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Interplay between perivascular and perineuronal extracellular matrix remodelling in neurological and psychiatric diseases

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Abstract

Vascular damage, central nervous system (CNS) injury, seizure or even psychological stress may trigger activation of microglia and infiltration of other immune cells, accompanied by high levels of expression and activity of extracellular proteases, such as matrix metalloproteinases (MMPs), and degradation/remodelling of the perivascular and perineuronal extracellular matrix (ECM). This acute response is followed by the recovery/chronic phase, during which the activation of astrocytes leads to the upregulated synthesis of ECM molecules, which, in combination with elevated expression of tissue inhibitor of metalloproteinases (TIMP) proteins, increases the aggregation of ECM molecules. This biphasic dysregulation of local balance between extracellular proteases and the ECM activates multiple temporally overlapping signalling cascades, involving receptor-type protein tyrosine phosphatases, integrins, Toll-like receptors, cell adhesion molecules, and ion channels, resulting in impaired synaptic plasticity and cognition. An additional level of complexity is related to the leakage of blood plasma proteins, such as fibrinogen, and the diffusion of perivascularly overproduced MMPs, TIMPs and ECM molecules into the CNS parenchyma, leading to diverse effects on neurons and incorporation of these molecules into the interstitial neural ECM. This review aims to outline these complex

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common mechanisms in stroke, CNS injury, depression, epilepsy, multiple sclerosis and cerebral small vessel disease and to discuss translational strategies to advance the development of new therapies for these neurological and psychiatric diseases.

KEYWORDS

cerebral small vessel disease, perineuronal extracellular matrix, perivascular extracellular matrix, stroke

1 | INTRODUCTION

The extracellular matrix (ECM) is a non-cellular three-dimensional macromolecular network composed of collagens, proteoglycans/glycosaminoglycans, elastin, fibronectin, laminins and several other glycoproteins (Theocharis, Skandalis, Gialeli, & Karamanos, 2016). Central nervous system (CNS) tissue, which mainly consists of closely apposed neurons and glial cells, also contains a variety of ECM molecules aggregating in the extracellular space, which accounts for 10%–20% of total brain volume (Bonneh-Barkay & Wiley, 2009; Dityatev, Seidenbecher, & Schachner, 2010). These ECM molecules are synthesized by various cell types (for their expression pattern, see Table 1) and released into the extracellular space to build a stable network surrounding neurons and glial cells (Lau, Cua, Keough, Haylock-Jacobs, & Yong, 2013). ECM molecules activate signalling through numerous cell surface receptors, shaping cell migration, proliferation and differentiation (Theocharis et al., 2016). Furthermore, the ECM contributes to brain development, synaptic plasticity, structural stability, synaptogenesis and neural regeneration (Dityatev & Schachner, 2003; Dityatev, Schachner, & Sonderegger, 2010; Song & Dityatev, 2018). In the healthy CNS, the ECM undergoes highly regulated dynamic turnover. In neurological disorders, the ECM is involved in (i) reactions to environmental changes, (ii) regeneration after tissue damage or ischaemia and (iii) neurodegeneration. However, there is still a limited understanding of the complex function of the ECM in neurological and psychiatric diseases. This review thus aims to provide an overview of the overarching features of ECM dysregulation in different CNS diseases. We will focus on the acute and chronic phases of ECM regulation and the complex interplay between the processes that regulate the perineuronal and perivascular ECM in the context of vascular, immunological and neurodegenerative problems in the diseased CNS.

2 | ECM MICROSTRUCTURE AND TURNOVER WITHIN THE HEALTHY CNS

In general, the ECM fills the extracellular space, but its composition is not uniform; three major ECM shapes can

be distinguished: (a) hyaluronic acid/lectican-based perineuronal nets (PNNs), (b) collagen/laminin-based perivascular ECM and (c) "hybrid" interstitial matrix, incorporating lecticans, collagens and laminins in different proportions. Table 1 outlines the expression patterns of perineuronal and perivascular ECM molecules, and Figure 1 illustrates how they interact to create diverse forms of ECM in the CNS.

2.1 | Perineuronal nets

PNNs are made of a highly condensed form of ECM. They are predominantly associated with parvalbumin (PV)-expressing, gamma-aminobutyric acid (GABA)ergic interneurons but are also detected around excitatory pyramidal cells and motoneurons. The mesh-like PNN structure encloses neuronal somata, proximal dendrites and the axonal initial segment. PNNs can be detected in multiple brain regions, including the cerebral cortex, hippocampus, cerebellum and basal ganglia (Brauer, Ha, Bigl, & Bru, 1993; Song & Dityatev, 2018). These matrices are mainly composed of chondroitin sulphate proteoglycans (CSPGs) of the lectican family, which bind to tenascin-R (Tn-R) with their C-terminus. The N-terminal domains are engaged in interaction with hyaluronan (HA), which is stabilized by hyaluronan and proteoglycan link proteins (Hapln1-4). The HA scaffold is synthesized by transmembrane hyaluronan synthases (HAS1-4), which are also required to anchor the ECM to the neuronal surface (Djerbal, Lortat-Jacob, & Kwok, 2017; Rooney & Kumar, 1993). The interactions between these molecules and how they are attached to the neuronal cell surface are demonstrated in Figure 1a. The lectican family contains aggrecan, brevican, neurocan and versican. These molecules and the CSPG phosphacan interact with membrane receptors such as neuronal cell adhesion molecule (NCAM) and receptor protein tyrosine phosphatases (RPTPδ or RPTPσ) (Djerbal et al., 2017), which bind to CSPGs with high affinity and subsequently dephosphorylate tyrosine residues in proteins. This intracellular signalling cascade is accompanied by inhibition of neurite outgrowth and is involved in the regulation of axonal growth, guidance, synaptic plasticity and regeneration after injury. Mature PNNs are able to restrict synaptic plasticity and are associated with the closure of critical periods, when

TABLE 1 Expression pattern of diverse ECM molecules in the human and mouse brains

Colour scale for each gene and each species			100%	80%		50%	25%	10%	5%	1%	0%

Molecule	Gene	Human						Mouse					
		Foetal astrocyte	Mature astrocyte	Neuron	Oligodendrocyte	Microglia	Endothelial cell	Astrocyte	Neuron	OPC	Oligodendrocyte	Microglia	Endothelial cell
Perineuronal ECM													
Hyaluronan synthase	HAS1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.4	0.3	0.1	0.1	0.1
	HAS2	2.5	0.1	0.2	1.6	0.1	0.1	3.2	0.2	3.4	0.1	0.1	0.1
	HAS3	2.5	0.2	0.2	0.7	0.1	0.1	0.2	1.3	0.2	0.1	0.1	0.1
Lecticans	ACAN	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.5	7.3	0.1	0.1	0.1
	BCAN	8.5	14.9	0.9	4.6	0.1	0.4	817.8	47.3	556.0	75.5	12	1.7
	VCAN	55.9	4.9	3.2	28.9	1.4	1.4	30.7	10.1	161.0	1.8	0.2	0.2
	NCAN	45.4	80.7	6.6	3.1	0.2	2.1	280.1	33.3	46.8	2.9	1.5	0.8
	PTPRZ1	259.8	140.5	20.5	131.7	2.0	4.2	1021.1	45.5	416.6	2.7	1.7	0.8
Tenascin-R	TNR	1.0	2.4	1.4	16.4	0.3	1.0	0.7	3.3	111.4	5.0	0.1	0.1
Tenascin-C	TNC	26.6	0.6	0.1	0.2	0.1	0.1	118.2	10.4	0.3	0.1	0.2	0.7
Link proteins	HAPLN1	1.2	0.4	7.6	0.8	0.1	0.1	63.3	11.8	13.3	0.5	0.3	0.5
	HAPLN4	0.7	0.1	0.8	0.1	0.1	0.1	1.4	0.4	1.1	0.5	0.3	0.1
Collagens	COL1A1	0.1	0.1	0.1	0.1	0.1	0.1	0.8	3.1	19.5	0.4	0.4	0.4
	COL1A2	1.5	0.1	0.4	0.1	0.1	2.4	6.4	1.6	34.5	0.5	0.7	2.9
	COL3A1	0.4	0.1	0.2	0.1	0.1	0.4	0.2	0.8	23.4	0.1	0.3	2.4
	COL5A2	0.9	0.3	0.8	0.1	0.1	0.2	2.6	2.1	2.3	0.1	0.1	2.9
	COL5A3	2.7	0.1	0.1	0.1	0.1	0.2	2.4	0.2	2.9	0.1	0.1	1.0
	COL6A1	5.9	1.1	0.3	0.3	0.1	0.5	0.3	6.4	6.1	0.2	0.3	0.2
	COL6A2	1.2	0.1	0.1	0.1	0.1	0.4	0.4	43.4	4.6	5.7	0.3	0.3
	COL19A1	0.1	0.1	0.6	0.2	0.1	0.1	0.1	2.8	1.1	0.1	0.1	0.1
Extracellular proteolytic pathway													
Matrix metalloproteinases	MMP2	1.0	0.3	0.3	1.8	3.3	0.9	0.1	8.0	19.8	3.0	23.7	1.1
	MMP3	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
	MMP9	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.3	0.4	0.1	7.8	0.7
ADAMs	ADAM10	6.8	7.4	9.1	15.6	22.6	6.3	24.9	12.7	31.4	6.5	17.6	104.7
	ADAM17	7.0	4.6	4.4	4.4	20.4	3.0	18.9	2.9	17.5	8.0	18.6	19.4
ADAMTSs	ADAMTS4	0.1	0.1	0.2	3.0	3.8	0.5	0.5	1.1	1.5	61.4	0.4	3.9
	ADAMTS5	0.2	0.1	0.3	0.2	0.1	0.1	2.8	0.5	1.4	0.1	0.1	0.2
Plasminogen activators	PLAT	3.2	0.2	1.0	2.0	0.2	7.0	120.3	13.5	29.5	78.8	0.8	160.9
	PLAU	0.2	0.4	0.1	1.5	28.6	0.5	0.8	0.4	4.8	2.9	213.0	0.8
Tissue inhibitors of metalloproteinases	TIMP1	7.8	4.2	1.3	1.1	3.3	3.7	0.6	0.6	0.3	0.2	0.2	11.4
	TIMP2	17.3	15.6	61.6	27.9	23.6	10.3	21.2	142.2	51	31.9	106.5	2.5
	TIMP3	10.2	54.3	6.9	4.2	0.3	56.9	144.7	7.8	34.6	1.7	0.9	46.4
	TIMP4	0.9	1.1	0.6	0.1	3.5	0.1	48.7	5.2	73.4	7.6	1.8	0.3
Perivascular ECM													
Laminins	LAMA1	5.0	2.4	0.1	0.1	0.1	0.1	0.3	0.4	3.3	0.1	0.1	6.7
	LAMA2	0.3	0.1	0.7	1.3	0.1	4.3	6.9	0.3	1.7	2.5	0.1	1.8
	LAMA4	2.3	2.1	0.5	1.2	0.1	4.3	6.6	0.7	3.7	0.2	0.2	112.4
	LAMA5	0.4	0.1	0.1	0.1	0.1	0.1	7.1	1.2	0.2	0.1	0.2	15.5
	LAMB2	1.25	2.0	0.1	0.1	0.1	2.7	30.1	1.4	2.4	0.5	13.5	54.1
	LAMC1	5.9	4.0	1.6	0.7	0.1	3.0	16.0	2.7	22.2	9.7	2.1	95.2
Collagens	COL4A1	1.3	0.2	0.5	0.1	0.1	1.2	13.3	6.1	30.5	1.6	2.4	413.7
	COL4A2	0.4	0.2	0.1	0.1	0.1	0.5	6.9	5.2	16.4	0.7	2.1	312.6
	COL18A1	0.2	0.1	0.1	0.1	0.1	0.6	0.6	1.0	12.8	0.1	0.2	24.9
Fibronectin	FN1	7.8	2.6	3.2	0.1	1.0	65.2	3.7	1.1	4.4	0.3	1.1	292.6
Perlecan	HSPG2	0.2	0.1	0.1	0.1	0.1	0.1	2.5	1.2	3.1	5.6	0.3	42.9
Agrin	AGRN	0.8	0.2	0.1	0.1	0.1	1.0	115.8	61.5	52.8	8.7	6.8	186.5
Nidogens	NID1	3.4	3.6	0.5	0.2	0.2	4.2	3.9	1.7	7.5	1.2	0.3	116.9
	NID2	0.4	0.1	0.4	0.5	0.1	2.1	7.9	0.9	4.0	0.3	8.3	70.7

The table is divided into perineuronal and perivascular components and molecules involved in the extracellular proteolytic pathway. The presented data were collected using an online mRNA databank (available at http://www.brainrnaseq.org). Numbers represent FPKM (fragments per kilobase of exon model per million reads mapped) values of mRNA. A colour scale for each gene in each species depicts the highest mRNA expression level among all considered cell types in red and the lowest in green. Yellow and orange colour coding represents intermediate expression levels.

Abbreviations: ADAM, a disintegrin and metalloproteinase; ADAMTS, ADAM with thrombospondin motifs; ECM, extracellular matrix; OPC, oligodendrocyte precursor cell.

experience-dependent plasticity is consolidated (Djerbal et al., 2017; Shen et al., 2009). Moreover, PNNs control the cell excitability of PV+ interneurons and the excitatory input to these cells (Dityatev et al., 2007; Hayani, Song, & Dityatev, 2018).

2.2 | Perivascular ECM

Cerebral blood vessels are composed of a luminal monolayer of endothelial cells connected through closely packed tight junctions (TJs) and encircled by pericytes and
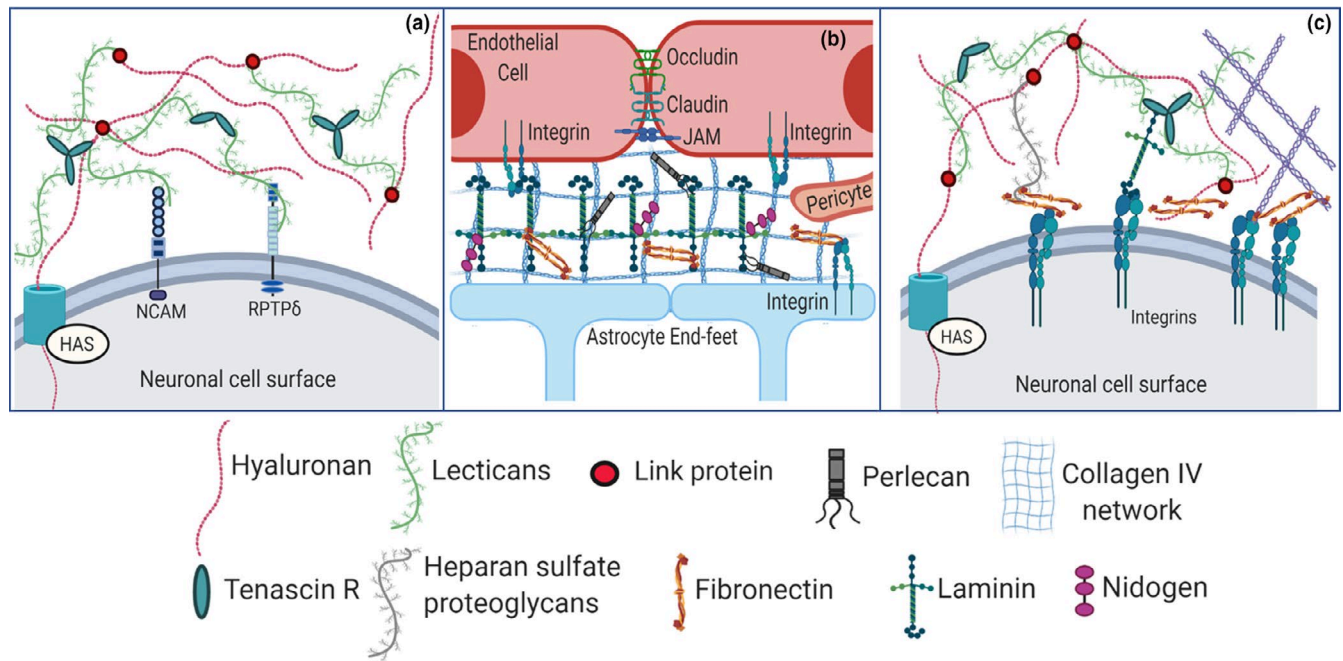
FIGURE 1 Three forms of ECM in the CNS. (a) The structure of a PNN: this dense mesh-like ECM is composed of an HA backbone connected to lecticans and stabilized by tenascins. Lecticans bind to NCAM and RPTPδ and other receptors. (b) The structure of the perivascular ECM in a CNS capillary: laminins and collagen IV form molecular networks that are connected to each other through nidogen, perlecan and fibronectin. The ECM is connected to the surfaces of perivascular cells through integrins. Closely apposed TJ proteins (occludins, claudins or JAM) enable BBB integrity. **(c)** The interstitial "hybrid" matrix: next to HA, PGs and tenascins, smaller amounts of adhesive glycoproteins (e.g. fibronectin, laminin) and collagens enable signal transduction by binding integrins. Abbreviations: HA, hyaluronan; BBB, blood–brain barrier; ECM, extracellular matrix; HAS, hyaluronan synthase; JAM, junctional adhesion molecule; NCAM, neuronal cell adhesion molecule; PG, proteoglycan; PNN, perineuronal net; RPTPδ, receptor protein tyrosine phosphatase δ; TJ, tight junction. The image was created using Biorender graphic software (https://biorender.com)

vascular smooth muscle cells (vSMCs) (Armulik, Abramsson, & Betsholtz, 2005). The outermost part of the vessel wall is embedded in astrocytic endfeet. Here, the perivascular ECM is important for maintaining and supporting the blood–brain barrier (BBB) as a mechanical and chemical barrier.

The perivascular ECM (from luminal to abluminal) consists of (i) the endothelial basement membrane (BM), which also encloses pericytes; (ii) the morphologically distinguishable BM around vSMCs; (iii) the astroglial and pial BM; and (iv) the fibrillar interstitial matrix, connecting the different layers. The astroglial and pial, or parenchymal, BM represents the outer layer of the brain parenchyma and encases arterioles when they penetrate the brain surface. This layer of flat pial cells, astrocytic processes and the ECM they produce is separated from the remaining vessel by a fluid-filled perivascular space, which disappears when the parenchymal arteriole branches into the microvascular capillary network (Wardlaw et al., 2020). Figure 1b shows the ECM microstructure of a CNS capillary. The 20–200 nm thick capillary BM is the merged remnant of the endothelial and parenchymal BM. Its ECM molecules are produced by all surrounding cells, including pericytes, endothelial cells and astroglial cells, but no longer by pial cells (Thomsen,

Routhe, & Moos, 2017; Yousif, Di Russo, & Sorokin, 2013). Laminins and collagen IV, the two main components of vascular BMs, form two three-dimensional networks that are non-covalently interconnected to each other by perlecan and agrin (two heparan sulphate proteoglycans, HSPGs) and nidogen. Interestingly, perlecan is involved in binding diverse growth factors (e.g. basic fibroblast growth factor, transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), heparin-binding epidermal growth factor (HB-EGF) and platelet-derived growth factor beta). The amount of perlecan produced and the cleavage of this product determine the impact of growth factors on ECM synthesis or angiogenesis (Göhring, Sasaki, Heldin, & Timpl, 1998; Thomsen et al., 2017; Whitelock, Melrose, & Iozzo, 2008). Glycoproteins such as fibronectin, fibulin 1 and 2 and secreted protein acidic and rich in cysteine (SPARC) are additional structural proteins of the vascular BM (McKee, Harrison, Capizzi, & Yurchenco, 2007; Thomsen et al., 2017; Yurchenco, 2015). The particular combination of ECM molecules varies between capillaries and pial arterioles. For instance, it was shown that laminin α1 chains or a special form of type IV collagen, composed of two α5 chains and one α6 chain, was associated with pial

cells rather than with capillaries (Joutel, Haddad, Ratelade, & Nelson, 2016).

The perivascular ECM is also different in the circumventricular organs and the choroid plexus, where highly permeable, fenestrated capillaries are needed to either sense signals in the blood and pass the information neurally to other brain regions or perform secretory functions. In these periventricular regions, the BBB is absent at the capillary level, and TJs are displaced from the endothelial cells to the ependymal cells lining the ventricles of the brain. A second, ependymal BM is separated from the capillary BM by a perivascular space. In contrast to the capillary BM, the ependymal BM contains laminin α1 chains and is similar in the collagen IV network in the renal glomerular BM, possibly accomplishing a size-selective filtering function (Jiménez, Domínguez-Pinos, Guerra, Fernández-Llebrez, & Pérez-Fígares, 2014; Urabe et al., 2002). In the subventricular zone of the lateral ventricle, the most neurogenically active zone in adulthood, there are very important ECM structures named fractones because of their fractal shape (Sato et al., 2019). Fractones represent extravascular speckled BMs that are structurally unconnected to the vasculature and differ in their molecular composition from vascular BMs. Fractones contact neural stem cells and contain laminins that interact with integrins on stem cells, along with HSPGs that collect and concentrate the neurogenic growth factor FGF2 to present it to FGF receptors on these cells.

Overall, ECM organization and blood vessel integrity depend on the binding of ECM molecules to cell surface receptors, predominantly of the integrin and dystroglycan families. An in vitro study showed a correlation between the binding of collagen IV to endothelial β1-integrin and the expression of the TJ protein claudin-5, which is related to BBB integrity (Osada et al., 2011). Mice lacking laminin or having missense mutations in one of the collagen IV genes develop brain haemorrhages linked to impaired BBB integrity (Gautam, Zhang, & Yao, 2016; Joutel et al., 2016). Therefore, the exact ECM composition and the amount of a particular ECM molecule have a vital role in BBB organization, and long-term changes caused by increased synthesis or proteolysis can lead to BBB disruption and damage of the surrounding CNS tissue.

2.3 | Interstitial matrix

The interstitial matrix is spread over the remaining extracellular space in the CNS tissue. This matrix can be viewed as a "hybrid" ECM that contains the components of the PNN, that is, an HA backbone combined with CSPGs, Tn-R and link proteins, as well as some quantity of mainly perivascularly expressed adhesive ECM glycoproteins such as laminins, fibronectin and fibrillar proteins such as collagens (Lau et al., 2013). Molecules

that attach preferentially to HA, including the CSPGs and HSPGs, were also shown to bind to collagen, laminin and fibronectin with decreasing affinity (Lasek, 2016; Rooney & Kumar, 1993). Figure 1c illustrates some of the molecular interactions involved. The "hybrid" part of the ECM is particularly interesting in that its composition reflects the activity of neuronal, glial, immune and vascular cells, since all of these cells are involved in the production or proteolytic degradation of ECM molecules (Table 1). It is plausible to assume that ECM molecules enriched in perineuronal and perivascular areas may diffuse out and influence the composition of the hybrid ECM associated with neighbouring synapses, neurons and glial cells. Incorporation of perivascular ECM molecules into the hybrid ECM may be of high functional importance because they may bind to and signal through integrins. For instance, laminin α5 acts through an integrin α3β1-Abl2 kinase-p190RhoGAP signalling cascade and partners with laminin β2 to regulate dendritic spine density and behaviour (Omar et al., 2017). Additionally, the regulation of synaptic plasticity was shown to be impaired in mice lacking integrin-binding fibronectin, laminins and tenascins (Dityatev, 2010; Dityatev & Schachner, 2003; Lasek, 2016; Senkov, Andjus, Radenovic, Soriano, & Dityatev, 2014).

2.4 | ECM turnover

The ECM of the CNS undergoes continuous dynamic turnover, accomplished by a highly regulated system of proteases and their tissue inhibitors. Extracellular proteases in the CNS include the plasmin system, activated by tissue-type (tPA) and urokinase-type plasminogen activators (uPA) (Stevenson, & Lawrence, 2018), more than 20 members of matrix metalloproteinases (MMPs), a disintegrin and metalloproteinase (ADAM) proteins, and ADAMTS (ADAM with thrombospondin motifs) proteins (Bonnans, Chou, & Werb, 2014; Lasek, 2016). As ECM molecules participate in synaptic plasticity and learning, a constant process of neuronal activity/experience-dependent change in the ECM structure is necessary. In particular, the role of MMP-9 in memory and learning has been widely investigated (Dzwonek, Rylski, & Kaczmarek, 2004; Lasek, 2016; Rosenberg, 2017). Additionally, ADAMTS-4 and ADAMTS-5 are highly interesting because they degrade the proteoglycans aggrecan, brevican, neurocan and versican, which are major components of PNNs (Gottschall & Howell, 2015). Furthermore, some of these proteases cleave the extracellular portions of cell surface receptors such as β-dystroglycan (by MMP-9), membrane-binding receptor substrates such as HB-EGF (cleaved by ADAM17) or activate growth factors such as brain-derived growth factor (BDNF) (activated by MMP-3 and MMP-7). Therefore, intracellular signalling cascades can also be regulated (Capone et al., 2016; Dzwonek et al., 2004; Mizoguchi & Yamada, 2013).

This extracellular proteolytic machinery is regulated at the biosynthesis level and by tissue inhibitors of metalloproteinases (TIMP) proteins. There are four homologous members of the TIMP family, which are generally capable of inhibiting all known MMPs; however, their efficiency varies. TIMPs also inhibit ADAMs and ADAMTSs; this inhibition is primarily accomplished by TIMP3 (Arpino, Brock, & Gill, 2015). Activity-dependent changes in local expression and activity of extracellular proteases are necessary to regulate physiological processes, and the long-term balance between proteases and their inhibitors is important for CNS homeostasis. As we discuss below, disruption of this balance drives progression of different CNS disorders and enhances or impairs regeneration and rehabilitation.

3 | BIPHASIC ECM REGULATION IN DIFFERENT CNS DISORDERS

Our current research related to cerebral small vessel disease (CSVD) inspired us to consider the processes controlling ECM regulation in such chronic diseases. Comparing these with time-dependent ECM regulation in other CNS disorders, we noticed several similarities. After vascular damage, hypoxia, CNS trauma, seizure or psychological stress, there is an acute inflammatory response, accompanied by high levels of expression and activity of extracellular proteases (e.g. MMPs, ADAMTSs and tPA), so the ECM is degraded. However, during the recovery/chronic phase, there is an overproduction of ECM, which is typically associated with elevated expression of TIMPs. Figure 2 schematically illustrates the time course of these processes.

In the following sections, we will present molecular details of processes leading to such a change in the ECM in diverse CNS diseases. Here, we start by considering
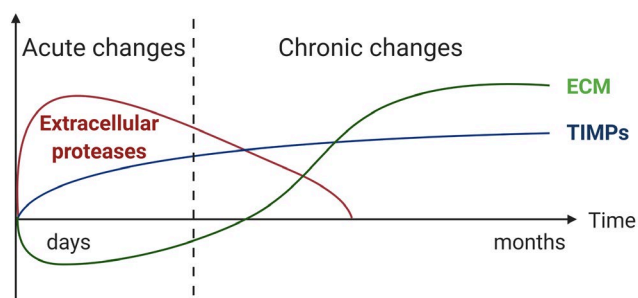

FIGURE 2 Schematic timeline of ECM regulation in different neurological and psychiatric disorders. Acute elevation of extracellular proteases leads to net ECM degradation, whereas a long-term increase in TIMP and ECM expression causes chronic ECM accumulation. Abbreviations: ECM, extracellular matrix; TIMP, tissue inhibitor of metalloproteinases. The graphic was made using *Biorender* graphic software (https://biorender.com)

mechanisms triggered by vascular damage, which includes BBB breakdown or microbleeds in a capillary, as a prime example. During the first 24 hr after damage, microglial cells, the immune cells resident within the CNS parenchyma, are activated and release cytokines and high amounts of proteases, especially MMPs, in a rather diffuse way. The elevation of proteolysis, an attempt to clean up the damaged area by phagocytosis of cell debris and ECM reorganization, nonetheless has the undesired consequence of cleaving TJ proteins, BM proteins and myelin in the surrounding healthy tissue as well. Consequently, axonal signal transfer becomes impaired, vascular wall thinning can be seen, and BBB integrity is lost. Due to the latter, plasma proteins and circulating immune cells pass over into the CNS parenchyma, which further amplifies the inflammatory response. In response to the release of cytokines, for example, by microglial cells, astrocytes become reactive. Only a few days after tissue damage or hypoxia, they start to form a scar to encapsulate the injured parenchyma.

For the following 2–3 weeks, proteases are still upregulated but now participate in a very organized and beneficial way in angiogenesis, axonal sprouting and PNN degradation. This regional ECM degradation is necessary to enable cellular differentiation and migration to form new blood vessels or axon extensions. Revascularization and reorganization of neuronal microcircuits partially compensate for neuronal damage or neuronal death. In parallel, the expression of ECM molecules is upregulated, but ECM proteolysis remains the predominant process at this stage. Only after extracellular proteases return to basal expression levels will net ECM overproduction take place. Therefore, the tissue regains structural integrity, enhanced cell adhesion and changes in neuronal connectivity can be stabilized.

Chronic changes over several months are mainly associated with reactive astrogliosis, during which TIMPs, CSPGs and HA are upregulated within the scar tissue and in areas adjacent to the pathology's origin. At this phase, an increase in the quantity of PNNs and the expression levels of PNN components is observed, which may change cell excitability and synaptic plasticity rules. CSPGs and HA may inhibit oligodendrocyte precursor cell (OPC) differentiation and migration and impair axonal remyelination. Moreover, ECM molecules related to perivascular ECM can be found inside the scar tissue and its surrounding areas in large amounts. Therefore, fibronectin, laminins or collagens also participate in modulating tissue regeneration by increasing integrin receptor binding and signalling.

In different CNS disorders, the long-term balance between ECM proteolysis and synthesis is disrupted. Deviation in each direction affects synaptic plasticity and tissue regeneration both in beneficial and detrimental ways, depending on the involved molecules. In the following sections, we will cover several diseases, highlighting similarities in their ECM

regulations and looking more closely at particular signalling cascades and how they affect regeneration.

4 | ECM DYSREGULATION IN DIFFERENT CNS DISORDERS

In the next paragraphs, we will go through different neurological and psychiatric diseases and cover their ECM regulation in human post-mortem tissue and animal models. Afterwards, we will evaluate the translational potential of these data for clinical research.

4.1 | Stroke

In a stroke, the brain parenchyma has its oxygen and nutrient supply restricted by (i) vessel occlusion or stenosis (ischaemic stroke) or (ii) vessel wall rupture or leakage, related to perivascular haemorrhage (haemorrhagic stroke). In ischaemic and haemorrhagic stroke animal models, the acute release of extracellular proteases is one of the first responses to the restricted blood supply in the brain. Many proteases are involved in this early response, but particular interest has been paid to MMP-2, MMP-3, MMP-7, MMP-9, and some members of the ADAM and ADAMTS families. For the first 48 hr, time courses of multiple protease expression were estimated in different stroke models, which varied but were in line with the hypothesis of acute detrimental proteolysis. The induced cleavage of TJs and almost all perivascular BM proteins leads to BBB breakdown and facilitates the extravasation of immune cells, plasma proteins and blood serum. In particular, the contribution of neutrophils reinforces the proteolytic inflammatory response by releasing cytokines and further ECM-degrading proteases, such as elastase, cathepsin and MMP-9, in particularly high amounts (Hu, De Silva, Chen, & Faraci, 2017). The disrupted BBB and elevated permeability evoke vasogenic oedema formation. The diminished energy and oxygen levels result in the failure of ion pumps, which are no longer able to maintain ion homeostasis. This leads to cellular swelling and intracellular $Na+$ accumulation (cytotoxic oedema), which draws additional fluid into the extracellular space (Michinaga & Koyama, 2015). Subsequently, increasing intracranial pressure impairs further tissue regeneration (Fukuda et al. 2004; Hamann, Okada, Fitridge, & del Zoppo, 1995; Petrovic-Djergovic, Goonewardena, & Pinsky, 2016). It was shown that astrocytes were not able to take up extracellular fluid after laminin–dystroglycan interaction was disrupted by ischaemic proteolysis, putatively through aquaporin 4 water channel disorganization. As a consequence, extracellular fluid clearance by astrocytes is impaired, which exacerbates the effect of subsequent vasogenic oedema but at least attenuates cytotoxic oedema by slowing astrocytic cell

swelling (Hawkins, Gu, Izawa, & Del Zoppo, 2013). MMP and VEGF inhibitors are thought to reduce vasogenic brain oedema due to reduced vascular permeability (Michinaga & Koyama, 2015). In a rat model of middle cerebral artery occlusion, serum levels of TIMP-1 were increased immediately after infarction (Romanic, White, Arleth, Ohlstein, & Barone, 1998; Wang, Barone, White, & Feuerstein, 1998), which was related to decreased stroke severity, especially MMP-9 inhibition (Fang et al., 2015). In an animal model of haemorrhagic stroke, the pharmacological induction of heat shock protein 70, an intracellular protein that is related to neuroprotection and reduced inflammation, decreased MMP9 and uPA expression and attenuated BBB damage and neuronal death in the peri-haemorrhagic area, resulting in an improved functional recovery as well (Manaenko et al., 2010; Sinn et al., 2007). Interestingly, early cleavage of perlecan through elevated cathepsin B and L generates protein fragments of domain V. This domain was proposed to play a protective role in clinical outcomes probably through integrin-mediated VEGF upregulation in endothelial cells, leading to enhanced angiogenesis and neuroprotective properties (Lee et al., 2011; Thomsen et al., 2017). Therefore, acute proteolysis could act in a beneficial way as well, although the harmful consequences are likely to dominate.

Depending on the duration of acute ischaemia, the downstream BBB of the capillary bed is progressively disrupted and can lead to extravasation of blood, called haemorrhagic transformation. In cases of permanently occluded vessels, proteolysis is not limited to the ischaemic core, which is why haemorrhagic transformation may occur in the still-perfused collateral vasculature of the peri-infarct region as well (Álvarez-Sabín, Maisterra, Santamarina, & Kase, 2013). Arterial recanalization and subsequent reperfusion have extensively demonstrated their ability to restore brain function when performed shortly after acute ischaemic stroke. Unfortunately, in some cases, sudden reperfusion can lead to haemorrhagic transformation and extensive brain oedema when the BBB is already heavily disrupted and thus boosts damage to the ischaemic core (Molina, 2011). In particular, recombinant tPA thrombolytic treatment is accompanied by an increased risk of haemorrhagic transformation, as tPA itself acts as a proteolytic enzyme and additionally activates MMP9 (Kelly, Shuaib, & Todd, 2006; Zhang, Yang, Sun, & Xing, 2014).

In vitro cytokines, especially TNF-α and IL1, which are released by inflammatory cells such as microglia or neutrophils during the acute phase, activate astrocytes (Liddelow et al., 2017). The astrocytes develop a dense net of membrane extensions, which fills the empty space generated by dead neurons, and start to secrete ECM molecules to encapsulate ischaemic infarct cores and haemorrhagic lesions. This scar formation contains perineuronal and perivascular ECM (Jones, Margolis, & Tuszynski, 2003; Sukumari-Ramesh,

Alleyne, & Dhandapani, 2012; Wang, Song, et al., 2018; Zbesko et al., 2018). It acts as a dense physical and chemical barrier, protecting the remaining brain from neurotoxic properties of the undergoing, liquefied tissue(Zbesko et al., 2018).

Carmichael and colleagues performed an extensive gene and ECM analysis in both permanently occluded and reperfused brain areas in rats at different time points, which makes it possible to obtain a clear picture of the pathological cascade in a temporal and spatial manner. They showed two differently regulated regions: from day three, there was a dense, CSPG-rich scar immediately adjacent to the infarct side, accompanied by many striking PNNs and partial neuronal death. In contrast, broad peri-infarct regions displayed an early loss of PNNs. These findings were confirmed in a photothrombosis model in rats (Quattromani et al., 2018). Regarding the recovery stage, proteases seem to participate in a beneficial way. Neuroprotective effects of ADAM17 and ADAMTSs have been reported even for early stages after ischaemia (Fan et al., 2016; Hurtado et al., 2002; Zhao et al., 2009).

ADAMTS-4 was found to increase shortly after ischaemia in the transient middle cerebral artery occlusion stroke model and was suggested to be particularly involved in PNN degradation to enable neuronal plasticity (Haddock et al., 2007). Furthermore, MMPs, especially MMP-2 and MMP-9, increase the availability of growth factors such as nerve growth factor, VEGF or BDNF by ECM cleavage and are involved in neural progenitor cell migration in vitro (Wang et al., 2006). In addition to both proteases, MMP-7 participates in angiogenesis to resupply, particularly the penumbra region, with blood and nutrients. This extracellular proteolysis goes together with an upregulation of intracellular growth-promoting genes to enable axonal sprouting, synaptogenesis, increased synaptic plasticity and revascularization (Carmichael et al., 2005; Nagy et al., 2006; Rosell et al., 2008; Zhao et al., 2006). This phase lasts up to three weeks and appears to be a very organized part of regeneration.

In parallel to proteolytic neuronal reorganization, mRNA analysis of CSPGs in the peri-infarct areas revealed an early, slowly increasing expression of brevican, versican and phosphacan, peaking after four weeks. However, aggrecan expression remained at a low, unchanged level and neurocan returned to normal expression after three weeks (Carmichael et al., 2005). Human post-mortem tissue shows a similar expression timeline for HA in the infarct core and in the peri-infarct areas until 37 days after stroke(Al'Qteishat et al., 2006). This chronic upregulation of PNN-associated molecules might represent the closure of the sensitive period for neuronal reorganizing and thus inhibit further changes in neuronal connectivity. Future studies should investigate the chronic regulation of perivascular ECM and whether BM thickening can be seen in long-term post-stroke observations, as is expected from the model presented in Figure 2 and 3.

4.2 | CNS injury

Both stroke and CNS injury models are favourable for analysing ECM regulation in time and space because of the knowledge of their pathological origin. Following CNS injury, the same biphasic ECM modulation has been found as described for stroke models: the repair of post-traumatic tissue damage involves (i) an initial inflammatory response, (ii) wound healing and (iii) long-term scar formation to encapsulate the injury (Scholtes, Brook, & Martin, 2012; Wang et al., 2000). In human spinal cord injuries (SCIs), MMP levels start to increase after two days and are predominantly associated with the accumulation of microglia/macrophages in the lesion epicentre. Inflammatory cells, including ramified microglia and neutrophils, are most numerous at days 1–3 but are also occasionally visible after several weeks (Buss et al., 2007; Fleming et al., 2006). In mouse models of SCI, the blockage of MMPs during the first three days is neuroprotective and promotes functional recovery (Noble, Donovan, Igarashi, Goussev, & Werb, 2002), whereas increased MMP-9 levels during the first 24 hr correlate with injury severity.

TIMPs seem to be involved in chronic scar formation and are beneficial in the first hours after injury by inhibiting diffuse proteolytic damage. TIMP-1 is upregulated in reactive A1 astrocytes (Liddelow et al., 2017). In rats that suffered from surgically induced SCI, chronic upregulation of the TIMP-1 gene within and below the injury could be recognized (Sandhir, Gregory, He, & Berman, 2011). Human post-mortem spinal cords showed TIMP-3 upregulation in perilesional reactive astrocytes eight months and one year after lesion (Buss et al., 2007). In TIMP-1-overexpressing transgenic mice, the activity of MMP-9 was reduced, which resulted in diminished brain lesion volume and BBB leakage in models of cerebral ischaemia and brain trauma (Tejima et al., 2009).

The chronic upregulation of ECM molecules, including CSPGs and tenascins, has been reported for up to eight weeks after SCI (Jones et al., 2003). Interestingly, the re-expression of tenascin-C (Tn-C) was found to contribute to axonal growth and guidance regulation and to enhance regeneration, in contrast to the regeneration-restricting effects of Tn-R and CSPGs as major components of glial scars (Faissner, 1997). Additionally, perivascular ECM molecules are incorporated and strengthen the scar tissue (Hirano et al., 2004; Liesi & Kauppila, 2002; Mckeon, Höke, & Silver, 1995; Roll & Faissner, 2014).

Another important factor after traumatic brain injury is fibrinogen, a blood plasma protein, which leaks into the CNS parenchyma because several blood vessels tear during the injury. It is converted into fibrin clots, which are usually degraded by the tPA/plasmin system. However, diverse epitopes are able to interact with CNS cells and affect their downstream signalling. Fibrin is proinflammatory, leads to
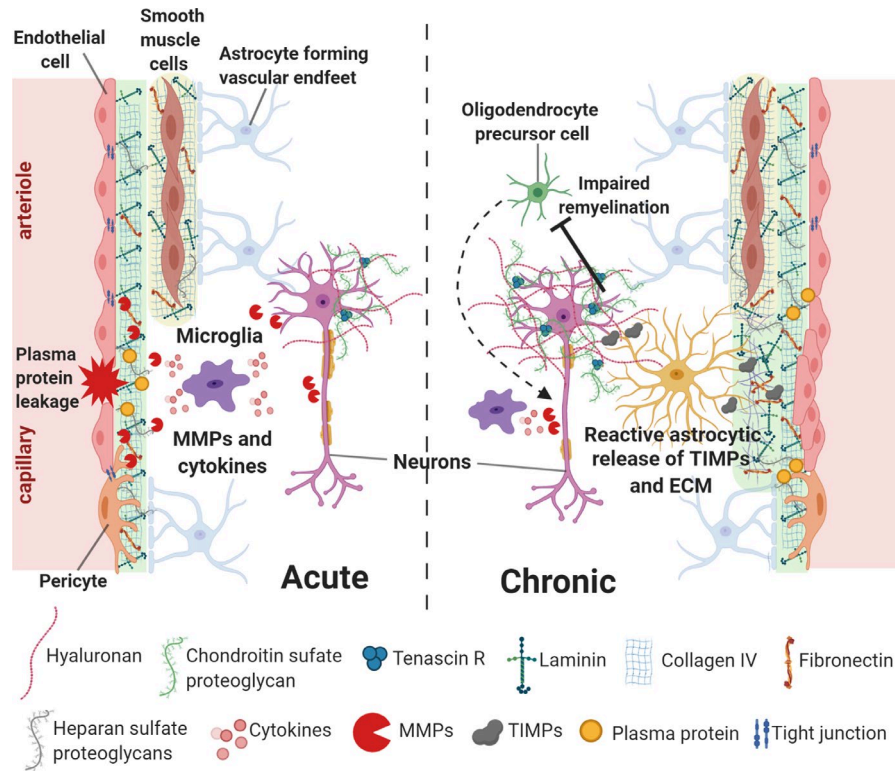
FIGURE 3 Schematic presentation of biphasic ECM regulation following vascular damage. After a vascular damage event, plasma proteins, such as fibrinogen and circulating immune cells (not shown here), leak into the CNS parenchyma and activate an initial inflammatory response. Amoeboid microglial cells phagocytize cell debris and release cytokines and extracellular proteases, which degrade perivascular ECM (BM and TJ), perineuronal ECM (PNNs) and myelin. BBB opening and myelin degradation further restrict tissue repair, whereas PNN degradation can enable developmental forms of structural plasticity to compensate for partial neuronal death and loss of neuronal connections. In the chronic period, reactive astrocytes synthesize high amounts of ECM molecules and upregulate TIMP expression, leading to net perivascular and perineuronal ECM overproduction and to the appearance of more frequent and prominent PNNs. Microglial cells are still active and degrade myelin. Inhibition of OPC differentiation and migration by ECM overproduction leads to long-lasting demyelination and impairs functional recovery. Abbreviations: CNS, central nervous system; BBB, blood–brain barrier; BM, basement membrane; ECM, extracellular matrix; MMP, matrix metalloproteinase; OPC, oligodendrocyte precursor cell; PNN, perineuronal net; TIMP, tissue inhibitor of metalloproteinases; TJ, tight junction. The graphic was made using *Biorender* graphic software (https://biorender.com)

endothelial cell contraction, accompanied by increased BBB permeability and inhibits neurite outgrowth by binding integrin receptors (Petersen, Ryu, & Akassoglou, 2018; Schachtrup et al., 2010). Moreover, fibrinogen carries latent TGF-β that can be converted to its active form to promote astrogliosis and scar formation (Asher et al., 2000; Kim et al., 2017; Schachtrup et al., 2010). These initial signalling cascades, caused by extravasation of fibrinogen, can be common to other neurological diseases accompanied by BBB breakdown and plasma protein leakage as well, including multiple sclerosis (MS), stroke, Alzheimer's disease (AD) or CSVD.

In addition to immune cells and astrocytes, pericytes appear to be important players in restricting tissue damage in an SCI animal model. After five days, when angiogenesis starts, type A pericytes were found penetrating the BM to massively invade the surrounding tissue. They produced high amounts of fibronectin. Only the border of the lesion was associated with GFAP + astrocytes, forming the outer scar. By genetically deleting the ras-genes in pericytes, which are important

for cell cycle progression and mitosis, one-third of injured animals failed to close the lesion (Göritz et al., 2011).

To conclude, CNS injuries show a rather similar pattern of ECM regulation as found in stroke and provide additional insights into several signalling cascades whose contributions need to be evaluated in other neurological diseases.

4.3 | Depression

Late-life depression increases the risk of developing AD, vascular dementia (VaD) and unspecified dementia; however, the underlying mechanisms are still unknown (Diniz, Butters, Albert, Dew, & Reynolds, 2013; Iadecola et al., 2019). However, recent data suggest the importance of ECM remodelling in depression. Koskinen, van Mourik, Smit, Spijker, and Riga (2019) investigated the role of ECM changes in a rat model of depression induced by social defeat stress. Two days after stress induction, rats performed worse in an object

recognition test, which measures spatial memory, compared to controls. After three days, they showed fewer PNNs around PV + neurons in the CA1 region of the hippocampus and lower protein levels of PNN components (Koskinen et al., 2019).

Analysis of chronic changes (two months after stress) revealed increased PNN numbers in the CA1 region of the hippocampus and highly upregulated protein levels of lecticans, Tn-R and the link protein Hapln1 (Riga et al., 2017). Additionally, the activity of MMP-2 was downregulated. These chronic molecular alterations were accompanied by impaired spatial memory and gradually emerging affective deficits. The latter raises the question of whether stress affects further brain regions or whether hippocampal ECM changes influence affective behaviour as well. Interestingly, both phases were separated by a period of normal hippocampal function, similar PNN numbers and similar protein concentrations of perineuronal molecules (Koskinen et al., 2019). According to these results, biphasic hippocampal ECM changes may be involved in stress processing and might be able to explain depressive behaviour and cognitive impairment after stressful periods of life. The number of PNNs was also increased in the medial prefrontal cortex (mPFC), habenula and thalamic reticular nucleus 10 days after chronic restraint stress (Pesarico et al., 2019). Further studies are warranted to investigate the expression/activity of extracellular proteases and TIMPs during acute and chronic phases of depression.

4.4 | Epilepsy

Epileptic seizures, for instance, induced in animal models by pilocarpine, pentylenetetrazole (PTZ) or kainic acid, upregulate the expression and activity of extracellular proteases, such as tPA and MMP-9 (Konopacki et al., 2007; Takács et al., 2010). Because elevated MMP-9 levels are associated with neuronal death, aberrant synaptic plasticity, sprouting of mossy fibres within the hippocampus, neuroinflammation, degradation of PNNs, impaired expression of TJ proteins and BBB alterations during epileptogenesis, MMP-9 is a strong candidate to have an impact on the formation of a new epileptic focus and could be a potential therapeutic target in epilepsy (Acar, Tanriover, Acar, & Demir, 2015; Dityatev, 2010; Lukasiuk, Wilczynski, & Kaczmarek, 2011; Mizoguchi & Yamada, 2013). To restrain MMP-9 activity, there is rapid upregulation of TIMP-1 mRNA and protein in hippocampal neurons and astrocytes following seizures (Rivera et al., 1997), but apparently, it is not sufficient. Our recent study demonstrates that pharmacological inhibition of MMP-2/9 with IPR-179 during the first week after induction of seizures by kainic acid persistently reduces the frequency of seizures for the following 6 weeks (Broekaart et al., 2019).

Seizures have been shown to upregulate the expression of multiple ECM molecules, including Tn-R, Tn-C, neuronal pentraxin NP2, hyaluronan and hevin (perisynaptically), and to downregulate the expression of phosphacan, reelin and hevin (somatically) (Dityatev, 2010). One theory of why seizures occur is an imbalance between excitation and inhibition. Following *status epilepticus,* there is persistently abnormal inhibition due to altered GABA receptor subunit expression (Zhang, Wei, Mody, & Houser, 2007). Based on the role of the PNN in synaptic stability and its location around GABAergic interneurons, disruption of this form of ECM may contribute to the progression of epilepsy (McRae & Porter, 2012). A majority of cortical GABAergic neurons implicated in seizure disorders are parvalbumin-expressing fast-spiking (100–800 Hz) interneurons (PV + FSNs) comprising 40%–50% of all GABAergic neurons, which are specialized in generating robust feed-forward inhibition (Deepa et al., 2006; Jiang, Lachance, & Rossignol, 2016; Rudy, Fishell, Lee, & Hjerling-Leffler, 2011). Approximately 80% of PV + FSNs are surrounded by PNNs. Upregulation of MMPs in the pilocarpine model leads to proteolytic degradation of PNN components, such as aggrecan, HA and proteoglycan link protein 1 (HAPLN1) and HAS3 (McRae, Baranov, Rogers, & Porter, 2012). Ihara's epileptic rats exhibit a decrease in neurocan expression at 2–3 weeks of age compared to Sprague Dawley rats, followed by a reappearance of hippocampal neurocan at 8 months. In spontaneously epileptic mice deficient in bassoon, a complex pattern of ECM changes has been found, with a reduction in brevican being the most prominently correlated with the severity of seizures (Blondiaux et al., 2019).

Degrading PNNs using chondroitinase ABC decreases, the threshold for PTZ-induced myoclonic seizures (Rankin-Gee et al., 2015). Additionally, HA deficiency in HAS3 knockout mice causes seizures, and some evidence suggests that this is due to changes in osmolarity (Arranz et al., 2014). Also, enzymatic digestion of HA with hyaluronidase leads to epileptiform activity in vitro (Vedunova et al., 2013). Moreover, depletion of brain HA has been shown to generate spontaneous seizures in cats (Young, 1963) and audiogenic seizures in neonatal mice (Balashova et al., 2019). Increased expression of integrins has been reported both in animal models of epilepsy and in human epilepsy (Wu et al., 2011). In nidogen-1 knockout mice, 30% develop severe seizure-like events. Although BM formation seems to be morphologically normal, decreased expression of laminins was found in the neuronal interstitial matrix, and a loss of interactions with integrins could lead to higher neuronal excitability (Dityatev, 2010; Vasudevan et al., 2010).

Another important signalling pathway involving ECM molecules and the interplay between vascular, immune and neural cell types is through Toll-like receptors (TLR1-4), which recognize multiple endogenous ligands released as

cellular or tissue danger/damage signals (alarmins) (Seong & Matzinger, 2004). Among these proteins are fibrinogen, heat shock proteins 60–70 (HSP60-70), high-mobility-group box protein 1 (HGMB-1), HA fragments and versican (Piccinini & Midwood, 2010). The rapid release of HMGB1 and activation of TLR4 signalling in astrocytes and neurons has been identified as a crucial event for initiating brain inflammation and decreasing the seizure threshold. Excitingly, pharmacological targeting of IL-1R1/TLR4 signalling resulted in a 50%–70% reduction in seizure recurrence (Weinberg, Blake, & McCown, 2013). The anticonvulsant effects of inhibitors of IL-1R/TLR signalling in various seizure models suggest that this system could be targeted to inhibit seizures in presently pharmacoresistant epilepsies (Vezzani, Maroso, Balosso, Sanchez, & Bartfai, 2011).

4.5 | Multiple sclerosis

Multiple sclerosis is characterized by chronic and progressive loss of myelin sheaths surrounding the axons in the brain and spinal cord. Demyelination and failure to remyelinate contribute to the neurological deficits associated with chronic progressive MS.

Importantly, ECM molecules and extracellular proteases are involved in guiding each stage of the (re)myelination process, such as OPC migration, proliferation and maturation (de Jong, Wang, Oomkens, & Baron, 2020). Immunohistochemistry and in situ hybridization have shown that several fibronectin-degrading MMPs, including MMP-3, MMP-7 and MMP-9, are upregulated in demyelinating lesions (Maeda & Sobel, 1996). MMP-3 and MMP-7 are potent proteases that degrade the interstitial ECM that is present in MS lesions. These proteins are potentially able to reintroduce a permissive environment for remyelination and improve the neuropathological conditions in MS; both MMP-3 and MMP-7 are upregulated at remyelination following demyelination in experimental rodent models (Wang, Gorter, et al., 2018). MMP-3 degrades CSPGs, aggrecan, versican, neurocan and phosphacan, while MMP-7 cleaves aggrecan (Muir et al., 2002).

Experimental autoimmune encephalomyelitis (EAE) is the most commonly used experimental animal model of MS and shares many key pathological characteristics with the human disease, such as neuroinflammation, demyelination and neuronal damage (Duffy, Lees, & Moalem-Taylor, 2014). Theiler's murine encephalomyelitis (TME) is another well-established virus-induced animal model for studying the pathogenesis of progressive MS (Dal Canto, Kim, Miller, & Melvold, 1996anto, Kim, Miller, & Melvold, 1996). An (early) upregulation of MMP-3 is observed in the inflammatory TME model (Hansmann et al., 2012) and in EAE (Weaver et al., 2005). Additionally, previous studies have

shown the protective role of MMP-12 in EAE, and they have demonstrated an upregulation of MMP-12 by microglia/macrophages in EAE and TME (Hansmann et al., 2012; Ulrich et al., 2006). Indeed, a recent study demonstrated that MMP-2 mRNA expression is only slightly upregulated in EAE (Weaver et al., 2005) and TME (Ulrich, Seeliger, Kreutzer, Germann, & Baumgärtner, 2008). MMP-9 mRNA expression is upregulated in an EAE model (Weaver et al., 2005) but not in the TME model (Ulrich et al., 2008). It is possible that MMP-9 is important for the infiltration of inflammatory cells into the CNS. Thus, the level of MMP-9 is significantly increased in the cerebrospinal fluid (CSF) and serum of MS patients in the acute phase of disease compared to healthy individuals (Bar-Or et al., 2003; Benešová et al., 2009; Ulrich et al., 2008; Weaver et al., 2005). In contrast, inhibiting MMP activity reduced the clinical symptoms in an EAE model by reducing BBB breakdown and demyelinating pathology (Gijbels, Galardy, & Steinman, 1994). Accordingly, PNNs are lost around neurons in demyelinated cortical areas, and many of the neurons appear to be compromised, as indicated by the accumulation of phosphorylated neurofilament protein in their cell bodies (Gray, Thomas, Betmouni, Scolding, & Love, 2008). However, aggrecan, neurocan and versican and high-molecular-weight hyaluronan are deposited at the border of active demyelinating lesions (Back et al., 2005). Additionally, the CSPG proteins neurocan, aggrecan, brevican and versican V1 are increased at the peak of clinical EAE severity, whereas the expression of versican V2 is reduced (Pu, Stephenson, & Yong, 2018; Sajad, Zargan, Chawla, Umar, & Khan, 2011). Keough and colleagues suggested that in an animal model of EAE, prevention of CSPG deposition into the lesion microenvironment may be a useful strategy to promote repair in MS and other neurological disorders (Keough et al., 2016). However, previous studies have shown that demyelination in experimental models leads to the upregulation of CSPGs, which may have beneficial functions at early stages of recovery by preventing premature OPC differentiation (de Jong et al., 2020). In the TME, ECM alterations correlate with the development of astrogliosis and include intralesional deposition of laminin, tenascin-C, neurocan and fibronectin, while phosphacan expression decreases and aggrecan expression remains similar (Haist, Ulrich, Kalkuhl, Deschl, & Baumgärtner, 2012). In the acute phase of demyelination, extracellular proteases degrade myelin, PNNs and perivascular ECM (Lau et al., 2013). Discontinuous BMs around cerebral blood vessels facilitate infiltration of circulating immune cells and even reinforce inflammatory responses (van Horssen, Bö, Dijkstra, & de Vries, 2006). Importantly, lesion areas and especially their edges are associated with the upregulation of CSPGs and high-molecular HA. This interstitial ECM upregulation might be related to chronic activation of astrocytes, which is initiated by cytokines released from inflammatory cells, to form a barrier that protects the remaining tissue, as described in stroke and SCI. Recently, atomic force

microscopy was employed to perform micro-indentation measurements of demyelinated tissue at the cellular scale. Analysis of mouse and human demyelinated brains indicates that acute demyelination results in decreased tissue stiffness that recovers with remyelination, while chronic demyelination is characterized by increased tissue stiffness, which correlates with augmented ECM deposition (Urbanski, Brendel, & Melendez-Vasquez, 2019). ECM was found to inhibit OPC migration into the lesion and their differentiation into mature oligodendrocytes and thereby impair remyelination (Kippert, Fitzner, Helenius, & Simons, 2009). Membrane spreading of already mature oligodendrocytes was shown to be impaired in the CSPG-rich environment. In mouse models of demyelination, the clearance of CSPG within active lesions was correlated with remyelination (Lau et al., 2013). Extracellular proteases are involved in remyelination by degrading myelin debris or enabling the generation of oligodendrocytes. Such findings could also be transferred to other CNS disorders accompanied by demyelination, including AD or CSVD. One might assume that chronic upregulation of perineuronal ECM in those diseases impairs remyelination as well by inhibiting OPCs and mature oligodendrocytes. Although a role for ADAMTSs in remyelination has not been examined, this could be a fruitful area of study because ADAMTSs may process CSPGs and support ECM turnover in non-CNS tissues and in the developing CNS (Apte, 2009).

4.6 | Cerebral small vessel disease

Age and hypertension are the leading risk factors for CSVD (Santisteban & Iadecola, 2018). However, insights from genetic animal models with mutations in genes encoding perivascular ECM molecules suggest that alterations in the brain ECM constitute another important risk factor. During ageing, cerebral arterioles exhibit stiffening and fibrosis, which is caused by vascular smooth muscle cell atrophy, decreased elastin production and increased elastin degradation and collagen synthesis. The perivascular ECM remodelling is probably linked to higher TGF-β secretion (Hajdu, Heistad, Siems, & Baumbach, 1990; Joutel et al., 2016; Morgan et al., 2014). Perineuronal ECM changes during healthy ageing are associated with lectican and HA overproduction, leading to higher numbers and more prominent PNNs. Elevated HA synthesis is related to HAS1 upregulation in numerous reactive astrocytes in the aged brain (Cargill et al., 2012; Song & Dityatev, 2018).

Hypertension is usually associated with cellular and ECM remodelling of the vessel wall, leading to narrowed, fibrotic cerebral blood vessels and endothelial dysfunction. Hence, in times of increased metabolic need, vessels are not able to dilate as much as necessary. The subsequent hypoxic injury cascade contributes to an inflammatory response and to the release of MMPs, especially MMP-3 and MMP-9, from activated microglial cells (Rosenberg, 2017). However, the release of extracellular proteases in an attempt to remodel the blood vessel wall has the undesired consequence of opening the BBB and damaging myelin fibres. In line with this view, treatment of spontaneously hypertensive stroke-prone rats (SHRSP), an animal model that mimics sporadic CSVD, with minocycline, an anti-inflammatory MMP inhibitor, reduced white matter damage, improved learning function in the water maze test and increased life expectancy (Jalal, Yang, Thompson, Roitbak, & Rosenberg, 2015). CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a familial form of CSVD accompanied by similar pathologies such as sporadic CSVD with microbleeds and small infarcts. In a genetic mouse model of CADASIL, a decrease in laminin and increases in fibronectin, collagen IV, MMP-2 and MMP-9 were found in cerebral arteries, which is similar to findings in SHRSP (Dziewulska, Nycz, & Rajczewska-Oleszkiewicz, 2017; Held et al., 2017). Furthermore, elevated perivascular TIMP-3 accumulation was found in the ECM, which resulted in a failure of the metalloproteases ADAM17 and HB-EGF to regulate cerebral arterial tone and blood flow responses. Under physiological conditions, the tonic activity of the ADAM17/HB-EGF/(ErbB1/ErbB4) pathway prevents excessive accumulation of K_V channels at the plasma membrane of vSMCs and thereby maintains myogenic tone. Elevation of TIMP-3 may thus change the contractility of vSMCs and impair vasodilatation and resting cerebral blood flow (Capone et al., 2016).

In conclusion, in sporadic CSVD, chronic alterations of the vasculature lead to multiple non-synchronized responses of the affected surrounding cells. In post-mortem human and animal brains, acute reactions can be found next to more chronic tissue alterations, which make it difficult to distinguish between acute and chronic effects. In other words, there is a limitation to observe isolated responses to local small vessel damage and to elucidate contributions of cells participating in such a response. This could be one of the reasons why there is no robust CSVD biomarker in serum or CSF. Another important issue is that the overproduction of TIMP-3 in the perivascular area may create a diffusion gradient of TIMP-3, so it will also affect the adjacent neuropil. It is plausible to expect that the accumulation of perineuronal and perisynaptic ECM molecules in CSVD might contribute to cognitive decline.

5 | TRANSLATION OF THE TWO-PHASE ECM DYSREGULATION MODEL INTO CLINICAL RESEARCH

Different CNS disorders show similarities in their time-dependent pathophysiological ECM regulation in animal

models and human post-mortem tissue. The transfer of this knowledge into translational research will require the development of biomarkers to monitor ECM remodelling in clinical settings. CSF and blood serum are in vivo biomarkers and could be instrumental to indicate the supposed time-dependent regulation of certain ECM molecules in the human CNS. In the healthy brain, CSF is involved in CNS waste cleaning and is in connection with the interstitial fluid of the extracellular space. That is, the reason why CNS ECM molecules can diffuse into the CSF and thus CSF might have the potential to mirror the increase or decrease in particular ECM molecules in the CNS. As the CSF drains into the venous blood system, these changes could also be visible in blood serum samples. Single studies have investigated ECM molecules in the CSF and blood serum in neurological disorders, such as brain tumours, traumatic brain injury or stroke (Al'Qteishat et al., 2006). Nevertheless, comprehensive correlation studies of blood and CSF samples as well as correlations of CNS ECM alterations and concentration changes in body fluids of several molecules are still missing. Furthermore, a detailed understanding of how and in which amount ECM molecules diffuse into the CSF in health and disease is restricted.

When BBB breakdown occurs, extracellular neural ECM molecules and extracellular proteases are able to pass in higher amounts directly into the vascular system. Thus, theoretically, the investigation of ECM molecules in the blood is of special value in diseases accompanied by BBB breakdown.

Patients with epilepsy or traumatic brain injury reveal early elevation of CSF MMP-9 levels. Stroke patients show an increase in MMP-9 levels and activity in their serum only a few hours after the incident as well (Grossetete, Phelps, Arko, Yonas, & Rosenberg, 2009; Li et al., 2013; Worthmann et al., 2010). In ischaemic stroke, higher serum MMP-9 levels correlate with an increased risk of haemorrhagic infarct transformation, major disability regarding walking independency and mortality, suggesting blood MMP-9 to serve as a prognostic biomarker (Iemolo, Sanzaro, Duro, Giordano, & Paciaroni, 2016; Montaner et al., 2001; Zhong et al., 2017). These findings support the idea of an acute increase in proteases in the CNS following damage in several neurological disorders. Furthermore, seven days after stroke, elevated serum TIMP-1 levels correlated well with clinical stroke severity (Worthmann et al., 2010). TIMP-1 upregulation is supposed to indicate the degree of astrocyte activation, which correlates with the size of stroke-related brain damage. An ongoing prospective clinical trial analyses reperfusion injury after ischaemic stroke and relates a broad analysis of blood biomarkers (inflammation, endothelial dysfunction, MMP and TIMP levels/activity) to brain imaging and clinical outcome at several time points (before reperfusion, 24-hr and 3-month follow-up). This study could not only reveal pathophysiological processes of reperfusion injury but also provide new insights into the time-dependent cascade of MMPs, their inhibitors, inflammation and endothelial dysfunction in ischaemic stroke (Piccardi et al., 2018). Additionally, HA concentration in post-stroke human brains correlates well with serum HA levels, which were found to increase up to 14 days post-stroke. Serum HA upregulation might be noticeable even longer and points towards chronic brain ECM upregulation. It would be interesting to investigate whether other ECM molecules, such as CSPGs, are chronically increased in CSF or serum to support our hypothesis of chronic ECM overexpression and to have sensitive readouts to control the effects of new drugs targeting extracellular proteolysis and ECM remodelling.

Long-term observations of patients with recurrent depression show downregulation of MMP-2 and MMP-9 serum activity, which was related to worse cognitive performance (Bobińska, Szemraj, Gałecki, & Talarowska, 2016). This does not prove the chronic upregulation of ECM molecules, but it shows a relationship between reduced proteolytic activity and cognitive impairment.

Regarding these studies, investigating extracellular proteases in CSF and blood, the concentration of latent proteases, such as MMP-9, correlates well with the respective clinical outcome. However, the quantity of proteolytic enzymes does not conclude to its real proteolytic activity in the CNS ECM. Therefore, such studies should combine expression and activity measurements. Another difficulty in interpretation of data is related to the fact that MMPs, TIMPs or most ECM molecules are also expressed outside of the CNS; hence, measurements of their concentrations are not tightly linked to processes in the brain. Therefore, a promising approach would be to measure the concentration of ECM molecules that are exclusively expressed in the CNS, for example, neurocan or brevican. For the acute stage, for instance, the cleavage products of those ECM molecules, such as cleaved fragments of brevican or low molecular weight HA, could indicate the real degradation activity in the CNS tissue, particularly if normalized to the concentration of full-length proteins or other neural proteins established as markers of BBB cleavage. Thus, future research should focus on longitudinal studies in the same patient with several timepoints at the acute and chronic stages of diseases and measurements of multiple CNS ECM molecules and proteases in serum and CSF to establish new sensitive and robust indices of ECM remodelling in the CNS.

Beyond serum and CSF biomarkers, molecular imaging, such as positron emission tomography (PET), could aid in the early and region-specific detection of ECM remodelling in the CNS. Several fluorescently labelled or radiolabelled MMP inhibitors have been developed as imaging agents for different diseases. Remarkably, pilot clinical studies of [^{18}F]**15** in MS patients described by Wagner and colleagues

form an excellent basis for the feasibility of MMP inhibitor probes for clinical trials (Wagner et al., 2011).

6 | CONCLUSIONS AND FUTURE DIRECTIONS

A healthy brain needs a proper balance in the expression of extracellular proteases, their tissue inhibitors and perineuronal/perivascular ECM to maintain ECM turnover at the level necessary for adaptive synaptic/vascular plasticity. However, in many CNS diseases, contradictory requirements for tissue remodelling versus homeostasis lead to ECM dysregulation as one of the common mechanisms presumably driving the progression of these disorders, particularly in the cognitive domain. As discussed, various experimental and biomarker studies have shown imbalances between the MMP/TIMP ratio in stroke, CNS injury and CSVD, accumulation of ECM molecules in the chronic stages of these diseases and depression, and PNN downregulation in epilepsy. The dysregulation in ECM and proteolysis is translated into physiological symptoms through activation of TLRs and RPTPs, modulation of integrins, and changes in expression of ion channels and cell adhesion molecules. Our hypothesis implies biphasic pathophysiological ECM regulation in clinical and animal studies in different CNS disorders and the importance of diffusional transfer of ECM molecules, extracellular proteases and their tissue inhibitors between perivascular and perineuronal compartments. The latter may explain why BBB breakdown and vascular damage are key pathogenic features of neurodegenerative diseases, which may result in a combination of impaired energy supply and extracellular environment inhibition of synaptic plasticity. There is, however, still limited knowledge of the molecular mechanisms underlying ECM remodelling and turnover in human diseases. Considering the higher ratio between astrocytes and neurons in the human brain compared to rodents and the importance of astrocytic activation in the overproduction of neural ECM, it is plausible that ECM-mediated mechanisms may play even more prominent role in humans as compared to rodents. Taking into account the recent advances in neural ECM research, it could be expected that disease-modifying ECM targeted therapy will be a promising therapeutic option for the treatment of neurological and psychiatric diseases. However, clinical trials with MMP inhibitors have generally been disappointing. For instance, treatment with MMP inhibitors 7 days after stroke increases ischaemic brain injury and impairs functional recovery at 14 days (Zhao et al., 2006). Another study reported that MMP2/9 ablation transiently reduced infarct volume at 24 hr after focal ischaemia but failed to provide long-term protection. The reason for this apparent failure might hide behind several limitations. Some are technical, such as the specificity and potency of MMP inhibitors.

Some are biologically fundamental. As elucidated in this review, the role of MMPs may change from detrimental to beneficial, or vice versa, during the course of disease. Therefore, timing is an important factor to be considered for therapeutic strategies targeting MMPs. Additionally, the spatial factor is important, particularly in CSVD, in which the superposition of processes triggered by multiple BBB breakdowns occurring at different time points is common. Thus, more sophisticated strategies should be employed, such as the use of prodrugs that could become conditionally activated by specific inflammatory cues and/or act on specific cell types. Systems biology analysis of cell-type-specific proteomes and single-cell genomic studies of the described complex processes may help in the design of such interventions.

CONFLICT OF INTEREST
The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS
PU and MK were involved in the literature search, the data analysis, the conceptualization and design of the study, the graphic design and the drafting of the manuscript.

AD, SS and SJ were involved in the conceptualization and design of the study, the graphic design, the critical revision of the manuscript for important intellectual content and the supervision of the study.

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