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The Mosaic of Extracellular Matrix in the Central Nervous System as a Determinant of Glial Heterogeneity

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Abstract

Accumulating evidence points to a primary role for non-myelinating glia as principal mediators of homeostasis in the central nervous system (CNS). However, the origins of the basis for glial heterogeneity are not well understood. Our recent studies contribute to an emerging view that the extracellular matrix (ECM) provides clues to glia underlying their specialized functions and, more importantly, the nature of how glia change in relation to neuropathology. In this review, we discuss how the dynamic mosaic of CNS ECM impacting CNS health and disease. Specifically, we focus on the roles of select extracellular matrix proteins, namely fibronectin (Fn), vitronectin (Vn), laminin (Ln) and tenascin-c (TnC), as prototypes for how ECM can modulate glial functions. We discuss the differences in expression patterns in the developing and adult CNS and relate these ECM molecules to specific changes in glial functions in neurological diseases. We also discuss how experiments have revealed the role of ECM molecules' influence on CNS development and the response of glia to injury and inflammation. We provide a new model to explain the nature of glial diversity as an adaptive response to the extracellular milieu, and provide a different approach to understand the complex nature of glial heterogeneity.

Keywords: astrocyte, fibronectin, tenascin-c, laminin, vitronectin

1. Introduction

Tissues are not made up solely of cells. A substantial part of Tissue volume is extracellular space, which is largely filled by an intricate network of macromolecules constituting the extracellular matrix (ECM). The vertebrate extracellular matrix was once thought to serve mainly as a relatively inert scaffold to stabilize the physical structure of tissues. But It is now clear that the matrix has a far more active and complex role in regulating the behavior of the cells that contact

it. Throughout the body, the ECM provides structure and organization to tissues through an intricately arranged scaffold comprised of a variety of secreted proteins and complex polysaccharides that are secreted locally and assembled into an organized meshwork in close association with the surface of the cells that produced them. Variations in both the relative amounts of the different types of matrix macromolecules and the way in which they are organized in the extracellular matrix give rise to an amazing diversity of forms, each adapted to the functional requirements of the particular tissue that influences their survival, development, migration, proliferation, shape, intercellular communication, and function. The extracellular matrix has a correspondingly complex molecular composition. Although our understanding of its organization is still incomplete, there has been rapid progress in characterizing many of its major components.

In this chapter, we will focus on a select group of ECM proteins—tenascin-C, fibronectin, vitronectin, and laminin—and their patterns of expression and influence on the response and function of glia in the developing and adult central nervous system (CNS). We will then provide a detailed discussion on the differences in the patterns of expression of these factors to specific changes observed in the context of neurological diseases using studies that have pioneered this new approach to understanding the contributions of glia to injury and inflammation. About 20% of the total volume of the adult CNS is extracellular space [1, 2] that contains

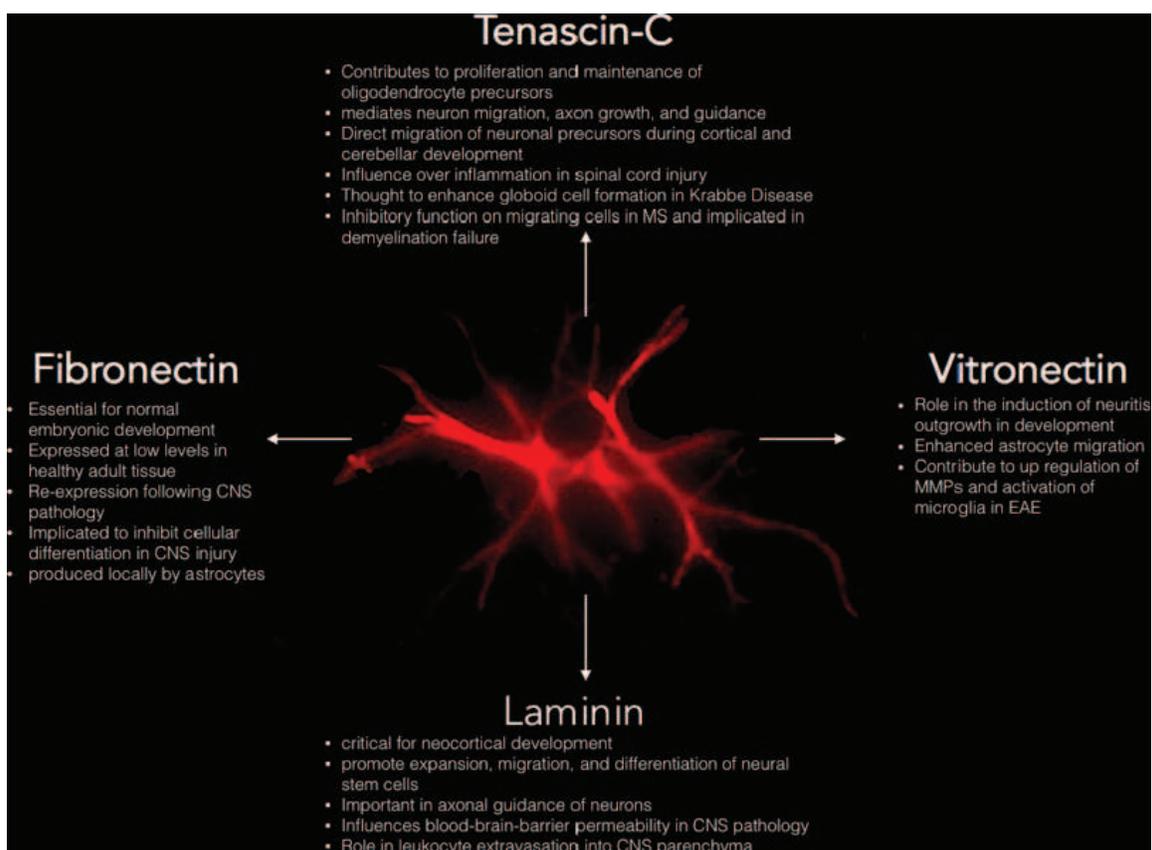


Figure 1. Schematic summary depicting the diverse impacts of select ECM proteins on astrocytes. Image shown is of a murine glial fibrillary acidic protein (GFAP+) astrocyte (red; center).

highly organized ECM [3]. As in peripheral tissues, the ECM is composed of both interstitial and basement membrane proteins of the ECM family; however, in the CNS, the ECM composition is remarkably different. Whereas the interstitial ECM of most peripheral tissues is enriched in collagen, laminin, and fibronectin, the ECM of the adult CNS is primarily a loose meshwork of hyaluronan, sulfated proteoglycans, and tenascin-R [4, 5]. The significance of these ECM proteins in the adult CNS has been extensively considered in recent reviews [6–8] and is beyond the focus of this chapter. Instead, we will focus on the Aforementioned ECM proteins and their significance for astrocyte function (**Figure 1**).

1.1. Fibronectin

Fibronectin (Fn) is a high-molecular weight, insoluble glycoprotein dimer that consists of three types of repeating amino acid modules, named type I, type II, and type III [9]. The structure of Fn varies, depending on whether it is secreted into the plasma or synthesized by resident cells. The majority of plasma Fn is produced by hepatocytes and is detectable in human blood at a concentration of 300 µg/ml [10, 11]. In contrast, cellular Fn contains the alternatively spliced extra domain A and/or extra domain B (the nomenclature for humans; for rodents: EIIA and EIIIB). In addition, Fn has been shown to be a critical component in other ECM proteins, including heparin, collagen, and fibrin, and together these protein networks contribute to the formation of the ECM [9]. One of the main functions of Fn is to serve as a scaffold for cell adhesion and migration, which influences the regulation of cell proliferation and differentiation [9]. A myriad of small proteins, such as growth factors, have been found to support these functions of Fn when they accumulate in the Fn network. As a result, local concentrations of these small proteins are seen to increase. The Fn matrix has been found to be essential for normal embryonic development by studying Fn-knockout mice [12]. In healthy adult tissue, Fn is expressed at low levels. Transient Fn re-expression either through plasma leakage and/or synthesis from resident cells is a common “default” response to tissue injury, ranging from skin wounds to joint inflammation [13] and myelin degradation [14]. In the CNS, myelin damage (demyelination) elicits the production of a temporary Fn matrix [14–18]. In this injury scenario, the Fn matrix is a result of plasma leaking into the CNS parenchyma [15, 16], and cellular Fn is secreted by resident astrocytes, microglia, and endothelial cells [14]. The generation of a temporary Fn scaffold comprised of both plasma and cellular Fn is a common response to tissue injury. We will discuss Fn re-expression during glial scar formation in multiple sclerosis (MS) and how clearance of the temporary Fn matrix is disturbed, which results in incomplete remyelination.

1.2. Tenascin-C

Tenascin-C (TnC) is a glycoprotein that is expressed in the ECM of various tissues where it has been found to regulate processes such as cell growth, migration, and adhesion during development, and represents 25% of the class of proteins that form the basic constituents of the brain ECM [19–22]. Tenascins are very large multimeric glycoproteins whose structure is well-conserved among vertebrates. TnC is built up in a modular fashion and consists of a cysteine-rich amino-terminus, EGF-like domains followed by fibronectin type III domains, and

a carboxyterminal domain resembling fibrinogen-b [23]. Tenascin-C binds and interacts with a wealth of extracellular matrix and cell surface ligands [20], which is heavily mediated by Fn type III modules. Integrins, cell-surface heparin sulfate proteoglycans, and cell adhesion molecules of the immunoglobulin superfamily have been found to be the major cellular receptors of TnC [24]. TnC commonly binds to other ECM proteins, such as fibronectin, phosphacan, and, particularly, lecticans. During CNS development, TnC is first expressed and accumulates around the fibrous processes of radial and Bergmann glial cells, which direct the migration of neuronal precursors during cortical and cerebellar development, respectively [25, 26]. During the later stages of development, TnC is expressed primarily by astrocytes, where it is thought to exert autocrine effects that regulate the proliferation of astrocyte progenitor cells [27]. TnC has also been found to modulate the stem cell compartment in the subventricular niche, where it is specifically enriched in the environment of mouse neural stem cell precursor cells (NSPCs) at embryonic day E14–E15 [28]. For example, TnC has been found to contribute heavily to the maturation of NSPCs [29], as well as the proliferation and maintenance of oligodendrocyte precursor cells [30–32]. *In vivo* and *in vitro* studies have demonstrated that TnC encodes for both permissive and inhibitory cues, which mediate neuron migration and axon growth and guidance by way of neuron-glia interactions [33–39]. Two to three weeks after birth, TnC expression decreases continuously, maintaining only a significant expression level in the neurogenetically active areas of the adult brain that encompass the subependymal zone and the hippocampus, as well as regions of plasticity in the hypothalamus [40–44].

1.3. Laminin

Laminins are major components of the basal lamina [45] and are also present in the ventricular zone (VZ) of the developing neocortex [46, 47]. Additionally, laminins were one of the first ECM proteins to be implicated in nervous system development as they were found to promote neurite outgrowth in an integrin-dependent manner [48–52]. During development, the extracellular matrix forms a basal lamina (BL) surrounding the brain and blood vessels throughout the CNS [53, 54]. In the neocortex, the BL at the pial surface is contacted by the end-feet of radial glial cells. A number of studies have shown how crucial the pial BL is for neocortical development. Removal of the BL leads to the detachment of radial glial cell fibers, which affects radial glial cell survival and proper cortical lamination [55–58]. Laminins have also been shown to promote the expansion, migration, and differentiation of neural stem cells (NSCs) *in vitro* [46, 59–67]. Mice lacking laminin $\alpha 1$ die during embryogenesis [68]; mice bearing a mutation that only affects the laminin $\alpha 1$ nidogen-binding domain survive until birth and display disruptions of the pial basal lamina as well as neuronal ectopias [69]. Additionally, laminin $\alpha 1$ inactivation in a subset of cortical neurons has been observed to cause cortical lamination defects [70]. However, defects in the maintenance and/or differentiation of NSCs has not been reported in these mutants. *In vivo* evidence for a role of laminins in controlling NSC behavior comes from studies of their dystroglycan and integrin receptors. In human patients, mutations within enzymes that glycosylate dystroglycan have been shown to produce cortical neuronal ectopias [71, 72]. Mice lacking dystroglycan in the CNS or bearing mutations in dystroglycan glycosyltransferase display BL disruptions and neuronal migration defects [73–75]. Laminins have also been found to play a role in axonal guidance *in vivo* [76].

In mice, laminin $\alpha 1$ deficiency results in the abnormal branching of myelinated axons from the corpus callosum [70]. These mutants also show abnormal neuronal migration, impaired activation of integrin downstream effectors, such as focal adhesion kinase and paxillin, and disrupted AKT/GSK-3 signaling, which has been implicated in neurite outgrowth [77]. The exact mechanisms underlying these abnormalities remain unknown. In the CNS, oligodendrocytes derive mainly from precursors residing in the ventral VZ and ganglionic eminences. They proliferate and migrate before becoming mature, myelinating cells [78]. Oligodendrocytes do not have a basal lamina, although there exists some evidence that developing oligodendrocyte precursor cells can secrete low levels of laminin [79], which suggests oligodendrocytes may interact with outside sources of laminin. Oligodendrocytes myelinate axons through extending multiple cell processes capable of ensheathing numerous axons [80, 81]. Expression of laminins during development correlates with the onset of CNS myelination [80, 82], and varied degrees of defects have been found in white matter tracts of patients suffering from congenital muscle dystrophy [83, 84]. Mice lacking laminin $\alpha 2$ have a developmental delay in oligodendrocyte maturation, resulting in hypomyelination [85, 86]. The degree of developmental delay is region-specific, which may reflect different laminin $\alpha 2$ requirements [86].

1.4. Vitronectin

Vitronectin (Vn) is a multifunctional plasma and ECM glycoprotein with multiple domains for interactions with plasma proteins like thrombin, anti-thrombin III, and plasminogen activator inhibitor-1 [87]. Vn is primarily synthesized in the liver [88] and has affinity for different integrins expressed on T-cells, platelets, endothelial cells, and macrophages. Comparatively little is known about the expression patterns of Vn during CNS development; however, a role for Vn in the induction of neurite outgrowth has been shown [89, 90]. In the normal adult CNS, vitronectin is localized mostly to blood vessels, with the exception of capillaries, suggesting that small amounts of vitronectin can be deposited in the CNS under normal conditions [91].

2. Matrix influence on astrocyte differentiation in CNS development

Astrocytes are specialized glial cells that are the major cell Component of the adult CNS, outnumbering neurons by over fivefold and Comprising roughly 20–40% of all glia [92]. They extend numerous processes that locally contact the surrounding neurons, other glial cells, and endothelial cells. Besides their pure barrier function, they also play a vital role in the control of cerebral blood flow and glucose homeostasis in the brain [92]. During the early development of the CNS, the overall expression of ECM molecules is relatively low and subsequently increases toward the end of embryogenesis and during postnatal development [93, 94]. Despite their prominent expression during neural development, little is known about the functional importance of specific ECM molecules for astrocyte development. While the importance of how chondroitin sulfate proteoglycans (CSPGs) influence the differentiation of NPCs to astrocytes during embryonic development cannot be overlooked, for the purposes of this book

chapter we will instead focus on the known role of tenascin-c in NPC differentiation into astrocytes. The tenascin gene family has recently gained increased attention with regard to glial development Owing to their late embryonic and early postnatal expression. Karus et al. have recently shown that TnC is capable of regulating the maturation of astrocytes during embryonic spinal cord development, primarily by orchestrating the responsiveness of NPCs to growth factors [27]. Within the developing brain and spinal cord, NPCs have been observed to initially generate neuronal cells. However, changes in the expression patterns of growth factor receptors result in the specification of astroglial cells. The expression of the epidermal growth factor receptor has been shown to be critical for normal astrocyte development [95]. During early embryonic stages, NPCs expressing Nestin, brain lipid binding protein (BLBP), and fibroblast growth factor receptors (FGFR) primarily generate neurons. Upon sustained fibroblast growth factor (FGF) signaling, these NPCs gain responsiveness towards epidermal growth factor (EGF). The expression of the EGF receptor is stimulated by TnC [27]. As a result, a rapid decline in neuron generation is observed in the embryonic spinal cord. Regardless of their location along the rostro-caudal axis of the developing spinal cord, the NPCs begin to express shared molecular markers with astrocytes, such as glutamate aspartate transporter (GLAST) and TnC [96]. Additionally, these cells begin to express additional markers such as S100 β , aquaporin-4 [97], and fibroblast growth factor receptor 3 (FGFR3). Subsequently, the NPCs differentiate into GFAP-positive mature astrocytes, which are then often classified into fibrous white matter and gray matter astrocytes. Moreover, CSPGs and potentially TnC are involved in the maturation toward GFAP-positive astrocytes [98].

Astrocytes have been shown to play a prominent role in the developing central nervous system. Astrocytes contribute significantly in coordinating neuronal migration, axon guidance, and synapse formation [92]. This coordination is directed through deposition of specific extracellular matrix protein in the developing CNS—namely fibronectin and laminin. In an early report, Stewart and Pearlman observed fibronectin-like staining in the developing mouse cerebral cortex [99]. The temporal and spatial expression of fibronectin led them to posit that the transient appearance of fibronectin-like immunostaining in the zones that contain early cortical afferents suggests a role for Fn in forming the migratory pathway for the growth cones of these axons. In this role, it may be acting in concert with other extracellular matrix components such as hyaluronectin [100], glycosaminoglycans [101, 102], and laminin [103], which have been shown to have similar spatial distributions. The decline of fibronectin-like immunostaining that occurs as cortical development progresses may be a part of the change from the immature state, which supports profuse axon elongation in the CNS, to the mature state in which neurite outgrowth is quite limited. In addition to fibronectin deposition, astrocytes produce and secrete laminin, a key extracellular matrix guidance molecule in the developing brain. Laminin is synthesized and secreted by astrocytes both *in vivo* [103–107] and *in vitro* [108–112]. Astrocytic laminin is deposited into the ECM and fixed on the cell surface through binding to specific transmembrane receptors known as integrins [113–115]. The regionalization of laminin on the astrocyte surface is determined by the clustering of integrins, which are bound to the microfilaments, into macromolecular complexes known as focal contacts [116, 117]. It is this organization of laminin into specific patterns on the cell surface that provides directional cues to the elongating neurite [118–120]. Similar to fibronectin and TnC, the

expression of laminin in the brain parenchyma is developmentally regulated and coincides with neuronal migration [119]. Once the wiring of the brain network is firmly established, laminin disappears from the brain parenchyma and is restricted to the basal lamina of the vasculature.

3. ECM regulation of astrocytes

Once established, the composition of the mature extracellular matrix is rather stable with little or no turnover of their components [24]. This stability is lost, however, when tissue damage results from injury, inflammation, or disease. Extracellular matrix degradation is triggered through inflammation, which results in changes to the matrix composition. Under these circumstances, the expression of various extracellular matrix molecules is highly up-regulated and major depositions are observed often marking lesion sites, in particular, in association with glial scar tissue formation. The freshly produced ECM components may be secreted by reactive astrocytes, oligodendrocyte precursors, microglia/macrophages, and eventually by meningeal cells. The lesion and consequent reactive processes induce a matrix accumulation that strongly resembles the “juvenile-type” of meshwork previously observed during early nervous system development. In many CNS diseases, it is becoming increasingly clear that some ECM molecules are aberrantly expressed and others cleaved into bioactive fragments known as damage-associated molecular patterns (DAMPs) or “alarmins” [121]. Through their ability to bind to different types of pattern recognition receptors (PRRs), these ECM molecules can influence the phenotype and magnitude of inflammation. Moreover, the enzymes and inflammatory mediators released by immune cells further degrade or alter the composition of the ECM. For the purposes of this book chapter, we will focus on the role of astrocytes in CNS injury and disease and how the extracellular matrix influences their response. We will highlight how the extracellular matrix proteins mentioned in the introduction could have profound effects on CNS injury and disease recovery by discussing their known roles.

3.1. Tenascin-c influences on astrocytes in diseases of the CNS

Tenascin-c can act as a DAMP, eliciting activation of innate immune cells via binding to a TLR-4 [122]. This was first demonstrated in a model of arthritis where inflammatory disease symptoms in TnC KO mice resolved rapidly; conversely, TnC injection elicited joint inflammation. TLR-4 stimulation up-regulate TnC in macrophages so tenascin-c can act in an autocrine loop to amplify acute inflammation [122]. Although acute TnC expression is required for proper wound healing [123], persistent expression can be detrimental; TnC is up-regulated in mice with Alzheimer’s disease, and its deletion reduces neuropathology and inflammation [124]. TnC is an important factor in propagating chronic inflammation and could act in a similar manner after spinal cord injury.

After spinal cord injury, *de novo* synthesis of TnC occurs around the site within three days. Expression of TnC has been shown to persist for at least 30 days post injury in this model [125]. TnC is expressed by astrocytes in the lesion border, within the dorsal columns, and within the

lesion epicenter. Interestingly, astrocytes cultured on TnC express fewer scar-related markers and proliferate less than astrocytes grown on control substrates [126], implying that TnC may restrict astrogliosis and scar formation after spinal cord injury. Additionally, *in vivo* work on spinal cord injury in tenascin-c knockout (KO) mice have shown that spontaneous recovery of locomotor functions after spinal injury is impaired in these animals when compared to wild-type mice. The impaired recovery was associated with attenuated excitability of the plantar Hoffmann reflex, reduced glutamatergic input, reduced sprouting of monoaminergic axons in the lumbar spinal cord, and enhanced post-traumatic degeneration of corticospinal axons [127]. In a follow-up study using a model of lumbar spinal cord hemisection injury, global deletion of TnC was associated with enhanced axonal plasticity and growth into the lesion site. While these recent reports provide contrarian views to the role of TnC in the injured spinal cord, the precise mechanisms responsible for these changes have not been determined. In their review on extracellular matrix regulation in the healthy and injured spinal cord, Gaudet and Popovich suggest performing complementary gain-of-function experiments in wild-type mice and analyses of specific cellular and molecular pathways (e.g., inflammation) in tenascin-c KO mice [121]. Clearly the authors state, consistent up-regulation of TnC after injury and its ability to bind/activate TLRs suggest that it is a candidate for controlling inflammation after spinal cord injury [121]. Further research will need to be performed in order to tease apart the role of this integral ECM protein in spinal cord injury.

TnC has also been implicated in globoid cell leukodystrophy (GLD), also known as Krabbe disease. GLD is a rare and often-fatal demyelinating disease caused by mutations in the galactocerebrosidase (*galc*) gene that results in the accumulation of galactosylsphingosine (“psychosine”) [128]. Aberrant deposition of the extracellular matrix protein TnC has been observed in the brains of GLD patients when compared to age-matched control subjects. Elevated deposition and expression of TnC have also been observed in brain tissues from twitcher mice, an authentic mouse model of GLD [129]. The elevated TnC levels have been implicated in enhancing astrocyte responses to psychosine and astrocytic production of matrix metalloproteinase (MMP)-3, which activates microglial responses, inducing the formation of “globoid-like” cells in culture [129, 130]. This dysregulation of astrocytes, in part mediated by altered ECM, is thought to enhance the demyelination seen in this disease [129].

Expression of TnC is also aberrant in multiple sclerosis (MS). This chronic inflammatory and CNS demyelinating disease involves autoimmunity directed against myelin. A neuropathological hallmark of MS is glial scarring, formed by reactive astrocytes. Multiple sclerosis lesions can be broadly defined as inactive, chronic active, and chronic. Inactive MS lesions and the center of chronic active lesions are characterized by few leukocytes and extensive glial fibrillary acidic protein immunoreactivity, indicative of astrogliosis. Within acute MS plaques, a significant loss of tenascin-c immunoreactivity has been observed, whereas tenascin-c was distributed throughout chronic MS plaques at levels similar to or greater than those seen in normal-appearing white matter. Particularly reactive astrocytes have been shown to strongly express TnC, and several reports have shown a correlation between TnC induction and acute inflammation, suggesting that enhanced tenascin-c expression might function as a defense mechanism to control the inflammatory reaction [22, 131]. However, the loss of TnC seen in

acute MS lesions is consistent with inflammatory cell-mediated breakdown of the extracellular matrix, which may be a marker of blood-brain barrier breakdown and leukocyte extravasation. Matrix metalloproteinases, which can degrade tenascins, are probably a factor in this inflammatory-mediated matrix breakdown. Such a breakdown in the TnC matrix might lead to a loss of matrix-cellular interactions, influencing the radial extension of the active lesion. Furthermore, the expression and preservation of TnC in normal-appearing white matter beyond the plaque edge may negatively influence migration. The increase in TnC seen in association with a reactive astrocyte subpopulation in extensively demyelinated and subacute lesions and scar formation in chronic MS lesions might also inhibit repair. It suggests that reactive astrocytes continue to produce TnC, which leads to the eventual increase in levels seen in chronic plaques. This increased production and deposition of TnC would then actively inhibit and prevent the differentiation of oligodendrocyte progenitor cells into oligodendrocytes within the lesion, leading to the failure to remyelinate axons, which is seen in MS pathology.

3.2. Astrocytic fibronectin in CNS disease pathology

Inflammation-mediated loss of myelin and incomplete remyelination are pathological hallmarks of multiple sclerosis (MS). Remyelination is essential for both restoration of saltatory conduction and axonal protection [132]. Although remyelination occurs in the early stages of MS, it declines as the disease progresses, resulting in chronically demyelinated plaques and axonal loss [133]. Oligodendrocyte progenitors, the cells responsible for CNS remyelination [134], are present in most MS lesions, but ultimately fail to differentiate into mature myelinating oligodendrocytes, which results in remyelination failure [132, 135]. One of the many factors regulating the migration, proliferation, and differentiation of oligodendrocyte progenitor cells into mature, myelinating oligodendrocytes is the extracellular matrix [136]. In multiple sclerosis brain tissue, enhanced fibronectin deposition was primarily localized to vessel walls, in particular in perivascular infiltrates, and correlated with the extent of inflammation. Fibronectin accumulation was also detected in the parenchyma of active demyelinating MS lesions, suggesting that, in addition to extravasation from affected blood vessels, fibronectin may be locally produced by endothelial cells, infiltrated macrophages in the CNS [15, 137], as well as astrocytes [14]. Recent data have now demonstrated that fibronectin inhibits the differentiation of oligodendrocyte progenitors and, as a result, remyelination [138]. This finding was furthered when Stoffels et al. observed that the production of fibronectin aggregates inhibited oligodendrocyte progenitor cell differentiation in both an animal model of MS and within chronically demyelinated lesions. When they examined the expression of fibronectin on demyelinating injury, they found that the formation of these inhibitory fibronectin aggregates is mediated by inflammation. In toxin-induced lesions, fibronectin expression was transiently increased within demyelinated areas and declined as remyelination proceeded. However, upon the examination of chronically demyelinated MS lesions, fibronectin expression persisted in the form of insoluble, degradation-resistant aggregates. This finding was also observed in a mouse model of MS, chronic experimental autoimmune encephalomyelitis, wherein fibronectin aggregates were found at the relapse phase but not in a toxin-induced demyelination injury model.

Frost et al. [139] showed that fibronectin promoted the migration of oligodendrocyte precursor cells. Connecting segment-1 fibronectin, an alternative splice variant of fibronectin, localized to astrocytes and astrocyte end-feet at the edge of MS lesions [16]. The CS-1 domain serves as a ligand for $\alpha 4\beta 1$, a leukocyte integrin involved in cell-ECM and cell-cell adhesion. The presence of CS-1 fibronectin in astrocyte end-feet may therefore contribute to entry or retention of $\alpha 4\beta 1$ integrin-bearing leukocytes further into the CNS parenchyma. These data indicate that fibronectin and its splice variants have an active part in MS lesion development and progression.

Fibronectin has also been shown to mediate the inflammatory response in spinal cord injury. After spinal cord injury, both a glial and fibrotic scar forms at the site of injury. An excellent review on the glial scar can be found in Sofroniew and Vinters, 2010. Along with the reappearance of tenascin-c, fibronectin deposition is also increased following spinal cord injury. While fibronectin has been shown to be a growth-permissive substrate for axons, the fibrotic scar is inhibitory to axon regeneration [140]. In a compression trauma model of spinal cord injury, Farooque et al. found that fibronectin was present within sites of severe spinal cord compression trauma; however, when distal portions of the spinal cord were probed for fibronectin antigen, there were no signs of deposition [141]. This indicates that fibronectin is deposited proximal to the site of injury. Additionally, fibronectin has been shown to stimulate astrocyte proliferation through two means: (1) the $\alpha 5\beta 1$ integrin found on astrocytes, and (2) the up-regulation of the P2Y1 receptor. The up-regulation of P2Y1 by fibronectin requires $[Ca^{2+}]_i$ and the activation of the integrin-linked kinase (ILK) and Akt [142]. The $[Ca^{2+}]_i$ stimulated by fibronectin is $\alpha 5\beta 1$ integrin receptor dependent and the phosphorylation of Akt or extracellular signal-regulated protein kinase (ERK1/2) induced by fibronectin mediates the action of cAMP response element-binding protein (CREB) and signal transducer and activator of transcription 3 (Stat3). Through these various pathways, fibronectin release could stimulate the astrocyte proliferation seen after spinal cord injury, that the increased expression of the P2Y1 receptor would provide more sites for ATP to bind, which could further aggravate the proliferation and inflammation of spinal cord astrocytes, thus worsening the recovery of Spinal cord injury patients [142].

3.3. Laminin in CNS disease pathology

Laminins are high-molecular weight (~400 kDa) proteins of the extracellular matrix. They are a major component of the basal lamina (one of the players of the basement membrane), a protein network foundation for most cells and organs. The laminins are an important and biologically active part of the basal lamina, influencing cell differentiation, migration, and adhesion. Laminin is vital for the maintenance and survival of tissues. In the central nervous system, laminins, similar to other extracellular matrix proteins, are broadly expressed during embryonic brain development. In the adult brain, however, the distribution of laminin is restricted to the vascular basal lamina and the ventricular-subventricular zone stem cell niche. We will be covering laminin expression as it pertains to the vascular basal lamina (i.e., basement membrane). There are two distinct continuous basement membranes that can be identified surrounding the cerebrovasculature: the vascular basement membrane and the

astroglial basement membrane. Both of the basement membranes are composed of the characteristic sheet-like structures of laminins, heparan sulfate proteoglycans, entactin, and type IV collagen. The only difference observed between the two basement membranes is the source of the structural components: endothelial cells are the predominate source for the vascular basement membrane, and astrocytes (specifically, astrocytic end-feet) are responsible for the formation of the astroglial basement membrane.

In multiple sclerosis lesions, alterations in the basement membrane are observed [16, 91, 143]. Abnormalities of the basal lamina surrounding the brain capillaries and local deposition of matrix molecules may influence blood-brain barrier permeability and thus leukocyte migration and retention. The basement membrane barriers previously discussed—vascular and astroglial—define the inner and outer limits, respectively, of the Virchow-Robin perivascular space where leukocytes accumulate before they migrate into the CNS neuroparenchyma. Recently, the presence of extensive basement membrane alterations in MS brain tissue was described [16, 143]. It was found that inflammatory MS lesions contained irregular and discontinuous basement membranes throughout the lesion area. It was also found that organized deposition of basement membrane proteins occurred within the perivascular infiltrates in MS lesions. This group hypothesized that these structures contributed to the influx of leukocytes by forming a reservoir of chemotactic agents. However, they also posited that the perivascular ECM structures might function as a conduit network, thereby facilitating the transport of myelin-laden macrophages out of the CNS toward cervical lymph nodes [144]. The deposition of such compact parenchymal basement membrane deposits may have further consequences such as hampering axonal regeneration and outgrowth through the formation of an anatomical barrier, which could lead to the persistence of MS lesions.

It has also been demonstrated that the only laminin isoforms present in the vascular basement membranes are $\alpha 4$ and $\alpha 5$, whereas isoforms $\alpha 1$ and $\alpha 2$ were restricted to the astroglial basement membrane [145]. When investigating the expression of these laminin isoforms in the brain tissue of experimental autoimmune encephalomyelitis mice, leukocyte infiltration was associated with a pronounced loss of laminin $\alpha 5$ immunoreactivity in the vascular basement membrane. However, in regions where laminin $\alpha 4$ and $\alpha 5$ were detected, no leukocyte infiltration was detected. Interestingly, there was major leukocyte infiltration occurring at sites where the parenchymal basement membrane contained both the laminin $\alpha 1$ and $\alpha 2$ chains, isoforms produced primarily by the astrocytic basement membrane. This suggests that leukocyte migration across the astroglial basement membrane is markedly different compared to the migration observed across the vascular basement membrane [145]. There was also a recent study looking into the differential distribution of several laminin isoforms in control and MS brain tissue. In this study, the authors confirmed the previous finding that the vascular basement membrane is mainly composed of laminin-5,-8, and -10, whereas the astroglial basement membrane predominantly consists of laminin-1 and -2. However, in active demyelinating MS lesions, they observed leukocytes accumulating around vascular basement membranes containing laminin $\alpha 5$. In addition, disruption and loss of vascular laminin expression in active demyelinating lesions have been reported [146].

Laminin also plays a role in maintaining the integrity of the blood-brain barrier (BBB). The BBB is a dynamic network that regulates material exchange between the circulatory system and the brain parenchyma, which aids in homeostatic maintenance of the central nervous system [147]. In the context of central nervous system injury, BBB malfunction has been reported. The BBB is mainly composed of brain microvascular endothelial cells, astrocytic end-feet, pericytes, and the basement membrane, of which laminin is a key component. Astrocytes wrap around endothelial cells using their end-feet, and pericytes, which are sandwiched between endothelial cells and astrocytes, signal to both cell types. Recently, it has been shown that pericytes are necessary for the formation of the BBB during embryogenesis, and loss of pericytes leads to compromised BBB integrity and age-dependent vascular-mediated neurodegeneration in adult mice, which suggests an important role for pericytes in BBB regulation. In a recent report, a group found that astrocyte laminin, by binding to the integrin $\alpha 2$ receptor, prevents pericyte differentiation from the BBB-stabilizing resting stage to the BBB-disrupting contractile stage, which helps to maintain the integrity of the BBB [148]. However, when astrocytic laminin was down-regulated using functional blocking antibodies and RNA interference, there were decreases in aquaporin-4 expression on astrocyte end-feet and decreases in tight junction protein expression. Further, in laminin knockdown animals, the lack of astrocytic laminin induced the differentiation of pericytes from the resting stage to the contractile stage. This loss of astrocytic laminins could be one of the major driving forces behind the leakiness of the BBB seen in many neurodegenerative diseases and CNS injuries.

3.4. Vitronectin in CNS disease and injury

Unlike the preceding extracellular matrix proteins, vitronectin has remained elusive in its functional role in central nervous system inflammation and injury. The earliest reports observed an enhancement of vitronectin expression in the blood vessel walls of active demyelinating lesions, in demyelinated axons, and on a small number of hypertrophic astrocytes. However, a negative role for vitronectin has not been found. In contrast, vitronectin has been shown to promote neurite outgrowth [149] and enhance astrocyte migration [150]. As vitronectin mRNA is almost undetectable in the normal adult brain, it might be synthesized by infiltrating leukocytes or derived from the plasma as a result of blood-brain barrier breakdown. In the EAE model of multiple sclerosis, vitronectin expression was shown to be enhanced, as well as contribute to the up-regulation of matrix metalloproteinases and activation of microglia [151]. Increasing research into the role of this under-studied extracellular matrix protein could provide clues as to its functional role in CNS inflammation.

4. Concluding remarks

In this chapter, we have outlined many lines of evidence linking the activity of astrocytes to changes in the ECM associated with neuropathology. We postulate that establishing the nature of astrocyte heterogeneity will be important for understanding the growing number of diseases in which astrocytes have been identified as having a primary or causal role. The growing awareness that astrocyte dysfunction, not just reactivity, contributes to neuropathology as a

concept we have called “gliodystrophy” [152]. This term reflects more than the presence of astrocytes in pathology, but denotes the loss or gain of astrocyte functions as a result of astrocyte plasticity and disease-associated heterogeneity. Therefore, understanding the basis for astrocyte heterogeneity, as a component of astrocyte dysfunction, is of increasing importance as astrocytes are recognized to play a central role in a wide range of neurological diseases.

How might we define astrocyte heterogeneity and is astrocyte reactivity a form of heterogeneity? To begin, we would propose that the heterogeneity of astrocytes is divergence in functions between ontogenically identical cells. By this definition, we would suggest that there would exist homeostatic heterogeneity among astrocytes related to their anatomical location. One could argue that the metabolic and physiological demands on an astrocyte within the cortical gray matter would be different from an astrocyte located within the heavily myelinated tracts of the corpus callosum. Indeed, astrocytes in these two locations are easily discernible by their overt appearance as either protoplasmic or fibrous [92]. Then, reactivity would add another dimension to this heterogeneity as each would, in theory, have potentially unique starting states from which reactivity could also be distinctive. If we depict this idea in a (perhaps overly) simplified manner (**Figure 2**), we could envision naive astrocytes within the CNS lying along an X-axis at different points. In response to a stimulus, you might then predict that each cell would in response to that trigger rise up the Y-axis to different points. When considered in terms of neurological diseases, identical acute injuries or trauma to different anatomical loci may be expected to evoke different responses from astrocytes in terms of their proliferation, gene response, and secretome contribution to the immediate environment. When considered in terms of chronic neurodegenerative conditions, where time plays a crucial role (as conveyed along the Z-axis in **Figure 2**), heterogeneous astrocytes may be expected to develop adaptations to disease in different ways. Where one activated cell may become quiescent, interacting less with its immediate environment and failing to sustain homeostatic functions, as one might envision occurring in a glial scar. Another astrocyte may instead adopt a gain of function with an enhanced or altered secretome that modifies its immediate environment and interacts with adjacent cells in a pathological way. This concept may contribute to how we might explain the role of astrocytes in dementia where dysregulation of synaptic connectivity and impaired cognitive function may relate to astrocyte senescence in Alzheimer’s disease [153].

From all of this discussion, we should also consider the potential utility of the information gleaned from what could be considered the basic biology of the astrocyte. How could we apply our present and future understanding of astrocyte heterogeneity to developing new, or possibly enhancing current treatments for neurological disease? One possible approach of harnessing the potential of heterogeneous astrocytes has already been applied to models of spinal cord injury and Parkinson’s disease. In these studies, Proschel and colleagues have determined that astrocyte transplants can dramatically improve the outcomes in these degenerative conditions. For instance, in 6-hydroxydopamine lesioned rats, the behavioral deficit and dopaminergic denervation of the striatum were attenuated when these animals received transplants of astrocytes pre-exposed to bone morphogenic protein [154]. In a previous study, this group also demonstrated enhanced axon growth in a spinal cord injury

model with these astrocyte transplants [155]. These data show that astrocytes possess therapeutic potential to address important neurological diseases. To build upon the ideas set forth by these transplant studies, one could ask how could we target the endogenous astrocytes to achieve similar outcomes? While the answer to this important question is likely complex, if our own ideas on the origins of astrocyte heterogeneity are valid, then select targeting of ECM-Astrocyte communication may be one approach to try. For instance, targeting of the $\beta 1$ integrin using the RGD peptide has been shown to prevent astrogliosis in the injured spinal cord and improve functional recovery [156]. With an advanced understanding on how the ECM controls, or at the very least influences, the function of astrocytes *in situ* during brain injury or disease, we may be able to target and promote brain recovery and repair.

In the future, we suggest that technical approaches are now available to advance this line of investigation in ways not previously feasible. For instance, cataloging astrocyte diversity using single-cell laser-capture sequencing may be expected to identify unique markers to distinguish different subtypes of astrocytes from tissues. This approach would also allow for the important distinction of acquiring astrocytes that are spatially and temporally associated with specific types of neural injury [157]. A similar approach has recently been used to identify markers of reactive astrocytes. Results from these types of future investigations should enable us to delve deeper into the complexity of astrocyte biology and better understand the nature and function of these cells as they maintain the CNS and react and participate in neurological disease states.

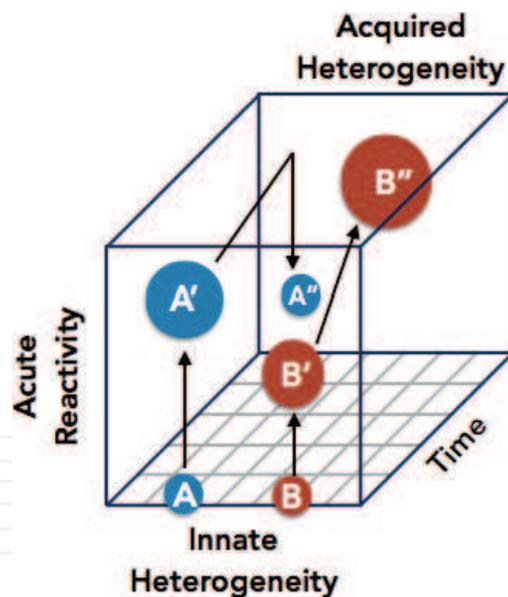


Figure 2. Hypothesized model of influence of ECM on innate and acquired astrocyte heterogeneity. Depicted are two different astrocytes, labeled A and B which have been positioned along the X-axis to reflect innate heterogeneity on the basis of their location within the central nervous system (CNS). In response to a stimulus (labeled A' and B', respectively), the innate heterogeneity impacts the reactivity, as depicted as different locations along the Y-axis. Lastly, with chronic stimulation, these two distinct cells develop distinct long-term phenotypes, labeled A'' and B'', where the innate heterogeneity results in different outcomes to the long-term stimulation. Whereas A depicted as a smaller sphere lower on the Y axis may become chronically less active, perhaps related to development of an astrocyte scar, the other astrocyte labeled B'' with chronic stimulation adapts to become a more active, perhaps physiologically adapted, phenotype contributing to neuropathology in disease.

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