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Document Version:
Accepted author manuscript (peer-reviewed)

Citation for published version:
Krishnaswamy, VR, Benbenishty, A, Blinder, P & Sagi, I 2019, 'Demystifying the extracellular matrix and its proteolytic remodeling in the brain: structural and functional insights', *Cellular and Molecular Life Sciences*, vol. 76, no. 16, pp. 3229-3248. https://doi.org/10.1007/s00018-019-03182-6

Total number of authors:
4

Digital Object Identifier (DOI):
10.1007/s00018-019-03182-6

Published In:
Cellular and Molecular Life Sciences

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Cellular and Molecular Life Sciences
https://doi.org/10.1007/s00018-019-03182-6

REVIEW

Demystifying the extracellular matrix and its proteolytic remodeling in the brain: structural and functional insights

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Received: 29 May 2019 / Revised: 29 May 2019 / Accepted: 31 May 2019
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Abstract
The extracellular matrix (ECM) plays diverse roles in several physiological and pathological conditions. In the brain, the ECM is unique both in its composition and in functions. Furthermore, almost all the cells in the central nervous system contribute to different aspects of this intricate structure. Brain ECM, enriched with proteoglycans and other small proteins, aggregate into distinct structures around neurons and oligodendrocytes. These special structures have cardinal functions in the normal functioning of the brain, such as learning, memory, and synapse regulation. In this review, we have compiled the current knowledge about the structure and function of important ECM molecules in the brain and their proteolytic remodeling by matrix metalloproteinases and other enzymes, highlighting the special structures they form. In particular, the proteoglycans in brain ECM, which are essential for several vital functions, are emphasized in detail.

Keywords Brain · Extracellular matrix · Matrix remodeling · Nodes of Ranvier · Perineuronal nets · Proteases · Synapses

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Abbreviations

AMPAR	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AP-1	Activator protein 1
ASD	Autism spectrum disorders
Bral	Brain-specific hyaluronan-binding protein
CAM	Cell adhesion molecule
Cbln	Cerebellin
CNS	Central nervous system
CREB	cAMP-response element-binding
CRP	Complement regulatory protein
CSPG	Chondroitin sulfate proteoglycan
DCC	Deleted in colorectal cancer
ECD	Extracellular domain
ECM	Extracellular matrix
GAG	Glycosaminoglycan
HA	Hyaluronic acid
HAPLN1	Hyaluronan and proteoglycan link protein 1
HAS	Hyaluronan synthase
HSPG	Heparin sulfate proteoglycan
LTD	Long-term depression
LTP	Long-term potentiation
L-VDCC	L-type voltage-dependent Ca^{2+} channels
MMP	Matrix metalloproteinase
NMDAR	*N*-methyl-D-aspartate receptor
Narp	Neuronal activity-regulated pentraxin
NF-186	Neurofascin-186
NGC	Neuroglycan C
NrCAM	Neuron–glia-related cell adhesion molecule
PNN	Perineuronal net
PSI	Phosphacan short isoform
PTR	Proteoglycan tandem repeat
RPTP	Receptor-type protein-tyrosine phosphatase
SGGL	Sulfoglucuronyl glycolipid
SNAP-25	Synaptosomal nerve-associated protein 25
TIMP	Tissue inhibitor of MMPs
TNC	Tenascin-C
TNR	Tenascin-R
tPA	Tissue plasminogen activator

Venkat Raghavan Krishnaswamy and Amit Benbenishty contributed equally.

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Journal : Large 18 | Article No : 3182 | Pages : 20 | MS Code : 3182 | Dispatch : 12-6-2019

Extracellular matrix

The extracellular matrix (ECM) encompasses all the secreted insoluble components that form a three-dimensional structure that scaffolds the cells [1, 2]. The ECM plays a vital role in maintaining the structural integrity of tissues and in transducing cellular communication by mediating signaling pathways. Several cell surface receptors, including integrins, cadherins, selectins, syndecans, and others are known to interact with the ECM molecules, thereby regulating vital processes such as migration, proliferation, and differentiation [3–7]. The ECM is primarily constructed of structural proteins, proteoglycans, glycoproteins, and matricellular proteins [2, 5]. The composition and characteristics of the ECM are constantly being modified during normal development and aging, and under pathological conditions, such as cancer [8–11]. The composition and modifications of the ECM dictate its mechanical properties; consequently, these properties largely control the biophysical, biochemical, and topological properties of different tissues [12–14]. The ECM components are regulated both at the transcriptional and translational levels. However, the most widely studied regulation is executed extracellularly, by different classes of proteolytic enzymes and their inhibitors, which maintain the homeostasis of the ECM deposition and degradation [2, 15]. In the current review, we discuss the composition, modifications, and structures of the ECM in the central nervous system (CNS). We focus on specialized ECM structures in the brain as well as proteolytic enzymes, such as matrix metalloproteinases (MMPs) that regulate the turnover, function, and architecture of the ECM.

Brain extracellular matrix

The ECM was initially referred to as a "ground substance" and was thought to be absent in the CNS [16, 17]. However, consistent efforts of cell and matrix biologists revealed not only the presence of ECM, but also its key role in the development and function of the brain. The total extracellular space, which is filled with interstitial fluid and matrix, is estimated to occupy 20% of the brain's volume [18–20]. The adult brain has a unique ECM composition with almost negligible presence of collagen and other fibrillar ECM proteins, with the exception of the basement membrane and meningeal layers [19]. The ECM of the brain is enriched with non-fibrillar components such as proteoglycans, glycoproteins, small linker proteins, matricellular proteins, and importantly, enzymes that regulate the ECM deposition and degradation. The ECM in the brain can be broadly classified into interstitial ECM and specialized structures around neurons [18–21]. In this review, we discuss the structure and functions of perineuronal nets (PNNs), and the ECM around the nodes of Ranvier and synapses.

Chondroitin sulfate proteoglycans

A large portion of the ECM in the CNS consists of proteoglycans [22]. Proteoglycans are molecules with sugar moieties termed glycosaminoglycans (GAGs), which are covalently attached to core proteins [23, 24]. The most important proteoglycans found in the CNS are chondroitin sulfate proteoglycans (CSPGs), which are mostly secreted, and membrane-bound heparin sulfate proteoglycans (HSPGs) [25, 26]. Owing to their abundance, diversity, and key role in the assembly of special ECM structures in the brain, in this review we focus mainly on CSPGs. Several studies have shown that CSPGs play a crucial role in the development and normal maintenance of the CNS, and regarding abnormalities in their expression, leading to a variety of pathologies [25, 27–31]. Almost all cell types in the developing CNS secrete CSPGs and provide critical cues for neural patterning [32–34]. In the mature brain, CSPGs are the conspicuous components of a specialized structure termed perineuronal nets (PNNs) [19, 35]. CSPGs are composed of a core protein, which is attached to a long linear polysaccharide termed chondroitin sulfate GAG, through three sequential sugars [36]. The polymerization of GAGs to the growing chain is catalyzed by the enzyme chondroitin synthase in the Golgi apparatus; it can result in very large proteoglycans with over 100 repeating GAGs [37]. Chondroitin sulfotransferase enzymes add negatively charged sulfate groups to the sugar molecules at multiple sites, thus affecting the interaction of GAG chains with the positively charged amino acids in the core protein. These post-translational modifications change the interaction dynamics of the proteoglycans with other molecules [38, 39]. The position of the sulfation determines the five different types of CSPGs: CS-A (C4 of GalNAc), CS-C (C6 of GalNAc), CS-D (C6 of GalNAc and C2 of GlcUA), CS-E (C4 and C6 of GalNAc), and CS-B [39]. CS-B, also known as dermatan sulfate proteoglycan (DSPG), results from epimerization of GlcUA to iduronic acid (IdoA) and is classified as a separate molecule [37]. The most common CSPGs in the adult mouse brain are CS-A, CS-C, CS-D, and CS-E. These proteoglycans are distributed non-uniformly within the CNS and their functions vary widely, based on the core protein, its glycation, and the sulfation of the GAGs [40–42]. Specifically, CS-E is abundantly expressed in the cerebral cortex, whereas the cerebellum is enriched with CS-D and a few CS-E subunits [43] (Fig. 1).

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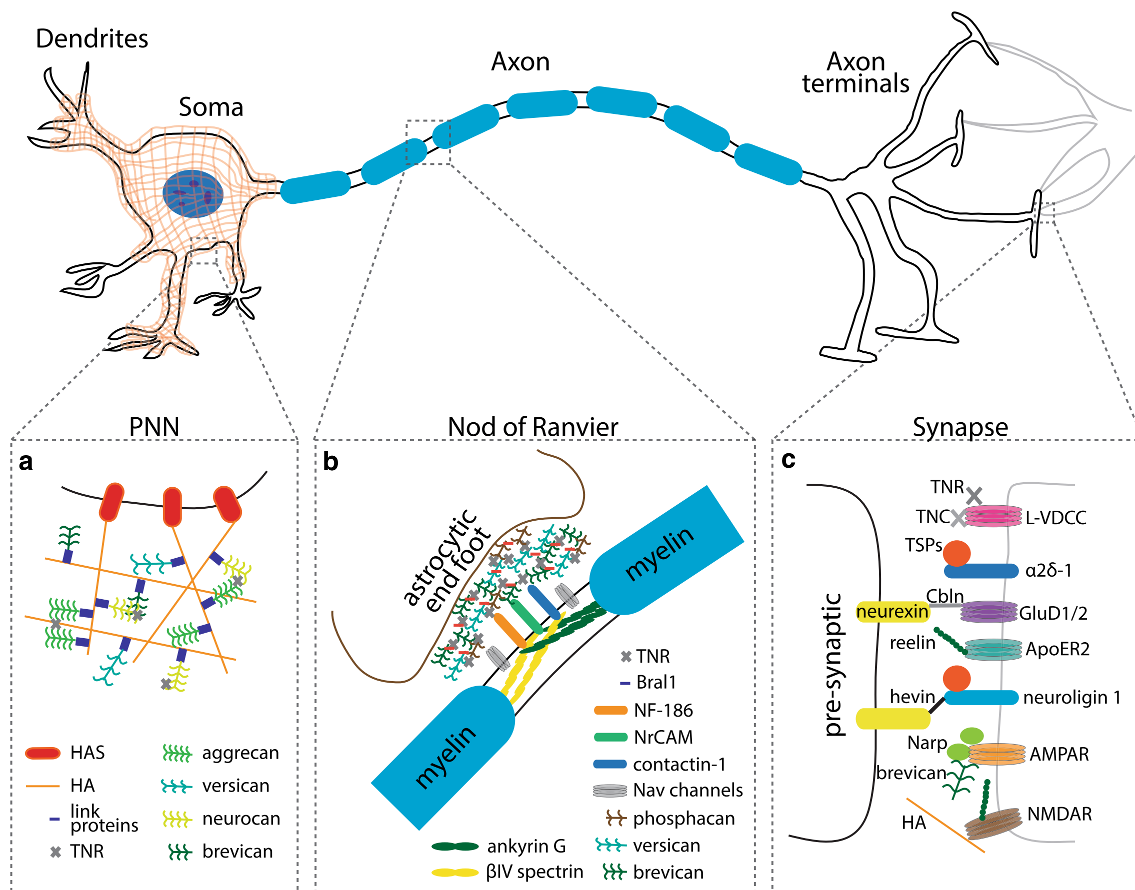

Fig. 1 Diagrammatic sketch of the special ECM structures around the neurons. **a** The perineuronal net (PNN), which enwraps the soma and dendrites, is primarily made up of lecticans (aggrecan, versican, neurocan and brevican) that are bound to the hyaluronic acid (HA) backbone synthesized by the membrane bound enzyme hyaluronic acid synthetase (HAS). Lecticans are connected to HA with link proteins, which are crucial for the structure. Other molecules such as tenascin-R (TNR), which interact with PNN molecules, also play an important role in stabilizing the structure. **b** The gaps between the myelin sheaths, namely, the nods of Ranvier, are exposed to a myriad of ECM molecules through which it can interact with the adjacent astrocytes. These ECM molecules not only stabilize the nodes but also act as a regulator of neuron-glia communication. **c** Different ECM molecules present at pre-synaptic boutons and post-synaptic clefts interact dynamically. These molecular interactions regulate vital processes like synaptogenesis, neuronal migration and cell–cell communications

Lecticans: special CSPGs of the central nervous system

The most important and widely expressed CSPGs in the CNS are aggrecan, versican, neurocan and brevican, collectively termed lecticans [44]. They are also known as hyalectans for their ability to bind to hyaluronic acid (HA; hyaluronan) [45]. Structurally, lecticans can be divided into three segments: a core protein and two globular domains at the N- and C- terminals. The core protein links the N- and C-terminals and has structurally diverse features that serve as anchors for GAG chains to bind. The C-terminal (G3 domain) contains EGF and complement regulatory protein (CRP)-like domains, which flank the c-type lectin domain. On the other side, the N-terminal globular (G1) domain binds to HA and is homologous to other HA-binding proteins like CD44. The N terminal globular domain (G1 domain) consists of two distinct structures, an IgG-like loop, which is less conserved (40% identity) across the lectican family, and a link protein-like tandem repeat (60% identity), also referred to as a proteoglycan tandem repeat (PTR), which has structural similarities to hyaluronan and proteoglycan link proteins (HAPLNs) [46, 47]. Both the IgG-like loop and the PTR domains consist of conserved cysteine amino acids, which are important for the disulfide bonds that bridge the two domains of the N-terminal. Aggrecan, an exception of the lectican members, contains an additional domain in the N-terminal, termed the G2 domain. This domain contains only the PTR structure and is connected to the G1 domain with an interglobular domain of approximately 130 amino acids.

184 The core protein in lecticans varies in length and is the
185 preferred site of glycosylation [44, 47]. The number of GAG
186 attachment sites differs between the lecticans, with aggre-
187 can having the most and brevican the least number of sites.
188 Human aggrecan, in contrast to its rat and mouse counter-
189 parts, contains an additional subdomain downstream of the
190 G2 domain, which acts as a binding region for keratan sul-
191 fate chains. The three subdomains in the G3 domain (EGF,
192 CRP, and c-type lectin) exhibit a structural resemblance to
193 the domain of the cell adhesion molecule, selectin. However,
194 the molecular arrangements between lecticans and selectins
195 differ; therefore, their interactions with other molecules vary
196 [25, 26, 48].

197 Molecular interactions of CSPGs

198 The G1 domain in the N-terminal of aggrecan was shown to
199 interact with HA and cartilage link protein 1 (also known as
200 HAPLN1). The link protein is a 50 kDa glycoprotein crucial
201 for stabilizing the structure between aggrecan and HA [49].
202 Other lectican molecules such as verscian and neurocan were
203 also shown to bind HA [48]. Initially, studies on the C-termi-
204 nal of lecticans showed that lecticans bind to sugar moieties
205 and GAGs without understanding much about their physi-
206 ological significance. However, later studies have shown that
207 they can bind to more prominent and crucial molecules such
208 as tenascin-R (TNR), which is a glycoprotein predominantly
209 present in the CNS [50]. Versican was the first lectican found
210 to bind to TNR [51]. Although most carbohydrate–protein-
211 mediated interactions are calcium dependent, deglycosyla-
212 tion studies revealed that the fibronectin type III domains
213 3–5 of TNR are involved in protein–protein interactions [52].
214 Inspite the common notion that all lecticans bind to TNR,
215 their molecular ultra-structural interactions are not fully
216 understood, with the exception of brevican. Surface plas-
217 mon resonance studies showed that brevican has a tenfold
218 stronger affinity than the other three lecticans [52]. Indeed
219 brevican is found in the brain and interacts with TNR, as
220 indicated by coimmunoprecipitation and immunohistologi-
221 cal studies [52, 53]. Notably, brevican and TNR co-localize
222 around the cell bodies and the proximal dendrites of large
223 neurons. The interaction between brevican and TNR is inter-
224 esting because of their presence in PNN (refer to the section
225 "Perineuronal Nets" for a detailed description of the PNN
226 structure and interactions of its components).

227 Much effort has been invested in identifying the carbo-
228 hydrate ligands of the lectin domain of lecticans. In vitro,
229 versican was shown to bind to heparin and heparin sulfate
230 through its lectin domains, suggesting that HSPGs can be
231 vital physiological partners of versican and other lecticans
232 [54]. However, more studies are required to better compre-
233 hend these interactions. Additionally, it has been recently
234 shown that C-type lectin domains of all four lecticans bind
235 to sulfatides and HNK-1-reactive sulfoglucuronyl glycolipids
236 (SGGLs) [55, 56]. Both of these cell surface glycolipids are
237 abundant in the nervous system. Sulfatides are produced by
238 the axon ensheathing oligodendrocytes, whereas SGGLs are
239 enriched in both the embryonic cerebral cortex and the adult
240 cerebellum [56, 57].

241 Neurocan and its interaction with other ECM mol-
242 ecules are one of the most extensively studied aspects of
243 brain ECM. It has been shown to interact with tenascin-C
244 (TNC), N-CAM, Ng-CAM/L1, Nr-CAM, contactin, TNR,
245 TAG-1/axonin, heparin-binding growth-associated mol-
246 ecule (HBGAM), and amphoterin [58–61]. Rauch and his
247 colleagues showed that all three domains of the neurocan
248 C-terminal, including the EGF repeat, the C-type lectin
249 domain, and the CRP-like domain, bind to the fibronectin
250 domain of TNC [60]. Concurrently, fibrinogen-like domains
251 in TNC interact with the core protein of neurocan [62].

Other CSPGs 252

RPTP-β and phosphacan 253

254 Receptor-type protein-tyrosine phosphatase (RPTP) is a
255 class of enzymes with at least eight sub-families [63, 64].
256 RPTP-β, also known as RPTP-ζ, is a variant expressed solely
257 in the nervous system [65, 66]. It is involved in oligoden-
258 drite survival, recapitulation during demyelinating diseases,
259 and in hippocampal memory formation. It is a membrane
260 glycoprotein with two extracellular domains (ECDs) and
261 two intracellular phosphate domains. The ECDs, a car-
262 bonic anhydrase-like domain and a fibronectin-type III-like
263 domain, are highly variant in their sequences, with some
264 of them sharing homology with cell adhesion molecules
265 (CAMs) [63, 67, 68]. In fact, the sub-families are classi-
266 fied based on the sequence features of the ECDs. Digestion
267 studies on RPTP-β with chondroitinase ABC, an enzyme
268 that digests CSPGs, indicate that the core protein is heavily
269 glycosylated [65]. Phosphacan, one of the products of the
270 alternative splicing of RPTP-β, lacks cytoplasmic domains
271 [69]. In 2003, Garwood et al. found a truncated form of
272 phosphacan that they named phosphacan short isoform
273 (PSI) [70]. PSI is a post-translationally modified protein
274 corresponding to the N-terminal carbonic anhydrase-like
275 and fibronectin type III-like domains and half of the spacer
276 region. Although PSI follows the expression pattern of full-
277 length phosphacan, it is not a proteoglycan [70]. Phospha-
278 can can bind reversibly with a very high affinity to many
279 CAMs (e.g., Ng-CAM/L1, NCAM, and TAG-1/axonin-1)
280 and to TSC [71]. Both RPTP-β and phosphacan play impor-
281 tant roles during embryonic development. Studies on mouse
282 embryos revealed that RPTP-β proteins are expressed on the
283 tangentially aligned neurons in the neocortex, cerebellum,

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and hippocampus. It was also suggested that the expression of RPTP-β proteins by neurons and PSI might modulate neurite outgrowth and synaptogenesis [72–74]. A detailed understanding of these functions in learning and memory consolidation is largely lacking. Additionally, considering their interactions with MMP-9 [75], investigating the role of RPTP-β in remodeling the PNN structures might reveal new functions for these proteins.

Neuroglycan C

Neuroglycan C (NGC), also known as CSPG5, is a transmembrane proteoglycan expressed only in the CNS [76–78]. It has four splice variants: NGC-I to IV with a core protein, the N-terminal domain decorated with chondroitin sulfate (CS) chains, an acidic domain, an EGF domain, a transmembrane segment, and a cytoplasmic domain responsible for the variants [78–81]. NGCs are developmentally regulated and are involved in synaptogenesis and neurite growth [82]. NGCs are present mostly in the cerebellum and retina as a proteoglycan but also in other regions as a protein without the CS chains [79].

Other prominent ECM molecules

Tenascins

The tenascin family in vertebrates comprises five members, which are characterized by typical motifs such as fibronectin type three (FNIII) domains, a cysteine-rich amino acid terminal, followed by EGF repeats, and finally a fibrinogen β-like carboxy terminus [83–85]. Among them, TNC and TNR are very relevant to the CNS [33, 83]. TNC proteins are found in developing mouse and chicken, and were initially termed J1-glycoproteins and contactins, respectively [86–88]. Both neurons and glia cells produce TNC, and it plays a key role in their interactions [89]. TNC domains are known for exhibiting both adhesive and anti-adhesive properties on neurons and other cell types [89]. The fibronectin domain is primarily involved in cell binding and neuronal migration, whereas the EGF repeats are attributed to its repulsive function [87, 89]. TNC forms a hexamer, which can be visualized through rotary shadowing electron microscopy. This highly symmetrical structure, termed hexabranchion, is composed of a central core from which six thin and rigid proximal arms emanate. The eight FNIII domains of TNC contain several alternate splice sites, which allow them to produce different isoforms with subtle structural and functional differences [90, 91]. The main binding partners of TNC are the G3 lectin domain of CSPGs, to which it binds through its fibronectin type III repeats 3–5 [90–92]. Importantly, studies with TNR knock-out (KO) mice proved this association to be essential for proper PNN assembly [93] (more detailed aspects of tenascins with respect to their functions are described in the PNN “functional attributes” section).

Hyaluronan and proteoglycan link proteins

Hyaluronan and proteoglycan link proteins (HAPLNs) are stabilizing proteins that non-covalently link the HA and G1 domains of lectins linking the structures that keep the PNN intact [94, 95]. Out of the four family members, three are found in the CNS: HAPLN1 (Crtl1), HAPLN2 (brain-specific hyaluronan-binding protein 1; Bral1), and HAPLN4 (Bral2) [96]. HAPLN1 and HAPLN4 are specifically present on neurons that bear PNN [97, 98]. They interact with CSPGs and HA in a tripartite complex, forming an exoskeleton framework in the PNN [99]. The PNN assembly around dendrites is strongly attenuated in mice lacking HAPLN1, as observed with wisteria floribunda agglutinin (WFA) staining [100]. Similarly, HAPLN4 reduction in the brain stem and cerebellum impairs PNN formation, along with downregulation of brevican and other PNN components [101–103]. HAPLN2, on the other hand, is produced by oligodendrocytes and is found around the nodes of Ranvier interacting with verscian V2 [104].

Hyaluronic acid

Hyaluronan, or hyaluronic acid (HA), is a GAG produced mostly in neurons by the enzyme hyaluronan synthases (HAS). Because HAS is a membrane-bound enzyme, it makes HA directly in the extracellular space by a process called extrusion [105]. Hitherto, three different isoforms of HAS have been identified, HAS1-3, each producing different lengths of HA at varying rates [106]. Transfection of HEK cells with HAS3 and HAPLN1 indicated that HAS3 alone is enough for synthesis of HA, whereas HAPLN1 is important for condensing the matrix to form a PNN-like structure (discussed in detail in the PNN section) [107]. Owing to the large size of the HA polymer, it can potentially bind to several proteins. In addition, HA can modulate the viscosity of the local ECM by adsorbing more water molecules [94, 108]. However, these important properties of HA and its role in maintaining the PNN morphology have not been investigated.

Perineuronal nets

Perineuronal nets (PNNs) are specialized ECM structures intimately enwrapping the cell body, soma, and dendrites of some neurons [35]. These honeycomb-like structures were first described in 1893 by Camillo Golgi in a nerve

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cell of the anterior horn of the cat spinal cord, and since then they have been identified in many animal species, including humans [35, 94, 109, 110]. The initial methods used to stain PNNs, such as methylene-blue staining, followed by ammonium molybdate fixation, were unreliable [109, 110]. Later, to stain PNNs, researchers started using lectins, which strongly bind to *N*-acetylglucosamine (a GAG), a prominent component in PNN [35, 111]. Initial theories suggested that PNNs consist of only a coagulation of soluble substances in pericellular space [35]. However, subsequent studies found PNNs to be much more complex structures intricately woven, not just by the neurons alone, but also by other cells such as microglia, astrocytes, and oligodendrocytes [112–115]. They are speculated to be involved in vital functions such as learning and memory by altering the neuronal connections [42, 94, 113, 116]. The chief components of PNN are hyaluronic acid, GAGs, lecticans, and link proteins, which connect them. The nets are established around the end of critical periods [42, 117], mainly in the cortex, hippocampus, thalamus, brainstem, and the spinal cord, at varying concentrations, and around different cell types [35, 94, 108]. The microenvironment of the PNN is crucial for its function and is very dynamic, since several ECM modulating enzymes are constantly secreted by the surrounding cells [94, 118, 119]. A great deal of structural diversity is exhibited in the PNN of different brain regions. In one study, Giamanco and his teammates performed a histological analysis on aggrecan KO mice and showed that there is a significant degree of molecular heterogeneity in these PNN molecules due to diversity in the glycosylation of aggrecan [120, 121].

Structural features: HLT model and further developments

In 1996, Ruoslahti proposed a concept in which the PNN is visualized as a supramolecular organization [122]. It was later designated as the "HLT (hyaluronan, lecticans, and TNR)" model by Yamaguchi [48]. This model is based on extensive studies on the recombinant G1 and G3 domains of the lecticans. The results indicated that the G1 domain of lecticans in the N-terminal is important for binding to HA, which in turn, binds to HAPLN, forming a tripartite complex [52, 90, 123]. Interestingly, the G1 domains of lecticans and HAPLN exhibit a high structural homology and share common binding properties, leading to a considerable degree of complexity in forming diverse quaternary structures [123–125]. Crystal structure analysis revealed that the C-type lectin domain of lectican and TNR forms a complex (the binding properties are discussed in the CSPG section) [52, 92]. Further electron microscopy studies on the TNR-aggrecan complex confirmed that the characteristic trimeric structure formed by TNR involves its N-terminal domain [92]. Although these observations are valid and highly useful, it is now apparent that the HLT model is incomplete and has been updated by numerous follow-up studies that unraveled the source, structure, and molecular interactions of the PNN components.

Some of the aforementioned ECM components are an integral part of PNN and are cardinal for its functions. Albeit its structure is not completely understood, the consensus is that lecticans interact with one another and bind to the hyaluronic acid backbone and other PNN molecules with link proteins bridging them. The most impressive aspect of the whole structure is that it can form "holes" in the network, providing a point of contact to the surrounding cells. In other words, PNNs can regulate the accessibility of cells by acting as a physical barrier, thereby controlling the cellular activity. Aggrecan is one of the most important CSPGs in PNN. Immunodetection experiments with WFA on mice lacking aggrecan showed a diminished reactivity to WFA. However, other PNN components are unaffected, indicating that this proteoglycan is necessary for maintaining PNN's overall structural assembly [120].

Another important and the most studied molecule in PNN is HA. This GAG is synthesized by HAS on the membrane and forms the backbone of the whole network, interacting with multiple proteins and proteoglycans [42, 98, 126]. In contrast to most other PNN components, HA and aggrecan secretion are not dependent on glial cells. In fact, PNNs can still form in cultures in the absence of glial cells or glia-derived components, emphasizing the key role of the neuronal-secreted aggrecan and HA as basic units of PNN [112]. The link proteins, especially HAPLN1 and HAPLN4, connect the HA polymer with lecticans. Binding of tensacins to the C-terminal domains of lecticans completes the lattice structure of the PNN.

Functional attributes

Numerous studies have aspired to reveal the roles of PNNs. Most concluded that PNNs are important for the stabilization of synapses [115, 127–129] and have been proposed as the key elements underlying long-term memory consolidation [113]. In line with this notion, a reduction in the distribution of PNNs or individual PNN components was observed in many psychiatric diseases related to mitigated learning, memory, and information processing, including schizophrenia, autism spectrum disorders, Fragile-X syndrome, mood disorders, Alzheimer's, and epilepsy (for a comprehensive review, see [129]). Intriguingly, contrary to these neuropathologies, subjects with Rett syndrome exhibit increased PNN labeling in the motor cortex [130]. A number of findings support the notion that PNNs play a key role in learning, memory, and information processing in health as well as disease.

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First and foremost, PNNs are established towards the end of the critical period, primarily around parvalbumin (PV) interneurons, which are implicated as important mediators of the critical period [131]. In fact, because of their stabilizing effect, PNNs are thought to have a plasticity-impeding function [118, 131–133]. They act as a barrier, blocking the formation of new synapses [134]; as an obstacle, limiting receptor mobility [135]; and as a scaffold, interacting with molecules that can inhibit synaptic formation [136]. Indeed, removal of these structures with chondroitinase ABC restores a critical-period-like phenotype of the neuronal system, allowing remodeling and the formation of new synapses [133]. Thus, the synapse stabilizing role of PNNs seems to have a dual complementary function: preserving the existing synapses while restricting changes. Reduced plasticity is typically regarded as a disadvantageous feature, since it is important for learning [137]. However, the stability of cortical circuits is probably also valuable in maintaining the "erudite" neuronal connection [131]. In general, studies showing that removal of PNNs improves plasticity have focused on the immediate effect during the proximal period, but failed to examine the long-term and wide-range effects. Do individuals with Alzheimer's or autism, and who have a decreased PNN distribution, possess improved learning abilities? Perhaps the extent and chronicity of reduced PNNs and sequential neuronal stability are detrimental.

The stabilizing effect of PNNs led Roger Tsien to argue that they are the best candidates responsible for holding long-term memories [138]. He based his hypothesis on the fact that ECM molecules in the PNN structure may have an exceptionally long protein turnover, as opposed to intrasynaptic proteins, which have a short turnover time (2–5 days) [139]. Importantly, although the turnover may be negligible, it does not indicate that PNNs cannot be rescued when degraded or absent. In fact, 9 days following the injection of the ECM-degrading enzyme hyaluronidase into one of the brain hemispheres of gerbils, PNNs reconstituted in the region, and by day 13, their numbers were comparable to that of the control hemisphere [140]. Furthermore, when embryonic PV neurons were transplanted into the visual cortex of adult mice, PNNs were deposited around them by day 21 following transplantation [141]. These findings imply that PNNs can be restored; hence, they might serve as a therapeutic target under pathological conditions. However, experiments directly linking PNN reconstitution to improved outcome should be conducted. In addition, the mechanism by which PNNs mediate plasticity needs to be better characterized.

In the cortex and hippocampus, two of the most relevant regions when considering learning, memory, and information processing, the majority of PNNs enwrap fast spiking parvalbumin(PV)-expressing interneurons [141–144]. The presence of PNN around PV interneurons was linked to lower excitability and to higher discharge frequency [145]. These "GABAergic" inhibitory neurons regulate the synchronous oscillatory output of pyramidal neuron assemblies [146]. Importantly, these gamma frequency band (30–80 Hz) oscillations were linked to various cognitive processes [146]. It is assumed that this gamma-band synchrony between neurons in higher and lower cortical areas is required for object representation, response selection, attention, and sensorimotor integration [147], as well as for memory [148]. PV cells are also essential for "ripple" oscillations (140–180 Hz) in the hippocampus, which occur during rest following learning phases and are thus associated with memory consolidation. Removal of the hyaluronic backbone of PNNs with hyaluronidase or CSPGs with chondroitinase ABC results in an increase in the frequency of these sharp wave ripples [149], emphasizing the potential role of PNNs in memory and learning. Unfortunately, it is not clear how the PNNs actually affect the activity of each neuron in the context of the neuronal system. To study this, one would have to record in vivo electrophysiological signals or image calcium influxes using Ca^{2+} indicators and differentiate between the cells enwrapped by PNNs and those that are not. However, currently no tools are available for in vivo staining of PNNs.

In addition to their role in modulating synapse formation and stability, PNNs may have an indirect effect on neuronal activity and cognitive function. These dense ECM structures have been shown to protect neurons from oxidative stress [143] and from attacks by activated microglia [150], minimizing the adverse neurological outcome of pathological conditions.

ECM at the synapse

Thrombospondins (TSPs) are a family of five extracellular calcium-binding glycoproteins (TSP1-5) that interact with the neuronal receptors α2δ-1 (Cacna2d1) and neuroligin 1 (NL1) and bind different components of the ECM [151]. These astrocyte-secreted factors are expressed mainly during the early postnatal period, when synapses between dendrites and axons form [152]. Importantly, they were shown to induce synapse formation both in vitro and in vivo [153]. Removal of TSPs from cultures [153], or knocking down endogenous NL1 [154], inhibited TSP1-induced synaptogenesis, whereas the addition of TSP1 and TSP2 to cultured neurons resulted in an increase in the number of synapses [153]. In accordance, TSP1/2 double KO mice have fewer synapses [153]. In line with their proposed role in synaptogenesis, TSPs are upregulated following spinal cord injury [155] and stroke [156, 157], and their inhibition hinders structural plasticity following injury in the cortex [158]. In particular, TSPs induce the formation of ultrastructurally normal synapses, but for activation of the excitatory

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postsynaptic sites, insertion of AMPA receptors (AMPARs) is required [153]. Interestingly, it was recently shown that brevican, a PNN-related protein, which is also secreted by astrocytes, controls interneuron plasticity by regulating the localization of potassium channels and AMPARs [159]. Indeed, brevican-deficient animals display impaired long-term potentiation (LTP) in the hippocampal CA1 region [160]. In another study, neuronal activity-regulated pentraxin (Narp or NP2) was also shown to recruit AMPARs to PV interneurons at excitatory synapses, consequently regulating the excitation/inhibition of homeostasis [161]. Knockout of Narp or its receptor resulted in enhanced epileptic activity and impaired hippocampal-dependent working memory [162]. Notably, Narp accumulation around PV interneurons is significantly enhanced by the existence of PNNs, pointing to an important indirect role of PNNs in maintaining the homeostasis of neuronal activity. In line with this finding, the expression of Narp is reduced in Alzheimer's disease and is correlated with cognitive performance [163].

Bridging the gap between the presynaptic and postsynaptic neurons (i.e., the synaptic cleft) is also important for synaptogenesis and maturation of synapses, and it relies on ECM molecules. For example, hevin (or SC1), an astrocyte-secreted protein, bonds presynaptic neurexins and postsynaptic neuroligins [164]. SPARC, a homolog of hevin, plays a contradictory role, hampering the activity of hevin and synaptogenesis [165]. Cerebellins (Cbln1–4) are another family of trans-synaptic linkers, bridging between neurexins (Cbln1-4) [166] or "deleted in colorectal cancer" (DCC; Cbln4) [167] and the postsynaptic delta-type glutamate (GluD1 and GluD2) receptors. For example, Cbln1 is secreted from presynaptic terminals in granular cells and is essential for stabilizing Purkinje cell synapses in the cerebellum, and loss of Cbln1 results in ataxia and diminished motor learning [168, 169]. In contrast with the cerebellum, the thalamic axons of Cbln1-null mice exhibited an increase in synaptic spine density instead of synapse loss [170]. Mutations in cerebellins or their neurexin receptors have been associated with neurodevelopmental disorders such as ASDs, Tourette, and schizophrenia (reviewed in [171]).

Reelin is a key regulator of neuronal layering and migration in the cortex, hippocampus, and cerebellum during development (reviewed in [172]). Reelin is also secreted by GABAergic interneurons and it surrounds dendritic spines of pyramidal neurons, thereby modulating synaptic signaling pathways and regulating synaptic plasticity and axonal and dendritic outgrowth [172–174]. In accordance, reelin-deficient mice exhibited reduced dendritic branching and lower spine density in vitro and in vivo [175]. Furthermore, factors downstream of reelin [176, 177] and reelin's ApoER2 receptor [178] were shown to regulate spinogenesis and spine morphology. Additionally, reelin also increases LTP [178, 179] by enhancing *N*-methyl-D-aspartate receptor (NMDAR)-mediated Ca^{2+} conductance and phosphorylation of cAMP-response element-binding protein (CREB) [180], and by controlling the maturation of NMDARs [181] and the insertion of AMPARs into synaptic membranes [182]. Importantly, a deficiency involving reelin's receptors results in diminished hippocampus-dependent contextual fear memory [179]. Accordingly, reduced reelin expression has been associated with neurological disorders, including ASD, schizophrenia, Alzheimer's, and with mood disorders such as depression and bipolar disorder (reviewed in [178, 183, 184]).

Tenascins, another important family of ECM molecules, are linked to synaptic plasticity, specifically TNR and TNC, which are predominantly expressed in the CNS [185, 186]. TNR, a major component of the PNN, is necessary for synaptic transmission and plasticity, and consequently for behavior. TNR deficiency in mice did not affect long-term depression (LTD) in the hippocampal CA1 area, but led to impaired LTP and increased basal synaptic transmission at this location, accompanied by anxiety and motor impairments [187–190]. TNR deficiency also resulted in a reduced number of active zones in perisomatic inhibitory synapses in the CA1 pyramidal cell layer, suggesting that TNR may play a crucial role in regulating the architecture of perisomatic inhibitory synapses [191]. In contrast to TNR, TNC is predominantly expressed during development [192]. However, although its levels are significantly decreased thereafter, LTP induces transient TNC expression in the adult brain, suggesting that it plays a role in synaptic plasticity [193]. Indeed, a deficiency in TNC leads to a reduction in L-type voltage-dependent Ca^{2+} channel (L-VDCC)-dependent LTP and abolished LTD in the CA1 region of the hippocampus. Moreover, gamma oscillations increased in TNC-deficient mice in the cortex and in CA1 (but not in other hippocampal regions). These animals also exhibited an impaired extinction of conditioned fear responses, with normal learning and memory in the contextual fear paradigm [194].

While the paramount role of hyaluronic acid as the backbone of PNN is well acknowledged, it was also shown to play a role in synapse maturation and LTP. Synapse stabilization (and reduced plasticity) is partially due to a shift in the NMDARs' (a subtype of the ionotropic glutamate receptors') composition, switching the subunit GluN2B to GluN2A. This shift seems to be mediated by hyaluronic acid, since its removal with hyaluronidase induces an increase in the surface expression of GluN2B in neuronal cultures and acute hippocampal slices [195]. A similar treatment of hippocampal slices also suppressed postsynaptic L-type voltage-dependent calcium channel (L-VDCC)-mediated signals and subsequent LTP, and in vivo removal of HA resulted in impaired contextual fear conditioning [196].

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ECM around the nodes of Ranvier

The nodes of Ranvier are gaps between myelin sheaths enwrapping axons. These gaps are rich in voltage-gated sodium (i.e., Nav) channels, allowing propagation of action potentials. Notably, in these gaps the axons are exposed to the ECM, which plays an important role in the stability of the nodes and, hence their efficacy [197]. The ECM around the nodes of Ranvier is rich in brevican, versican, phosphacan, and TNR [198–200]. Interestingly, in wild-type animals, TNR and phosphacan seem to appear only in large-diameter axons, whereas in brevican-deficient animals they are found in nodes of both small- and large-diameter axons [102]. The specialized ECM complex around the node binds to the cell adhesion molecules neurofascin-186 (NF-186), neuron–glia-related CAM (NrCAM), and contactin-1, which interact with the neuronal cytoskeletal proteins ankyrin G and βIV spectrin at the node, bridging between the node and the perinodal astrocyte processes [200]. In addition, the hyaluronan-binding, brain-specific link protein Bral1 also co-localizes with brevican and versican in the nodal ECM [201], and in a subset of CNS nodes Bral1 localization depends on them [198], whereas in others it seems to be independent of brevican. Mice lacking paranodal junctions and versican, brevican, or Bral1 have fewer NaV channel clusters. Furthermore, animals deficient in paranodal junctions and either versican or brevican have profound motor dysfunction compared to animals lacking only paranodal junctions [198].

The immediate roles of ECM around the nodes of Ranvier regarding plasticity and learning have not been clearly characterized. However, they are important for the propagation of action potentials, resulting in activity, which is key for instigating new synapses and their maintenance, and for controlling their strength [197]. Moreover, recent evidence points to activity-dependent myelination as a central mechanism for plasticity [202]. Hence, the efficiency of the nodes, which is partially dependent on the proximal ECM assembly, is arguably key for learning and memory [202].

Extracellular matrix remodeling enzymes in the brain

Matrix metalloproteinase-9

Matrix metalloproteinases (MMPs) are a large family of zinc-containing endopeptidases with pivotal functions in ECM remodeling. There are at least 25 different MMPs identified so far and they can be subdivided into multiple groups based on their structure and function [203]. MMP-9 belongs to the gelatinase family and is implicated in numerous physiological and pathological processes [204]. It has been shown that MMP-9 protein levels and its proteolytic activity were rapidly increased by stimuli that induce long-lasting LTP [205]. A deficiency in MMP-9, or its pharmacological blockage with broad-spectrum MMP inhibitors, antisense oligonucleotides, or neutralizing antibodies results in altered LTP in the hippocampus (summarized in [206]). Furthermore, multiple studies have shown that the same LTP-inducing stimuli also evoke local MMP-9 release, resulting in dendritic spine enlargement [207–210], whereas specific blocking of MMP-9 in slices prevented late LTP [211]. Similarly, LTP elicited in hippocampal cultures has also been demonstrated to depend on MMP activity and to involve enhanced MMP-9 levels [212–214]. Interestingly, LTP-evoking stimuli in the prefrontal cortex of rats resulted in overexpression of the endogenous tissue inhibitor of MMPs (TIMP)-1, an intrinsic inhibitor of several MMPs, including MMP-9; perhaps acting as a homeostatic modulator [211, 215].

Upregulation of MMP-9 expression in the hippocampus was also found following exposure to the enriched environment paradigm [216]. This paradigm, in which animals are housed in cages with excessive sensory and motor stimuli, is known to increase synaptic plasticity [217]. Induced seizures, however, cause upregulation of TIMP-1 [215, 218, 219] and hippocampal spine loss that is blocked in MMP-9-deficient mice. In line with its role in mediating hippocampal LTP, MMP-9 deficiency was associated with poor memory in contextual fear conditioning and appetitive learning [205, 220–222]. In a different study, spatial learning was found to elevate MMP-3 and MMP-9 levels. Importantly, spatial learning was also found to depend on these MMPs, evidently through their ability to activate NMDA receptors [223].

As in the hippocampus, MMP-9 deficiency also reduced experience-dependent plasticity in the barrel cortex [224]. In contrast, in the visual cortex, non-specific MMP inhibition did not affect homeostatic plasticity; however, it did prevent an increase in dendritic spine density evident one week following monocular deprivation [225]. Emphasizing the location-dependent role of MMP-9 in plasticity, disruption of MMP-9 activity abolished late-phase LTP in the basolateral and central nucleus of the amygdala, but did not affect LTP in the cortical pathway leading to the lateral amygdala [226]. Furthermore, MMP-9 deficiency did not affect amygdala-related tasks, such as discrete cue conditioning or aversive learning [205, 220].

There are also a few indirect indications that MMP-9 mediates plasticity. For example, activator protein 1 (AP-1), a transcription factor associated with plasticity, learning,

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787 and memory, regulates MMP-9 and TIMP-1 [219, 220, 227, 228]. Interestingly, local dendritic translation of MMP-9 mRNA was found to be controlled by the fragile X mental retardation protein, FMRP, which is silenced in subjects with Fragile-X syndrome (FXS) [229, 230]. Indeed, animals with FXS have increased MMP-9 expression, coinciding with longer and thinner spines and abnormal spine turnover, which are normalized by treatment with various MMP-9 inhibitors [207, 231, 232].

Although the molecular chain of events is still vague, a number of mediators downstream of MMP-9 activity have been suggested, including β-dystroglycan, ICAM-5, neuroligin-1, and integrins, especially β1 integrins [205, 233–236]. Another hypothesis regarding how MMP-9 contributes to enhanced plasticity concerns its ability to cleave pro-BDNF to BDNF, a key regulator of synaptic structure and function [237]. Notably, MMP-9 mRNA, protein, and enzymatic activity are present at the dendritic spines of excitatory synapses, whereas they are absent in inhibitory synapses [222, 238–240]. Although MMP-9 has been the main focus of brain metalloproteinase research, MMP-3 is emerging as a key player, since it may act upstream and activate MMP-9 [241]. Unravelling the substrates of MMP-9 in the brain is also important in the context of PNN integrity. For instance, *Fmr-1* KO mice exhibit elevated MMP-9 levels in the brain, and a genetic reduction of MMP-9 expression promotes the formation of PNNs [142]. This finding is intriguing, since it remains unclear how MMP-9 affects PNN formation or degradation, given that none of the PNN elements was shown to be a substrate of MMP-9 [242–244].

A disintegrin and metalloproteinase with thrombospondin motifs

A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) are another family of extracellular matrix remodeling enzymes with multiple domains. ADAMTS-1 and ADAMTS-4, which belong to a subgroup called aggrecanases or proteoglycanases, were found to be upregulated following induced seizures in rats. Their expression leads to proteolysis of brevican, which is associated with a reduction in synaptic density in the dentate gyrus of the hippocampus [245]. Following spinal cord injury, local ADAMTS-4 administration resulted in enhanced axonal regeneration/sprouting, significantly promoting motor function recovery [246]. In vitro, ADAMTS-4 was also found to induce neurite elongation, which can explain the increase in synaptic density [247]. Similarly, the expression of synaptic markers, such as synaptosomal nerve-associated protein 25 (SNAP-25) and post-synaptic density (PSD) -95, was lower in ADAMTS-1 null female mice. Interestingly, this was not the case in male animals, suggesting a sexual dimorphism of ADAMTS-1 involvement in synaptic density. Nonetheless, these alterations in the expression of synaptic proteins were not found to cause deficits in learning and memory; therefore, their significance is unclear [248].

Recently, it was reported that cortical fast-spiking PV interneurons enwrapped in PNN express the metallopeptidases ADAMTS8, ADAMTS15, and Neprilysin [145]. Notably, aggrecan and versican, CSPGs of the PNN, are substrates of ADAMTS-8 and ADAMTS-15. Thus, the expression of these proteases in PNN-enwrapped cells might reflect their involvement in the local regulation of its structure and function [145].

The tissue plasminogen activator

Traditionally referred to as a dissolver of clots, tissue plasminogen activator (tPA), a member of the serine proteinase family, has drawn attention as a possible mediator of neuronal plasticity. It was found to be an important protease associated with various aspects of neuronal plasticity, learning, memory, and emotion [249–251]. In fact, its expression is induced in the hippocampus following various modes of neuronal activation such as seizures, kindling, or LTP [252]. tPA-deficient mice exhibit an impairment in spatial navigation tasks, cerebellar motor learning, fear conditioning, and passive avoidance [250, 253–255]. tPA deficiency concurrently results in reduced LTP [250, 256], and overexpression of tPA, results in elevated LTP [257]. Zhuo et al. [258] found that the lipoprotein receptor-related protein (LRP), a receptor of tPA, is abundantly expressed in hippocampal neurons and is essential for the effects of tPA on hippocampal LTP. Proteolytic mechanisms that mediate plasticity have also been described, such as conversion of pro-BDNF to BDNF by tPA [259], or activation of plasmin, which can cleave ECM components such as fibronectin or laminin [206]. The activity of tPA is spatially and temporally controlled by serine protease inhibitors (i.e., serpins), such as plasminogen activator inhibitor-1 or neuroserpin [206]. Interestingly, transgenic expression of urokinase plasminogen activator in the brain increased the longevity and reduced body weight in mice [260, 261]. However, they performed poorly in the cortex and limbic system-associated learnings [262]. More studies are required to completely delineate this enzyme's potential in not only memory and learning but also in other diseases and afflictions like cancer and obesity.

MMP inhibitors in brain disorders

Multiple studies have corroborated the important and diverse functions of MMPs in the health and pathology of CNS, including in development, vascular integrity and function, neuronal activity, and cancer progression, pointing to MMP inhibitors as a potential "game-changer" in the treatment 885

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modalities [263–265]. Indeed, such inhibitors are studied rigorously in various pathologies, with some promising results. For example, Ro31-9730 and minocycline, non-specific MMP inhibitors, have been shown to neutralize the unwarranted MMP activity and improved outcomes in experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis [266, 267]. In rodent models of stroke, the broad specific inhibitors GM6001 and BB-94 showed encouraging results when given immediately following stroke induction [268, 269]. However, in a different study, prolonged treatment for a week with the MMP inhibitors FN-439 or BB-94 hindered recovery from stroke [270], implying that MMP inhibition can have a contradictory impact on stroke outcome. Hence, a delicate balance between MMP activity and their inhibition must be maintained. Remarkably, the field has revived interest in blocking MMP-9 and MMP-2 in stroke owing to the design of SB-3CT, a thiirane-based gelatinase inhibitor, by Shahriar et al. [271, 272]. Administration of SB-3CT in a mouse model of stroke resulted in protection from brain damage, compared with mice that did not receive the treatment. Inhibition of gelatinases by SB-3CT was also shown to protect neurovasculature from embolic focal cerebral ischemia [273]. Importantly, it was argued that selective MMP inhibitors will benefit only during the acute phase of the injury, suggesting that the timing of the use of the MMP inhibitors in stroke is critical [274].

The use of protease inhibitors, specifically MMP inhibitors, has also been tested in human clinical trials for other pathological conditions. In a study on 60 patients with acute ischemic stroke, a combined treatment of tPA and minocycline was more effective compared with tPA alone [275]. In another study on a small cohort of multiple sclerosis patients ($n = 16$), doxycycline was given together with interferon-β-1a for 4 months, resulting in a better score in the expanded disability status scale (EDSS), with negligible toxicity [276]. However, the study concluded that in spite of the safe and effective therapeutic potential of these molecules, a larger study should be performed. A combinatorial treatment of glioma and recurrent glioblastoma patients with marimastat and temozolomide increased their progression-free survival (PFS) [277, 278]. However, other studies had only discouraging outcomes [279, 280]. Vandenbrouke and Libert summarized several reasons for the failure of the trials. This includes metabolically unstable molecules, poor oral bioavailability, and lack of a complete understanding of MMPs [281].

One of the recent developments in treatments based on MMP inhibitors lies in the field of fragile X syndrome (FXS). FXS has been shown to have elevated serum MMP-9 levels in both humans and mouse models. Numerous studies have shown compelling results supporting the involvement of MMP-9 in this neurodevelopmental disorder. Follow-up studies on MMP-9 inhibition and genetic KO in rodents indicated that they rescued the characteristic phenotypes in the neurons and that the rodents displayed enhanced learning in behavioral tasks. The broad specific antibiotic, minocycline, with its already proven abilities to inhibit MMPs, was tested extensively in mouse models and later in a human clinical study, and showed marked improvements. The study concluded that further long-term studies are required. Very recently, other molecules such as metformin [282], lovastatin, along with minocycline are being clinically investigated on human subjects [283]. Although studies like this are important and encouraging for finding a drug for FXS, the lessons that can be learned from the MMP inhibition-based trials should be prioritized and implemented. MMP biology is highly enigmatic; thus, a higher degree of comprehension is required. More importantly, novel approaches such as use of a highly specific antibody or protein-based inhibitors is essential for producing tangible MMP inhibitors for treating brain disorders [284].

Summary and future perspectives

The field of ECM biology has taken an unprecedented journey from mere speculation of its presence to its undeniably vital role in several brain functions including learning and memory. The ECM in the brain forms unique structures, which perform a plethora of cellular functions. A special class of CSPGs, termed lecticans, dominates both the interstitial ECM and special structures like PNN. Although the composition of PNNs and the importance of each constitutive element to the development of the nets have been characterized in numerous studies [128, 132, 285–287], a number of questions remain open regarding the significance of the structure of the net. How does the density of the net affect its function? Is it important how large the holes of the net are, or the extent to which the net enwraps the dendrites? In addition, it has been shown that differences exist in the molecular composition of the nets between different locations in the CNS [288, 289]. However, the variance within each population is not clear, and the impact of such differences. Although attempts to rescue phenotypes in behavioral disorders like FXS by modulating ECM-regulating proteases are actively being pursued, a complete understanding of the role of ECM in attaining tangible targets for treatment is still a distant goal. Additionally, lack of specific inhibitors to suppress the unwanted protease activity impedes progress in comprehending the disease phenotype, at least in conditions like FXS. A new class of novel inhibitors and specific antibodies for inhibiting MMPs are being developed, and this might pave the way for treating diseases like FXS where the protease levels and activity are unwarranted (Reviewed in [284, 290]). In Toto, the full potential of the brain ECM

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in several physiological and pathological processes remains to be deciphered completely.

Acknowledgements Irit Sagi is an Incumbent of the Maurizio Pontecorvo Professorial Chair and has received funding from the Israeli Science Foundation (1226/13), the European Research Council AdG (THZCALORIMETRY—DLV-695437), and the USA-Israel Binational Science Foundation (712506-01). She is grateful for the Azrieli Foundation for its generous grant to conduct research on the extracellular matrix of the brain.

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Journal : **Large 18**	Article No : **3182**	Pages : **20**	MS Code : **3182**	Dispatch : **12-6-2019**

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