may enhance repair following SCI. Oligodendrocyte precursor cells (OPCs) modified to express ciliary neurotrophic factor survived to a greater extent compared to unmodified OPCs following transplantation into the contused spinal cord [9]. Survival correlated with enhanced remyelination of spared axons and recovery of locomotor function. Co-transplantation of NT-3 expressing SCs with neural stem cells (NSCs) improved locomotor recovery over transplants of unmodified SCs and NSCs [23]. Axonal growth is commonly reported in response to cellular delivery of neurotrophins [21,22,42,50]; however, functional recovery is variable and often modest. Many cells endogenously express neurotrophins, thereby reducing the effect of additional secretion on locomotor recovery. Coupling enhanced neurotrophin release with other cell-type specific functions, such as remyelination by OPCs, can improve the utility of these combination therapies.

3.1.2. Scaffolds and neurotrophin release

Regeneration through biomaterial scaffolds is dependent on axon sprouting and growth at the interface of the spinal cord lesion. Many axon pathways will retract in response to injury and may not enter the scaffold. The addition of neurotrophic factors may provide a spatial cue for regenerating axons to prevent dieback and induce growth into a scaffold. BDNF release from collagen matrices promoted greater neural regeneration into agarose scaffolds following cervical SCI (Fig. 1) [62]. Similarly, BDNF release from collagen scaffolds elicited greater axon extension into the injury zone and functional improvement in a thoracic hemisection model [24]. In addition to stimulating axon growth, BDNF release from poly-lactic-co-glycolic acid (PLGA) microspheres in an agarose scaffold may reduce glial scarring and CSPG deposition, thereby improving axon regeneration at the scaffold-host interface [31].