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Lectican proteoglycans, their cleaving metalloproteinases, and plasticity in the central nervous system extracellular microenvironment

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Abstract

The extracellular matrix in the central nervous system actively orchestrates and modulates changes in neural structure and function in response to experience, after injury, during disease, and with changes in neuronal activity. A component of the multi-protein, extracellular matrix aggregate in brain, the chondroitin sulfate-bearing proteoglycans known as lecticans, inhibit neurite outgrowth, alter dendritic spine shape, elicit closure of critical period plasticity, and block target reinnervation and functional recovery after injury as the major component of a glial scar. While removal of the chondroitin sulfate chains from lecticans with chondroitinase ABC improves plasticity, proteolytic cleavage of the lectican core protein may change the conformation of the matrix aggregate and also modulate neural plasticity. This review centers on the roles of the lecticans and the endogenous metalloproteinase families that proteolytically cleave lectican core proteins, the matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs), in neural plasticity. These extracellular metalloproteinases modulate structural neural plasticity—including changes in neurite outgrowth and dendritic spine remodeling—and synaptic plasticity. Some of these actions have been demonstrated to occur via cleavage of the proteoglycan core protein. Other actions of the proteases include cleavage of non-matrix substrate proteins, whereas still other actions may occur directly at the cell surface without proteolytic cleavage. The data convincingly demonstrate that metalloproteinases modulate physiological and pathophysiological neural plasticity.

Keywords

chondroitin sulfate proteoglycan; extracellular matrix; metalloproteinase; MMP; ADAMTS; neural plasticity

I. Introduction to the brain extracellular microenvironment

The extracellular microenvironment in the nervous system orchestrates, modulates and accommodates changes in neural structure that occur during development, with sensory

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experiences, after injury or with disease, and in response to changes in neural activity. Structural changes in neurons, especially in the adult, are related to functional plasticity and the classic example would be enlargement of dendritic spines seen after Hebbian plasticity. Structural neuronal plasticity may be directed by intrinsic mechanisms or guided by signals from the extracellular microenvironment. Some of these plastic alterations in the nervous system include but are not limited to:

maintenance of the size and shape of dendritic spines that regulate formation of memory (Kozorovitskiy et al., 2005; Kitanishi et al., 2009; Yang et al., 2009; Kasai et al., 2010)

formation of circuit connectivity during development (Schwartz and Domowicz, 2004; Carulli et al., 2005; Maeda et al., 2010)

axonal outgrowth and sprouting after central nervous system (CNS) injury or with disease (Schauwecker and McNeill, 1996; Deller et al., 2000; Thon et al., 2000; Yuan et al., 2002; Mayer et al., 2005; Deller et al., 2006; Busch and Silver, 2007; Fawcett, 2009),

experience-dependent termination of developmental critical periods (Pizzorusso et al., 2002; Pizzorusso et al., 2006),

glial involvement in synaptic plasticity (Faissner et al., 2010),

trafficking of neurotransmitter receptors (Frischknecht et al., 2009).

Among these, alterations in dendritic spine structure related to memory is especially intriguing since it occurs in response to long-term potentiation (or depression) (Yang et al., 2008) and stability of these altered spines is associated with lifelong memories (Yang et al., 2009). The microenvironment is not passive to accommodate changes in neuronal structural plasticity, and in response to changes in neuronal activity it provides signals that orchestrate subsequent structural changes (or the absence of further structural changes) (Dityatev et al., 2010).

The molecular components in the extracellular microenvironment are secreted from neurons, astrocytes, microglia and pericytes, oligodendrocytes and other non-neural cell types. The proportion of brain volume that is extracellular space has been estimated to be about 20% (Sykova and Nicholson, 2008). Within this space lies a meshwork of deposited interacting molecules collectively called extracellular matrix (ECM) and diffusing within the matrix are a plethora of soluble factors. Multiple ECM molecules interact to form large, stable aggregates and the composition of the aggregate depends upon the brain region and subregion, the stage of development, and/or pathological state of the brain (Galtrey and Fawcett, 2007). These matrix molecules are abundant and the turnover of the aggregates is slow. Several families of proteases are also secreted by neurons and glia and these proteases selectively cleave matrix protein substrates in the aggregate. Growing evidence indicates that proteolytic cleavage of matrix proteins disrupts the matrix aggregate and may play a role in plasticity (Gottschall et al., 2005). This review will focus on how the components of the ECM control plasticity, and describe evidence that proteases that cleave these proteins may also influence plasticity in the CNS.

II. Extracellular matrix in the CNS

a. lectican components of the matrix

A small family of high molecular weight, chondroitin sulfate (CS)-bearing proteoglycans (PGs) termed the lecticans are the most abundant proteins of ECM in the CNS. These proteins, brevican, aggrecan, versican, and neurocan, have core proteins that range in size from 145 kD to more than 300 kD. They have common domain structure at their termini

including an N-terminal globular (G1) region that contains an immunoglobulin-like loop and a hyaluronan-binding domain, and a C-terminal globular G3 region consisting of a C-type lectin domain, EGF-repeats and a complement regulatory protein-like motif (Zimmermann and Dours-Zimmermann, 2008). Link protein stabilizes hyaluronan-lectican interactions. The C-terminal domain binds to membrane-associated sulfoglycolipids or glycoproteins such as the tenascins or fibulins (Aspberg et al., 1997; Miura et al., 1999; Olin et al., 2001) (Figure 1A). However, the most prominent feature of these large proteins is a poorly conserved central region that contains glycosaminoglycan binding motifs where CS chains are covalently “O-linked” to serine residues. CS is a linear polysaccharide of varying length made up of the repeating disaccharide units glucuronic acid and N-acetylgalactosamine that are sulfated at specific positions by sulfotransferases. Multiple sulfotransferases are responsible for the 4-*O* and 6-*O* sulfation of N-acetylgalactosamine residues and the 2-*O* sulfation of glucuronic acid. The extent of sulfation varies dynamically during development and with disease and injury. For example, the over-sulfated forms (those that contain two sulfate groups per disaccharide, the most common being 4,6-*O*-disulfate on N-acetylgalactosamine) of CS are preferentially expressed in the glial scar after spinal cord injury (Maeda, 2010). The CS chains are large and highly negatively-charged which provides them with unique structure, and as will be seen, function (Esko et al., 2009). Interestingly, compared to cartilage, the CS chains attached to aggrecan derived from brain appear to be fewer in number and/or length (Fryer et al., 1992). In fact the larger lecticans aggrecan and versican V2 can be observed on a low percent SDS-PAGE gel (and Western blots) without the need for chondroitinase (Ch’ase) treatment when extracted from brain (our unpublished observations). When hippocampal protein extracts were treated with Ch’ase, there was a clear increase in brevican core protein without CS, while there was no such increase observed with aggrecan or versican V2. These observations suggest that there are fewer or shorter CS chains on aggrecan and possibly other lecticans in brain compared to cartilage.

A major function of PGs that bear CS chains that has been known for many years is inhibition of neurite outgrowth including growth cone retraction, axon turning *in vitro* away from PG, and the inability of axons to penetrate a lectican-containing glial scar *in vivo* (Snow et al., 1990; Oohira et al., 1991; McKeon et al., 1995; Zimmermann and Dours-Zimmermann, 2008). Much of this inhibition is due to the presence of the highly negatively-charged CS chains, yet significant growth inhibition activity is retained after removal of the CS chains (Schmalfeldt et al., 2000; Monnier et al., 2003). This finding suggests that a proportion of the neurite growth inhibitory activity is conferred by the core protein itself. Signaling of neurite growth inhibition occurs via activation of the Rho family GTPases, particularly activation of Rho A and downstream Rho-associated protein kinase (ROCK) (Schmandke and Strittmatter, 2007) and protein kinase C (Sivasankaran et al., 2004). Indeed, inhibition of RhoA or ROCK abrogates lectican-dependent neurite outgrowth inhibition in several *in vitro* models (Monnier et al., 2003) and *in vivo* with an optic nerve crush model (Lingor et al., 2007). Growth inhibition is stimulated after lectican binding with high affinity and specificity to the transmembrane receptor protein tyrosine phosphatase (RPTP) (Shen et al., 2009), other receptor tyrosine phosphatases (Fisher et al., 2011), or to the epidermal growth factor (EGF) receptor (Koprivica et al., 2005). The most compelling evidence that RPTP is responsible for neurite growth inhibition is that after spinal cord lesion, axons penetrated regions of the CS containing glial scar more readily in RPTP deficient mice compared to wild type mice (Shen et al., 2009). More recent data indicated that lectican inhibition of neurite outgrowth may be reversed by activation of cell surface integrins, which suggests that “inside-out” signaling may be a common pathway for at least several molecules that inhibit axon outgrowth (Tan et al., 2011).

b. Developmental expression and deposition of ECM

Astrocytes, oligodendrocytes and neurons are mainly responsible for ECM synthesis, and these cells differentially regulate the expression of matrix molecules in a developmentally-dependent manner (Carulli et al., 2005). The makeup of ECM in the developing brain is quite different from the mature adult, but like adults, it is thought to contain a tripartite molecular aggregate consisting of hyaluronan, a lectican and tenascin or another large globular, interacting protein. As might be expected given the massive structural migration, growth and neuronal network formation that occurs during development, the ECM is looser and more flexible compared to the adult, and occupies a larger volume fraction of extracellular space (Sykova and Nicholson, 2008). Further, since the length of the core protein varies significantly among the lecticans, the “tightness” of the ECM aggregate depends in part on the type of lectican involved in its formation; i.e. the longer the lectican core protein, the looser the lattice. Thus, neurocan and larger versican variants are abundantly and transiently expressed throughout the first several weeks of life after which their expression is down-regulated. Subsequently in the young adult, there is the appearance of the shorter versican V2 isoform, along with greatly accelerated expression of brevican and aggrecan (Milev et al., 1998). Hyaluronan is more highly expressed during development than in adult brain (Margolis et al., 1975; Zimmermann and Dours-Zimmermann, 2008), and turnover of the ECM is more rapid during post-natal development than seen in the adult.

The most prominent and well-studied feature of ECM in mature brain is the presence of the perineuronal net (PNN). PNNs are deposits of matrix aggregates that surround perikarya, proximal dendrites, and axon initial segments. These nets may be detected using lectins such as *Wisteria floribunda* that bind to the glycosaminoglycans (either directly or indirectly) and they identify a subset of mainly inhibitory interneurons. PNNs contain the same tripartite aggregate found in the neuropil (Deepa et al., 2006) and these nets are abundant in several regions in the brain including hippocampus, cerebral cortex, cerebellum and brain stem. Immature PNNs first appear around postnatal day 7 and reorganize their ECM aggregates with maturity (Koppe et al., 1997). More diffusely deposited, yet abundant ECM surrounds the axon bouton and dendritic spine, with an absence at the synaptic cleft (Langnaese et al., 1996; Hagihara et al., 1999). Therefore, the ECM that surrounds the synapse may be important in regulating structure and function of the synapse.

It is well established that there are marked changes in both morphological and functional neuronal plasticity that take place in the CNS of older individuals, especially in important areas for cognition including hippocampus and cerebral cortex. Deficits occur in long-term potentiation and long-term depression, mechanisms suggested to be the neural substrates for motor and cognitive learning (Mora et al., 2007). Structurally, the most consistently reported change in the aged brain is a loss of dendritic spines and changes in the complexity of apical dendrites, especially in cortical pyramidal cell dendritic spines of older primates. These changes are accompanied by significant increases in lectican expression in frontal cortex (Tanaka and Mizoguchi, 2009) and in other brain regions (our unpublished observations). Whether there is some direct cause and effect relationship between changes in plasticity and increased lectican expression with age is unknown.

c. Critical periods involve changes in ECM

During developmental critical periods, a particular repertoire of synaptic connections is selected from a wider range of inputs and made permanent, and these synapses are selected based on a necessary behavioral experience. The visual critical period occurs early in development and closes around sexual maturation (Knudsen, 2003). The most well-studied system where ECM proteins are involved in *in vivo* plasticity is in the concept of ocular dominance. If during the critical period binocular vision is deprived by closing one eye over

an extended time, a preponderance of neurons in visual cortex lose responsiveness to stimulation in the eye that had been deprived and there will be more neurons that respond to stimulation of the non-deprived eye. In fact, the deprived eye may permanently lose visual capability. If performed at the end of the ocular dominance critical period, monocular deprivation for the same length of time will no longer result in a loss in visual acuity in the adult. It was discovered more than 20 years ago that upon closure of the visual system critical period, diffuse lecticans condense to form PNNs in cortex, hippocampus and other regions (Hockfield et al., 1990), and it was hypothesized that they contribute to decreased plasticity observed after the end of the critical period. Several more recent, fascinating studies have focused on the disruption of lecticans in PNNs (and all lectican-containing matrix) via administration of Ch'ase directly in the neuropil in an attempt to promote plasticity after critical period closure.

Monocular deprivation in adult rats does not alter the visual system. However, in adult rats that received a Ch'ase injection in visual cortex and underwent monocular deprivation during development, there was a loss of cortical PNNs due to deglycosylated lecticans and reactivation of ocular dominance toward the ipsilateral, non-deprived eye which suggested that removal of CS chains reactivates cortical plasticity (Pizzorusso et al., 2002). Monocular deprivation initiated before the end of the critical period results in the classical, permanent, pathological ocular dominance. However, when Ch'ase was injected into visual cortex of adult rats monocularly-deprived during the critical period and then reverse sutured as adults, there was a restoration of dominance and a return of visual acuity in the eye that was originally deprived. Interestingly, a reduction in dendritic spines observed with monocular deprivation was reversed with Ch'ase injection into visual cortex (Pizzorusso et al., 2006). These results indicate an inhibitory role for the ECM in plasticity, perhaps through prevention of synapse formation or consolidation of inhibitory synaptic transmission. A very recent study demonstrated that the link protein Crtl1, which is important for maintaining stability in the ECM aggregate, is up-regulated as PNNs begin to form and Crtl1 knockout mice exhibited ocular dominance plasticity well into adulthood (Carulli et al., 2010). A similar action of PGs was demonstrated with "permanent" fear memories. Fear conditioning is a behavior which results in permanent memory in adult animals but it is a behavior that can be extinguished in immature animals. However, injection of Ch'ase into the amygdala of adult animals erased fear-conditioned memories indicating that deposition of CSs mediate the formation of erasure-resistant fear memories (Gogolla et al., 2009).

In each of these cases, the marker for the action of Ch'ase in the brain was the loss of lectin-positive PNNs around inhibitory interneurons, and thus the authors suggested that the removal of CSs around these neurons was crucial for reactivation of plasticity. Using lectin histochemistry such as *Wisteria floribunda* staining, PNNs are quite prominent and other parenchymal CSs are not well-recognized (Ajmo et al., 2008). It is just as likely, however, that Ch'ase degrades CS chains on lecticans in more diffuse ECM not stained by *Wisteria* lectin, and thus may disrupt the ECM surrounding axo-dendritic synapses which could have a profound influence on plasticity. Ch'ase removes CS from lecticans, but leaves intact lectican core protein, which was shown to be inhibitory toward neurite outgrowth *in vitro* (Schmalfeldt et al., 2000) and may exert inhibition on neural plasticity *in vivo*. Deglycosylation of the lecticans may increase access for endogenous proteases capable of degrading the core protein which could increase the propensity toward neural plasticity. There are two families of endogenous metalloproteinases that cleave the lecticans and loosen the ECM which could result in changes in neural plasticity: the matrix metalloproteinase (MMP) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) families (Figure 1B).

d. Changes in ECM in Alzheimer's disease and spinal cord injury

i. Alzheimer's disease—In Alzheimer's disease (AD), gliosis was associated with an increase in lectican expression (Canning et al., 1993) and antibodies that recognize the sulfated forms of CS (CS-4 and CS-6) were detected around senile plaques. This suggested a possible cooperation between lectican CS and amyloid in producing the dystrophic neurite outgrowth typically seen around plaques (DeWitt et al., 1993). Additionally in a mouse model of AD, the sulfated form of brevican migrated faster on a polyacrylamide gel, but the molecular weight of the brevican core protein without CS was not different from nontransgenic controls, which may indicate a change in brevican CS length, the numbers of CS chains, or sulfation of CS in these mice (Ajmo et al., 2010). Indirect evidence from several studies suggests that neurons surrounded by a PNN are protected from neurotoxicity in human AD tissue (DeWitt and Silver, 1996; Morawski et al., 2010a; Morawski et al., 2010b). Little additional information is known about the role of CS and the lecticans in AD beyond what is indicated by these somewhat contradictory studies.

ii. spinal cord injury—Spinal cord injury results in the formation of a glial scar, and the lecticans are one component of the glial scar that prevents functional recovery. The glial scar formed after spinal cord injury is an evolving structure and after 3–5 days it consists of tightly packed astrocytes with gap junctions and tight junctions and little extracellular space. Regulation of expression of each lectican is complex and these actions have been reviewed (Condic and Lemons, 2002; Viapiano and Matthews, 2006). Axonal damage caused by the injury is accompanied by dystrophic neurons unable to penetrate the negatively-charged core of the glial scar to allow for reinnervation and functional recovery. Treating injured rat spinal cord tissue with Ch'ase enhanced neurite outgrowth in the tissue (Zuo et al., 1998b). This finding led to use of Ch'ase in animal models of spinal cord injury to promote functional recovery, with positive results. Intrathecal injection of Ch'ase after spinal cord injury promoted regeneration of ascending and descending sensory neurons, increased post-synaptic activity, and restored motor function (Bradbury et al., 2002), a finding confirmed in other studies (Barritt et al., 2006; Huang et al., 2006). Injection of Ch'ase into the ipsilateral cuneate nucleus after C6–C7 spinal cord transection reduced PNNs and led to an increased area occupied by the spared forepaw afferents, which directly linked the functional improvement with axonal sprouting (Massey et al., 2006). However, Ch'ase on its own is not the most effective therapeutic treatment. Transgenic mice that expressed Ch'ase under the *Gfap* promoter exhibited recovery from rhizotomy, but not dorsal thoracic hemisection (Cafferty et al., 2007). Further, Ch'ase combined with rehabilitation has been shown to be a beneficial combination that takes advantage of a plasticity window opened by Ch'ase treatment (Wang et al., 2011). Other inhibitory targets for degradation, however, may also be beneficial and worthy of exploration.

III. Proteoglycanases

On western blots lecticans appear as high molecular weight bands that represent CS-bearing, intact proteoglycan conjugates and low-molecular weight bands that represent proteolytic fragments. These endogenous fragments were stable as they were observed in the absence of protease inhibitor cocktail and appeared no different even in samples with lengthy postmortem intervals (Westling et al., 2004). The fragments are formed generally by proteolytic cleavage in a conserved motif near the junction between the N-terminal G1 domain and the central domain since cartilage explant experiments demonstrated that aggrecan proteolysis involved separation of the N-terminal G1 domain fragment from the remainder of the molecule (Sandy et al., 1987). Proteolysis occurred in the interglobular domain between a Glu³⁷³ and Ala³⁷⁴ which subsequently led to cloning of the second

member of the ADAMTS family of proteinases (Sandy et al., 1992; Kuno et al., 1997; Tortorella et al., 1999; Arner, 2002).

a. Matrix metalloproteinases (MMPs)

More than 24 mammalian MMPs have been cloned as a subfamily of the larger metzincin family of metalloproteinases and their gene products act on diverse substrates including all ECM molecules, other proteinases, growth factors, and cell adhesion molecules (Sternlicht and Werb, 2001). Several MMPs are capable of cleaving lecticans. MMP domain structure consists minimally of a prodomain followed by a catalytic domain with a conserved zinc-binding site (HExxHxxGxxH) (figure 2A-I); other MMP members have a C-terminal hemopexin/vitronectin-like domain connected to the catalytic domain with a linker region, and the gelatinases (MMP-2 and -9) contain three fibronectin type II domains (Figure 2A-II); or membrane-associated isoforms with a transmembrane or GPI domain and a short cytoplasmic tail (Figure 2A-III) (Sternlicht and Werb, 2001). Regulation of MMPs occurs at multiple levels, including transcription, proximity to the cell surface, zymogen activation, degradation/inactivation and endogenous inhibition (Parks et al., 2004). MMP expression is generally low in the adult CNS but is up-regulated in response to various CNS injuries and diseases (Yong et al., 2001; Yong, 2005). A free cysteine thiol group in the MMP prodomain associates with the active site zinc ion and this interaction must be disrupted to activate the proteinase. Activation may occur via furin (or other protease) proteolytic cleavage of the prodomain (Sternlicht and Werb, 2001; Parks et al., 2004) or perhaps by thiol reactive reagents, reactive oxygen, or denaturants (Nagase et al., 1991) that disrupt the latent form of the enzyme. Activation of MMPs may involve complex proteolytic cascades and some activated MMPs may activate other pro-MMPs (Cowell et al., 1998; Knauper et al., 2002). The MMPs are primarily inhibited by α_2 -macroglobulin in the circulation, but tissue inhibition is due to binding to endogenously produced inhibitors termed tissue inhibitors of the metalloproteinases (TIMP), TIMP-1 through -4 (Brew et al., 2000).

b. A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)

Another family of proteinases capable of cleaving lecticans is the ADAMTS family. ADAMTS1 was first isolated from a cachexigenic tumor cell line (Kuno et al., 1997) followed by cloning of a related gene in cartilage whose protein showed aggrecanase activity (Tortorella et al., 2000). The ADAMTS family consists of nineteen members and proteolytic substrates include procollagen (ADAMTS2, 3, and 14), von Willebrand factor (ADAMTS13) and the lecticans (ADAMTS1, 4, 5, 9, and 15) (Tang and Hong, 1999; Apte, 2004; Tortorella et al., 2009). The ADAMTS domain structure consists of an N-terminal signal peptide for entry into the secretory pathway, a pro-proteinase domain, the metalloproteinase domain with a zinc binding site, a disintegrin-like domain, a thrombospondin type-1 repeat, which binds lecticans and is crucial for proteolytic cleavage (Tortorella et al., 2000), a cysteine-rich and spacer region and, depending upon the family member, different domains at the C-terminus (Jones and Riley, 2005; Porter et al., 2005) (Figure 2B). ADAMTSs are activated most frequently in the Golgi network through cleavage at the pro-proteinase convertase consensus sequence (RXX[K/R]) by furin or a furin-like protease (Wang et al., 2004; Tortorella et al., 2005). However, at least *in vitro*, MMP-9 cleaved the pro domain to form active ADAMTS4, albeit at a different site than furin (Tortorella et al., 2005). ADAMTS4 undergoes autocatalytic C-terminal truncation to form p53 and p40 species, and although the affinity for binding glycosaminoglycan was reduced with these smaller isoforms (Tortorella et al., 2000), the ability to cleave aggrecan and versican increased (Gao et al., 2002). ADAMTS1, 4, 5, 9, and 15—family members with lecticanase activity—are expressed in the CNS (Yuan et al., 2002) (our unpublished observations). TIMP-3 dose-dependently inhibited the ADAMTSs with high affinity

(Kashiwagi et al., 2001), although TIMP-1 and TIMP-2 are capable of inhibition at much higher concentrations (Hashimoto et al., 2001).

c. Neoepitope antibodies and lectican proteolytic fragments

The ADAMTS and MMP cleavage sites for aggrecan, brevican, and versican are conserved in human, bovine, and rodent (Yamaguchi, 2000) and cleavage of each of these lecticans results in an N-terminal fragment with a known C-terminal peptide sequence. Using these sequences, neoepitope antibodies were developed to recognize the ADAMTS fragments: NITEGE for a 53 kD fragment of aggrecan (Lark et al., 1995; Lemons et al., 2001), EA[T/M/V]ESE for a 55 kD fragment of brevican (Yamada et al., 1995; Matthews et al., 2000; Mayer et al., 2005), and NIV[S/N][F/S]E for a 60 kD fragment of versican V2 (Westling et al., 2004) (Perides et al., 1995; Howell and Gottschall, 2012). The MMP cleavage sites on lecticans are distinct from the ADAMTS sites, and neoepitope antibodies have also been developed for the major MMP fragments: DIPES for aggrecan (Fosang et al., 1992; Mort and Roughley, 2004) (although there are multiple MMP-cleavage sites in aggrecan) (Nagase and Kashiwagi, 2003), SAHPSA for brevican (Ajmo et al., 2010), and PLPDSR for versican V2 (unpublished observations). A predicted cleavage site at Glu⁵⁰⁵-Ala⁵⁰⁶ in neurocan (Prange et al., 1998) would produce identified N- and C-terminal fragments (Matsui et al., 1998; Asher et al., 2000), but there is no evidence for cleavage at this predicted site *in vivo*. Using these neoepitope antibodies, one can identify selectively endogenous ADAMTS and MMP activity in brain regions and changes in lectican proteolysis may be attributed to the appropriate proteolytic family.

Data indicate that the proteolytic fragments of lecticans also have direct functional activity. In human gliomas, expression of intact brevican is upregulated (Jaworski et al., 1996) along with an increase in the brevican N-terminal fragment (Viapiano et al., 2005). Intracranial graft of a normally non-invasive glioma cell line transfected with the brevican fragment mediated glioma invasion (Zhang et al., 1998), and ADAMTS cleavage of brevican was required for the increased invasiveness (Viapiano et al., 2008). Additionally, the brevican N-terminal fragment bound fibronectin, increased production of several integrins and neural cell adhesion molecule, and increased adhesion in a glioma cell line. This mechanism involved phosphorylation of both the EGF receptor and its downstream effector extracellular signal-regulated kinase (ERK)1/2 resulting in increased fibronectin secretion (Hu et al., 2008). A versican G3 domain peptide mediated increased cell attachment, neurite outgrowth, dendritic spine density and functional glutamate receptors and excitatory neurotransmission in primary rat neurons through activation of the EGF receptor and phosphorylation of ERK (Xiang et al., 2006). While intact versican in the adult CNS is inhibitory toward neurite outgrowth, perhaps liberation of the C-terminal versican fragment through proteolytic cleavage could allow the fragment to bind to other ECM molecules to mediate neural plasticity.

d. Tissue plasminogen activator (tPA)

The tissue plasminogen activator (tPA)/plasmin system is also capable of cleaving lecticans. Plasminogen is expressed by neurons, whereas tPA is expressed by both neurons and microglia (Tsirka et al., 1997). tPA converted plasminogen to plasmin which degraded phosphocan in an epilepsy model (Wu et al., 2000) and NG2, neurocan, and brevican in models of spinal cord injury (Davies et al., 2004; Barritt et al., 2006; Nolin et al., 2008). The tPA/plasmin system also contributed to the clearance of lectican core proteins after spinal cord injury. tPA/plasmin was upregulated after spinal cord injury and, combined with Ch'ase, led to synergistic clearance of lecticans and increased neurite outgrowth and functional recovery (Bukhari et al., 2011). Overall, these studies indicate that the tPA/plasmin system could play a role in functional recovery after CNS injury.

IV. Proteoglycanases and neural plasticity

a. Neurite outgrowth in the CNS

During perinatal development, postmitotic neurons migrate to an appropriate brain location and undergo axonal growth and extension in search of a dendrite (in most cases) to form a functional synapse. The growth cone, the dynamic, actin-rich structure at the end of the axon, expresses receptors for molecular guidance molecules and interaction with these molecules in the microenvironment guides the axon to the appropriate destination. Metalloproteinases appear to be important in mediating this effect as several vertebrates express metalloproteinases in the growth cone (Muir, 1994; Nordstrom et al., 1995; Webber et al., 2002). Further, *in vitro* evidence suggests that MMPs may interact and/or cleave extracellular growth molecules and receptors, for example, through cleavage of the exodomain of the netrin receptor deleted in colorectal carcinoma (DCC) (Galko and Tessier-Lavigne, 2000) and interaction with semaphorin-3C (Gonthier et al., 2007). As the animal matures the transition from juvenile to adult ECM and loss of permissive growth cues helps maintain established neural networks, but also diminishes neurite outgrowth. As mentioned above, injury to the CNS results in the formation of a glial scar, and the cellular components of the scar upregulate the production of inhibitory growth molecules including lecticans. Dorsal root ganglion (DRG) neurons cultured on injured spinal cord exhibited reduced neurite outgrowth that was improved with Ch'ase treatment of the spinal cord (Zuo et al., 1998b) which implicates lecticans as a major player in inhibiting neurite outgrowth.

b. MMPs and neurite outgrowth

Although CS chains on lecticans are important inhibitors of neurite outgrowth, proteolytic cleavage of the core protein may also play a role in stimulating plasticity, and evidence indicates that MMPs are mediators of neurite outgrowth. *In vivo*, MMP-3 colocalized with neocortical neurons and when treated with an MMP-3 (but not MMP-2/9) specific inhibitor, the neurons exhibited reduced neurite outgrowth (Gonthier et al., 2007). However, *in vitro*, dorsal root ganglion (DRG) neurons displayed slow growth on a lectican substrate that increased with either MMP-2 or Ch'ase treatment that either degraded or deglycosylated the lectican, respectively (Zuo et al., 1998a). Further, the membrane-bound MT5-MMP was found in growth cones in DRG neurons *in vitro*, promoted neurite outgrowth (Hayashita-Kinoh et al., 2001), and cleaved pro-MMP-2. In activity-dependent neurite outgrowth in cultured sympathetic neurons, MMP-2 mediated pro-NGF to NGF proteolytic cleavage and thus NGF-dependent neurite outgrowth (Saygili et al., 2011). Besides physiological neurite outgrowth, MMPs may also mediate neurite outgrowth during recovery from CNS injury. After dorsal spinal column transection, MMP activity appeared as “tracts” that colocalized with neurofilament-positive axons and decreased lectican staining around the lesion core (Duchossoy et al., 2001). In a model of optic nerve crush, an intravitreal peripheral nerve graft stimulated MMP activity while reducing TIMP expression, resulting in axonal outgrowth and dissolution of the glial scar (Ahmed et al., 2005). As a means to improve recovery after injury, different stem and progenitor cells were transplanted after CNS injury and mediated MMP-dependent increased neurite outgrowth (Heine et al., 2004; Pastrana et al., 2006; Zhang et al., 2007; Filous et al., 2010; Busch et al., 2011). Further, these studies demonstrated that the respective transplanted cells secreted MMPs—namely MMP-2—which mediated these effects through increased cleavage of matrix components including the lecticans. MMP-9 knockout mice exhibited greater locomotor activity recovery after spinal cord injury compared to wildtype mice (Noble 2002), which suggests a negative role for the MMPs in axonal regeneration. An increase in MMP-9—related to inflammation—was detrimental to neurite outgrowth after CNS injury (Noble et al., 2002; Busch et al., 2009; Zhang et al., 2011). MMP-9 was also found in regenerating nerves *in vivo* and mediated axonal extension in PC-12 cells (Shubayev and Myers, 2004). Overall, it appears

that not all MMPs function similarly to promote neurite outgrowth, perhaps due to the particular physiological or pathological circumstances as well as age (stage of development).

c. ADAMTSs and neurite outgrowth

Little is known about the possible role of ADAMTS in neurite outgrowth. In an indirect study, entorhinal cortex lesion (ECL) resulted in sprouting in the outer molecular layer of the dentate gyrus that was associated with ADAMTS-dependent cleavage of brevican (Mayer et al., 2005). In one study that directly examined the effect of ADAMTS on neurite outgrowth (Hamel et al., 2008), embryonic neurons transfected with ADAMTS4 cDNA exhibited longer neurites as well as an increased number of secondary neurites when grown on either an astrocyte monolayer or poly-L-lysine. Further, transfection with a proteolytically inactive form of ADAMTS4 promoted neurite outgrowth at least to the same extent as active ADAMTS4. Exogenous ADAMTS4 protein treatment resulted in a dose-dependent increase in neurite outgrowth that was dependent upon activation of the ERK1/2 pathway. This data suggests that the ADAMTSs could play a multimodal role in plasticity, not only through cleavage of lecticans, but also through binding to a neuronal cell surface receptor and activation of intracellular signaling, perhaps through activation of small GTPases including Rac1 and Cdc42, or inhibition of Rho A. Overall, while there is indirect evidence that increased metalloproteinase cleavage of lecticans promotes plasticity, future research to knockdown proteases in transgenic animal models, with RNA interference and/or by other methods will provide the ultimate test as to extracellular metalloproteinase involvement in plasticity.

d. MMPs and post-synaptic actions

The presence and increased expression of MMPs in regions of synaptic remodeling in animal models of plasticity initially led to the notion that MMPs play a role in the normal physiology of the synapse (Zhang et al., 1998; Szklarczyk et al., 2002; Reeves et al., 2003). Since that time, a plethora of data indicate that MMPs influence electrophysiological properties of the synapse, act on a variety of protein substrates present at the synapse to modulate synaptic transmission, and alter the structural and functional properties of dendritic spines.

Early data that indicated a role for MMPs in synaptic plasticity demonstrated that intracerebroventricular administration of a broad spectrum MMP inhibitor after lesion of the entorhinal cortex resulted in a failure of the post-lesion compensatory plasticity, including a failure to develop the capacity for LTP within the sprouting pathway and some indication for a loss of sprouting *per se* in inhibitor-treated animals (Reeves et al., 2003). Subsequently, several studies demonstrated that endogenous, basal production of MMP-9 was important for the maintenance but not the induction of LTP in mice, that memory was impaired in MMP-9 deficient animals (Nagy et al., 2006; Bozdagi et al., 2007; Wojtowicz and Mozrzymas, 2010) and that MMP-9 treatment *in vitro* was sufficient to drive a permanent enlargement of dendritic spines that was associated with LTP (Wang et al., 2008). Interestingly, it appeared as though an increase in expression and activity of the MMPs occurred during the memory acquisition phase when animals were tested in the water maze (Meighan et al., 2006). Several studies confirmed that changes in MMP expression and activation were associated with altered morphology of dendritic spines. In cultured hippocampal neurons, treatment with MMP-7 converted mature mushroom-shaped dendritic spines into immature filopodia (Bilousova et al., 2006), and interestingly it appeared to slow pre-synaptic vesicle recycling and reduced levels of synaptic proteins in the active zone of the synapse (Szklarczyk et al., 2007). Similarly, MMP-9 caused elongation of compact spines, a response that was dependent on the presence of $\alpha 1$ integrin (Michaluk et al., 2012).

Several substrates for the MMPs and related proteases have been identified that are highly expressed and functional within the synapse and its surrounding microenvironment. Lecticans that are deposited around the synapse and inhibit plasticity are cleaved by both MMPs and ADAMTSs and affect dendritic spine shape (Mayer et al., 2005) (our unpublished observations). Both lectican and ADAMTS expression is induced by TGF β 1 (Hamel et al., 2005). High resolution *in situ* zymography located MMP activity at the glutamatergic synapse (Gawlak et al., 2009), and the activity-induced disappearance of extracellular epitopes of the NR1 subunit of the NMDA receptor was blocked by MMP inhibitors. Apparently, MMP-3 was identified at this synapse (Pauly et al., 2008). Another synapse localized protein, ICAM-5, contains an ectodomain that was shed at the synapse during LTP and the release of this protein fragment was prevented by pre-treatment with an MMP inhibitor (Conant et al., 2010). In addition, methamphetamine caused shedding of the ICAM-5 ectodomain and this protein fragment interacted with α 5 β 1 integrin which increased the phosphorylation of cofilin, an actin depolymerizing protein that causes severing of actin filaments (Conant et al., 2011), a process that has been linked to MMP-dependent spine maturation. Thus, it is evident that cleavage of synaptic substrates by both the MMPs and ADAMTSs are important for various processes of synaptic plasticity.

V. Conclusions

A plethora of data indicates the importance of extracellular metalloproteinases of the MMP and ADAMTS families to neural plasticity. Prominent substrates for these metalloproteinases, the lecticans, are not only crucial components of the ECM in the CNS, but also exert influence and control over neural plasticity. Manipulation of lectican glycosylation through the use of Ch α ase after injury to the CNS increased axonal sprouting and improved functional recovery, but fewer studies have focused on endogenous metalloproteinases. Indeed, data indicate MMPs mediate neurite outgrowth as well as changes in postsynaptic structure and synaptic plasticity. Much less is known about the ADAMTSs, but data suggests a role in neurite outgrowth and perhaps a direct action on neurons beyond proteolytic cleavage of ECM substrates. Future research will hopefully further elucidate the intricate role of extracellular metalloproteinases in neural plasticity. Perhaps extracellular metalloproteinases could serve as a potential target that may be exploited to modulate neural plasticity especially after injury to the CNS or in neurological disease.

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Chondroitin sulfate proteoglycans in the brain matrix regulate neural plasticity.
Extracellular metalloproteinases alter structural and synaptic plasticity.
These changes may be due to substrate cleavage or perhaps direct action on cells.

Figure 1.

Schematic showing disruption of synaptic stability by proteolytic cleavage of lecticans present in perisynaptic extracellular matrix complexes as a hypothetical means to stimulate structural plasticity at synapses. (A) Binding of brevicin as part of the matrix aggregate to membrane associated hyaluronan adjacent to active sites of synapses promotes synaptic stability. Proteolytic cleavage of brevicin, as illustrated in (B), completely dislocates the aggregate resulting in the production of C-terminal and smaller N-terminal fragments of brevicin, and the freeing of tenascin-R from the aggregate. The lack of an intact matrix aggregate is thought to allow for structural neural plasticity. Abbreviations: Ig-like (immunoglobulin-like); HA binding (hyaluronic acid binding domains also known as proteoglycan tandem repeat); GAG attachment (glycosaminoglycan attachment regions where CS chains are covalently bound); CS (chondroitin sulfate); CRP-like (complement regulatory protein like motif).

Figure 2.

Diagram of MMP and ADAMTS domain structures. (A-I) The minimal MMP domain structure includes the signal peptide, the pro-domain, and the catalytic domain with a zinc binding site (MMP-7 and -26). (A-II) Other MMPs also contain a hinge region as well as a hemopexin-like domain (MMP-1, -3, 8, 10, -11, -12, -13, -19, -20, -27, and -28). The gelatinases (MMP-2 and MMP-9) also contain three fibronectin type II domains. (A-III) Several MMP members are membrane bound with a transmembrane domain (MT1-MMP, MT2-MMP, MT3-MMP, and MT5-MMP) and contain a short cytoplasmic tail at the C-terminus. Other members are linked to the membrane via glycosylphosphatidylinositol (GPI) linkage (MT4-MMP and MT6-MMP). (B) The ADAMTS domain structure consists of a signal peptide, pro-domain, catalytic domain with a zinc binding site, a disintegrin-like domain, a thrombospondin type-1 repeat, a cysteine-rich region, and a spacer region. The ADAMTS members differ with respect to additional domains at the C-terminus (including additional thrombospondin type 1 motifs). Shown in this figure is ADAMTS4, which contains no additional C-terminal domains.