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Review article

Extracellular matrix components as therapeutics for spinal cord injury

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ABSTRACT

There is no treatment for people with spinal cord injury that leads to significant functional improvements. The extracellular matrix is an intricate, 3-dimensional, structural framework that defines the environment for cells in the central nervous system. The components of extracellular matrix have signaling and regulatory roles in the fate and function of neuronal and non-neuronal cells in the central nervous system. This review discusses the therapeutic potential of extracellular matrix components for spinal cord repair.

Contents

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1. Introduction

Spinal cord injury (SCI) causes neural cell death and tissue architecture destruction, resulting in functional impairments. Endogenous restoration after SCI is limited because the central nervous system (CNS) has limited intrinsic repair capacity. Several repair strategies aiming to protect neural tissue or evoke or amplify endogenous repair are being tested in clinical trials; so far, none has emerged as a standard of care. Extracellular matrix (ECM) regulates the maintenance and functioning of developing and mature nervous tissue. After injury, ECM reorganizes and becomes involved in key events, including inflammation, cell survival, axon growth, gliosis, re-vascularization, and plasticity. Thus, manipulation of ECM after injury may benefit nervous tissue repair. Here, we focus on the potential of specific ECM components to improve recovery after SCI through promoting axon growth and enhancing cell transplant survival.

2. Spinal cord injury and extracellular matrix

2.1. Spinal cord injury (SCI)

SCI results in immediate death of neural cells (i.e., neurons, astrocytes, oligodendrocytes) and non-neural cells (i.e., microglia, epithelial cells, ependymal cells) and disruption of ECM. Due to pathophysiological events, including inflammation, bleeding, oxidation, and hypoxia, more cells die and additional ECM breaks down in time. There are several endogenous repair attempts after SCI, including axon growth/sprouting [42], re-vascularization, and neural stem cell proliferation and differentiation [60], but in general these attempts fail or have limited success. Tissue and function loss after SCI is typically permanent.

Numerous protective and regenerative strategies are explored for their potential to repair SCI [1]. Protective strategies focus on rescuing neural cells by enhancing intracellular survival programs, reducing inflammation, reducing bleeding, or promoting antioxidation. Regenerative strategies typically focus on promoting axon growth/sprouting by enhancing intracellular growth-promoting programs and/or reducing growth-inhibition within the injury environment. Other strategies may focus on promoting neural plasticity by implementing electrical stimulation and/or rehabilitative motor training [30]. So far, the efforts in the laboratory and clinic have not resulted in a standard of care for SCI.

2.2. Extracellular matrix (ECM)

Within the CNS, ECM forms an intricate 3-dimensional network that anchors and supports the neuronal and non-neuronal cells, which also secrete the various ECM components, and has crucial roles in their fate and function. ECM is important for shaping the CNS, through regulating cell migration, axon guidance, and synaptogenesis. In mature, healthy CNS, ECM is involved in regulatory signaling directly through cell surface receptors or indirectly as a carrier and reservoir for growth factors and molecules. ECM is crucial for sustaining proper CNS function by promoting stability, rather than 'plasticity', through maintaining synapses and restricting aberrant remodeling.

ECM in the mature, healthy CNS consists of the basement membrane (BM), interstitial space (IS), and perineuronal nets (PNNs) (Fig. 1). The BM serves as a boundary between endothelial cells and parenchyma, and is composed primarily of collagen, laminin, fibronectin, distroglycan, and perlecan [21]. The BM is the most regenerative compartment of CNS ECM. The IS (space between the cells) contains more diffuse ECM than the BM with little collagen and fibronectin and large amounts of glycoproteins and proteoglycans (i.e, tenascins, chondroitin sulfate proteoglycans (CSPGs)) linked to hyaluronan (HA) [41]. The ECM in PNNs is similar to that in the IS, but more compact, and therefore with higher concentrations of CSPGs and other growth-inhibiting components (tenascin R, link proteins) [21]. PNNs can be found at presynaptic terminals, synaptic boutons, nodes of Ranvier, and around some, but not all, neurons [6].

Collagen, fibronectin, and laminin are associated with wound healing and regeneration and, therefore, are the primary focus for therapeutic purposes. Collagen is a fibrous protein providing structural support and scaffolding to cells. Because collagen is easily accessible, inexpensive, and biocompatible, it is widely used for drug/growth factor delivery systems in SCI (a search of *collagen AND spinal cord injury* produced 388 hits in PubMed and over 53,000 hits in Google Scholar). Here, we focus on original studies published in the past five years.

Fibronectin is an important glycoprotein in the developing CNS due to its involvement in cell migration [54]. Fibronectin has important roles in tissue repair because of its cell adhesion properties and its ability to sequester nutrients and growth factors. A search of *fibronectin AND spinal cord injury* produced 105 hits in PubMed and over 19,000 hits in Google Scholar. There are relatively few recent studies involving fibronectin as a therapeutic for SCI; thus, we reviewed a full range of articles.

Laminin is a heterotrimeric glycoprotein composed of alpha, beta and gamma subunits. Laminin organizes in sheet-like polymers which are involved in cell growth and migration during development [24]. In the mature CNS, laminin is mainly present in regenerative niches and along blood vessels [19]. In the mature peripheral nervous system, laminin presence remains moderately high [25]. A search of *laminin AND spinal cord injury* produced 149 hits in PubMed and over 21,000 hits in Google Scholar. We reviewed a full range of articles because there are relatively few recent studies on laminin as a therapeutic for SCI.

2.3. ECM after SCI

After SCI, the breakdown of ECM contributes to nervous tissue destruction. Resident and invading inflammatory cells start secreting ECM components and matrix metalloproteinases (MMPs) that further destruct ECM. The role of ECM on the inflammatory response after injury was recently expertly reviewed [14]. The ECM present at any given time after an insult depends on the injury-induced cellular responses, which relies on the type of injury. In contusive injuries, with an intact dura mater, glia are the predominate source of ECM deposition. In laceration and stab injuries, with a compromised dura mater, fibroblasts penetrate the injury site and contribute to the ECM deposition. Regardless of the type of injury, there is an abundant expression of CSPGs in the ECM. Many, but not all, CSPGs mediate axon growth-inhibition through receptor protein-tyrosine phosphatase sigma (RPTPs) and the related leucocyte common antigen-related phosphatase (LAR), the epidermal growth factor (EGFR), and the nogo-receptors NgR1 and NgR3. Thus, this fairly common change in the ECM after SCI is unfavorable to endogenous regeneration.

2.4. ECM modulation for spinal cord repair

Considering the roles of ECM, rendering the ECM milieu optimum for repair is a legitimate therapeutic approach. This is supported by the unique composition of ECM in regenerative niches within the mature CNS and in peripheral nerves, particularly in Schwann cell basal lamina, which is known to facilitate repair [4]. Considering its ability to promote and sustain stability within the CNS, targeted manipulation of ECM after damage offers a means to elicit tissue repair and functional recovery after SCI. For instance,