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Neuronal Growth Cones and Regeneration: Gridlock Within the Extracellular Matrix

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SPECIAL ISSUE

Neuronal growth cones and regeneration: gridlock within the extracellular matrix

A discussion of the extracellular matrix as an axonal outgrowth regulator following central nervous system injury with emphasis on proteoglycan structure and function, receptors, and degradation, and related immune responses

"The Matrix is everywhere. It is all around us…What is the Matrix? Control."

From Morpheus in "The Matrix", 1999

Abstract

The extracellular matrix is a diverse composition of glycoproteins and proteoglycans found in all cellular systems. The extracellular matrix, abundant in the mammalian central nervous system, is temporally and spatially regulated and is a dynamic "living" entity that is reshaped and redesigned on a continuous basis in response to changing needs. Some modifications are adaptive and some are maladaptive. It is the maladaptive responses that pose a significant threat to successful axonal regeneration and/or sprouting following traumatic and spinal cord injuries, and has been the focus of a myriad of research laboratories for many years. This review focuses largely on the extracellular matrix component, chondroitin sulfate proteoglycans, with certain comparisons to heparan sulfate proteoglycans, which tend to serve opposite functions in the central nervous system. Although about equally as well characterized as some of the other proteoglycans such as hyaluronan and dermatan sulfate proteoglycan, chondroitin sulfate proteoglycans are the most widely researched and discussed proteoglycans in the field of axonal injury and regeneration. Four laboratories discuss various aspects of chondroitin sulfate proteoglycans and proteoglycans in general with respect to their structure and function (Beller and Snow), the recent discovery of specific chondroitin sulfate proteoglycan receptors and what this may mean for increased advancements in the field (Shen), extracellular matrix degradation by matrix metalloproteinases, which sculpt and resculpt to provide support for outgrowth, synapse formation, and synapse stability (Phillips et al.), and the perilesion microenvironment with respect to immune system function in response to proteoglycans and central nervous system injuries (Jakeman et al.).

Introduction

Proteoglycans (PGs) were originally isolated from cartilage tissue in 1891 followed by the development of carbohydrate chemistry within the early 20th century, which lead to the elucidation of different carbohydrate chain structures associated with PGs. Throughout these early years, PGs were seen as scaffolding within the extracellular matrix (ECM), and were thought to merely provide "structural support". In the later part of the century, these functions were joined by data indicating PGs also provide proper spacing for the function of trophic factors and their receptors, and that PGs may provide direct signals to regulate central nervous system (CNS) function. Fast forward to 2014, where PGs are now known to be a prominent part of a regulatory matrix surrounding all cells, and are of particular interest for the CNS and peripheral nervous system (PNS) functions that include differentiation, cell migration, cell division, cell-cell recognition, receptor function, ionic balance, growth factor function, immune response regulation, and both inhibition and promotion of axon growth and guidance.

In this review, four laboratories come together to discuss some of the "next generation understandings" of how PGs of the ECM function, and how their unique structures, functions and dynamic interactions contribute to their roles in CNS injuries. Chondroitin sulfate proteoglycans (CSPGs) might be thought of in terms of cellular and molecular "traffic"…

Attention – Construction Area

Beller and Snow begin by examining the most fundamental aspect of CSPGs – their structure – taking a historical perspective on our understanding of CSPGs and linking this with key advances that have identified the importance of individual moieties of the large and highly complex CSPG family of molecules. Beller and Snow place particular emphasis on growth cone behaviors following injury and restoration of growth cone/axonal function through specific modifications of CSPG microdomains.

Caution – Heed the Traffic Lights

CSPGs are large, highly negatively charged molecules. Thus, they were often supposed to act solely by blocking the binding of matrix molecules to their cell surface receptors non-specifically, *i.e.*, *via* steric hindrance. While this is likely to be accurate in some cases, specific receptors were also thought to be possible, but the extensive glycosylation of CSPGs precluded a typical ligand-receptor interaction and challenged receptor identification. The quest to identify CSPG receptors has finally been realized, leading to a new understanding that CSPGs act through multiple receptor types, *i.e.*, members of the LAR and NgR families, suggesting functional redundancy and the need to target the specific receptors present in a given region. Here, Shen et al. discuss the pathway to the identification of CSPG receptors, examining work from the laboratories of Flanagan, Coles, David, Giger and Li. Collectively, these data show that CSPGs have multiple mechanisms by which to inhibit axon growth. Such CSPG receptor characterizations are now seen as exciting roads to the development of specific therapies to promote axonal regeneration and recovery of function.

Slow – Demolition Zone

Important for repair following CNS injury are the processes

of neuroplasticity and synapse formation. Although many researchers have taken advantage of a bacterial enzyme, chondroitinase ABC (Chase) to cleave CSPG sugar chains, leaving behind a less inhibitory CSPG protein core, thus far, this methodology is more useful as an experimental tool than as a clinical application, given issue with stability and adequate delivery. Phillips and colleagues discuss the sculpting and reorganization of CSPGs through their natural degradation enzymes, the matrix metalloproteinases (MMPs). They discuss neuroplasticity and synaptogenesis by showing a wide variety of roles for MMPs during injury-induced neuroplasticity, illustrating how models of CNS deafferentation can be used to identify time dependent enzyme function under conditions of reactive synaptogenesis, and by presenting novel MMP interactions that may further clarify their control of regenerative processes. They present new studies showing how MMPs interact with immune molecules to mediate cellular responses in the local regenerative environment, and are regulated by novel binding partners in the brain ECM.

Stand Back – Ambulance to the Rescue

The ECM is reasonably stable, albeit engaging in routine dynamic maintenance activities. However, once injured, the terrain at the injury site is dramatically changed, becoming disorganized, reactive, and a site of acute neuroinflammation. Glial cells become reactive, dramatically changing the nature of ECM components, now in an attempt to cordon off the insult for repair and to minimize damage. To make matters worse, such deleterious changes do not rapidly resolve as one sees in the periphery, but rather, remain elevated and thereby orchestrate the plethora of hallmarks characteristic of chronic injury. Jakeman and colleagues review literature that characterizes the reactions of glial cells and changes in the perilesion border following contusive brain injury. They discuss strategies to modify the inhibitory perilesion microenvironment without eliminating the protective functions of glial cell activation, much like the goals stated by Beller and Snow, who also seek to modify the inhibitory aspects of CSPGs, while leaving the beneficial components intact. Clearly, minimal interference is a common goal.

New Roadway – Promoting Young Researchers in the Field of Spinal Cord Injury Research

Thus, in this Special Issue, we review past achievements in ECM and proteoglycan research addressing axonal injury and regeneration, and also celebrate new advances and exciting potential for future discoveries in this arena. Dually, we also celebrate some of the young researchers who are driving the field forward. For each article, significant contributions have been provided by young researchers at all levels. Dr. Justin Beller is a postdoctoral fellow at The University of Kentucky, Spinal Cord and Brain Injury Research Center (SCoBIRC), with a strong background in CNS injury, neuropharmacology, and regulatory sciences. From the Jakeman laboratory at Ohio State University's Center for Brain and Spinal Cord Repair, Kent Williams, M.S., is a recent graduate, and is interested in a technical position; and another graduate, Bryan Brautigam, M.S., is interested in a career in teaching. From the Phillips laboratory at Virginia Commonwealth University's Department of Anatomy and Neurobiology, Julie Chen is in the process of completing her Ph.D., and Adele E. Doperalski, Ph.D., is a current Postdoctoral Fellow. Yingjie Shen, Ph.D., formerly a Postdoctoral Fellow with Dr. John Flanagan, is a newly appointed Assistant Professor at Department of Neuroscience, Ohio State University. Each researcher is moving forward to become the backbone for advances made in the field of regeneration, in particular, examining the critical role played by the ECM in controlling the success and failure of regeneration and recovery of function. We salute these, and all young pioneers in the field, for whom we have high hopes of discovering treatments, therapies, and cures for spinal cord and brain related injuries.

Addendum: Since the acceptance of this publication, Justin A. Beller, Ph.D., has taken a position at Bend Research, Inc., in Bend, OR; and Lyn Jakeman, Ph.D., has moved to Washington, DC to serve as the Program Director for the National Institutes of Health, National Institutes of Neurological Disorders and Stroke (NIH/NINDS).

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