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ADVANCED REVIEW

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Exploring the properties and potential of the neural extracellular matrix for next-generation regenerative therapies

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Abstract

The extracellular matrix (ECM) is a dynamic and complex network of proteins and molecules that surrounds cells and tissues in the nervous system and orchestrates a myriad of biological functions. This review carefully examines the diverse interactions between cells and the ECM, as well as the transformative chemical and physical changes that the ECM undergoes during neural development, aging, and disease. These transformations play a pivotal role in shaping tissue morphogenesis and neural activity, thereby influencing the functionality of the central nervous system (CNS). In our comprehensive review, we describe the diverse behaviors of the CNS ECM in different physiological and pathological scenarios and explore the unique properties that make ECM-based strategies attractive for CNS repair and regeneration. Addressing the challenges of scalability, variability, and integration with host tissues, we review how advanced natural, synthetic, and combinatorial matrix approaches enhance biocompatibility, mechanical properties, and functional recovery. Overall, this review highlights the potential of decellularized ECM as a powerful tool for CNS modeling and regenerative purposes and sets the stage for future research in this exciting field.

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1 | INTRODUCTION

The extracellular matrix (ECM) is a complex network of proteins and other molecules that are secreted by the resident cells of any tissue or organ. Our understanding of the external cell microenvironment has evolved over the last decades and transitioned from being a mere support and "glue"-filling space to a relevant entity that plays a central role in physiological and pathological processes of complex organs such as the central nervous system (CNS) (Celio, 1999; Zimmermann & Dours-Zimmermann, 2008). The general function of the ECM in the CNS can be summarized on three levels: (1) it acts as a biological scaffold for the growth and development of neural cells, (2) it controls the diffusion and availability of soluble factors and ions for biochemical signaling and communication, and (3) the various molecular interactions in the ECM define the biomechanical properties of the tissue. The biochemical composition and biophysical properties of the ECM change dynamically over the course of life and under disease conditions, and thus its instructive signaling to surrounding cells.

Although the ECM has been estimated to represent 15%–20% of the CNS volume in adults, and up to 40%–60% in fetal stages (Jovanov Milošević et al., 2014; Krishnaswamy et al., 2019; Zimmermann & Dours-Zimmermann, 2008) its composition has not been yet fully characterized (Long & Huttner, 2022). This is in part because the study of the ECM is particularly challenging given its complexity, insolubility, as well as its numerous post-translational modifications and higher-order complexation, which hinder the implementation of biochemical methods aimed at profiling the ECM proteome (Naba et al., 2012; Naba et al., 2017; Shao et al., 2023). Consequently, changes in the ECM associated with different physiological and pathological conditions and their respective functional consequences may have been significantly underestimated. Recently, the development of several high-throughput methods has begun to reveal novel aspects of the ECM in multiple contexts (Ricard-Blum, 2020). In general, the CNS ECM is composed of a highly dynamic network of polysaccharides and proteins that is in a constant state of remodeling and plays key roles in

regulating many aspects of neural development and function, including proliferation, differentiation, migration, neuromodulation, synapse stabilization, and maintenance of homeostasis among many others (Bonnans et al., 2014; Hayes & Melrose, 2021; Kjell et al., 2020; Long & Huttner, 2019). Here, we will review relevant aspects of the composition, as well as the structural and mechanical properties of the CNS ECM under physiological and pathological conditions, and how the use of decellularization-based strategies can help to understand the biological implications of context-specific ECM signals for in vivo applications.

2 | THE ECM IN CNS

In the CNS, the ECM is organized into three major compartments with unique compositions: the interstitial matrix (IM), the basement membrane (BM), and perineuronal nets (PNNs; Figure 1). The IM is the major component of the ECM in the CNS and is composed of constituents secreted primarily by glial cells surrounding neurons. It contains hyaluronan, proteoglycans, linker proteins, glycoproteins such as tenascins, laminins and fibronectin, and fibrous proteins including elastin and collagens, that impart a soft-like nature (Lau et al., 2013; Lei et al., 2017; Rauch, 2007; Tewari et al., 2022). In addition to specific ECM-cell signaling promoted by some proteoglycans and glycoproteins incorporated into the IM, the network established by these molecules provides the ECM with a high hydration capacity to maintain the extracellular space volume and resistance to mechanical stress (Frantz et al., 2010; Hrabetova et al., 2018; Perkins et al., 2017). The BM is a thin layer of specialized ECM that surrounds blood vessels, regulates the movement of fluids and soluble molecules transit from the vessels to the CNS parenchyma, and provides structural support to the nervous tissue (Amin & Borrell, 2020; Tewari et al., 2022). The vascular BM plays a central role in the structure and function of the blood-brain barrier (BBB), as the absence of BM components such as laminins or collagens severely compromises BBB integrity. The BM is in direct contact with the neural epithelium and transmits external signals that strongly influence its behavior (LeBleu et al., 2007; Mouw et al., 2014). During fetal development, BM components such as laminins, nidogens, collagen IV, and heparan sulfate proteoglycans support both the stemness and neurogenic potential of neural progenitors for a proper brain development (Amin & Borrell, 2020; Long & Huttner, 2019; Tewari et al., 2022). The PNNs are a dense and specialized ECM composed of proteoglycans, glycoproteins, and additional molecules (Dityatev et al., 2010; Ramsaran et al., 2023) that surround the soma, dendrites, and initial axon segment of some neurons in the CNS. PNNs appear in the postnatal stages and are modulated in an activity-dependent manner (Mauney et al., 2013; Carulli et al., 2021; Carulli & Verhaagen, 2021; Fawcett et al., 2019). PNNs form a mesh-like structure that offers structural and functional support for synaptic plasticity, homeostasis, and the regulation of perisomatic inhibition, with important implications for memory modulation (Dityatev et al., 2010; Kwok et al., 2011; Ramsaran et al., 2023). Distinct neuronal compartments are surrounded by other specialized ECMs, the perisynaptic and perinodal matrices, which modulate neurotransmission at neuronal synapses and axonal nodes of Ranvier, respectively. They have a relatively similar composition to the PNN, containing proteins such as laminin, fibronectin, and type IV collagen, as well as proteoglycans and glycosaminoglycans (GAGs). The perinodal matrix is formed during postnatal development, after myelination is complete, facilitates the accumulation of ions in the node, and supports axonal conduction. This matrix is important for the formation, maintenance, and plasticity of the nodes of Ranvier (Bekku et al., 2009; Bosiacki et al., 2019; Celio & Blumcke, 1994; Dours-Zimmermann et al., 2009; Fawcett et al., 2019; Kwok et al., 2011).

2.1 | Biochemical properties of ECM

The composition of the ECM in the CNS is formed by a highly diverse network of a variety of versatile polysaccharides and proteins that functionally define important aspects of the neural microenvironment (Dankovich & Rizzoli, 2022; Ricks et al., 2014; Shabani et al., 2021). The ECM contains high levels of GAGs, which are unbranched polysaccharide chains composed of repeating disaccharide units: an amino sugar (N-acetylglucosamine or N-acetylgalactosamine), and an uronic acid (glucuronic or iduronic). Because the amino sugars are in most cases sulfated and the carboxyl groups are present in all their sugar residues, GAGs are highly negatively charged and can attract positively charged ions and water molecules, forming a hydrated gel-like substance that helps to cushion and protect cells from mechanical stress. Based on the composition of the sugar residues and the number and location of the sulfate groups, GAGs can be classified into four distinct groups: hyaluronic acid (HA), chondroitin sulfate (CS)/dermatan sulfate (DS), heparan sulfate

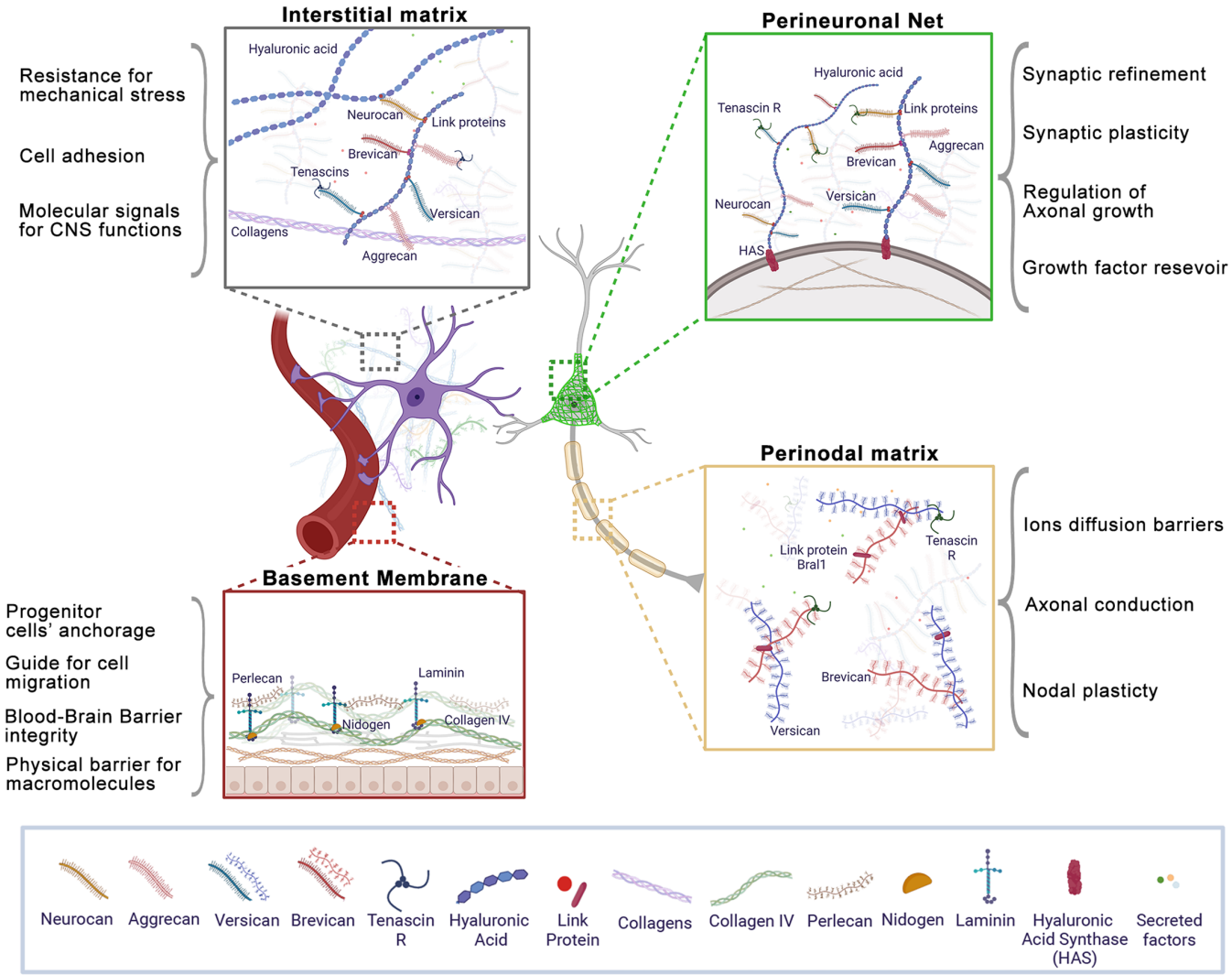

FIGURE 1 Extracellular matrix compartments in the CNS. This schematic summarizes the organization and principal functions of the major ECM compartments in the CNS.

(HS), and keratan sulfate (KS). HA is a relatively simple GAG, unique among the other GAGs because it is the only one without sulfate groups and is not covalently attached to proteins in the ECM. Instead, it forms a large linear molecule of sugar residues that interacts noncovalently with other ECM components, such as collagens and proteoglycans, to form a network that provides structural support and hydration to tissues. During development, HA plays an important role as an extracellular space filler, as well as in cell proliferation, migration, and differentiation (Long & Huttner, 2019). HA also helps regulate inflammation and immune responses and is essential for wound healing and tissue repair (Bourguignon et al., 2007; George & Geller, 2018). The rest of the GAGs covalently interact with ECM core proteins to form a large variety of proteoglycans.

The *matrisome* is a term that defines the ensemble of proteins and associated factors that make up the ECM of any tissue. The matrisome classification, well established and continuously updated by the Matrisome Project initiative (Naba et al., 2012; Naba et al., 2017; Shao et al., 2023), is a widely used resource for stratifying ECM components based on in silico and in vivo curated data. This classification takes into account structural and/or functional features to separate the ECM proteome into two main categories: the *core matrisome*, which refers to the ECM proteins that are mostly associated with the structural support of tissues and include proteins such as collagens, proteoglycans, and glycoproteins; and *matrisome*-associated proteins, which include growth factors, cytokines, and ECM remodeling enzymes, among others, that are involved in regulatory or signaling functions (Naba et al., 2017). Here, we provide a brief overview of the most relevant proteins in the CNS ECM (summarized in Table 1).

TABLE 1 Summary table displaying some of the most relevant proteins present in the CNS ECM and their functions.

ECM categories	ECM subcategories	ECM proteins highly present in the CNS	Main function in the CNS
Core Matrisome	Collagens	Collagen I, Collagen IV, Collagen VI	They are a major component of the basement membrane. They are also present in the interstitial matrix. These molecules provide structural support to the tissue, resisting tensile forces and helping to maintain the integrity of the BBB.
	Proteoglycans	CSPGs: Neurocans, Brevicans, Aggrecan, and Versicans	They are the most abundant proteoglycans in the CNS. They play multiple roles in neuronal migration, axon guidance, and synaptic plasticity.
		HSPGs: Glypicans, Perlecan, Syndecans, and Agrin	The interaction of HSPGs with growth factors and other secreted molecules depends on their sulfation pattern. Together, they regulate cell migration, axonal growth, and synaptogenesis during brain development.
	Glycoproteins	Laminins, Fibronectin, Tenascins	They are known as adhesion molecules that contribute to cell attachment to the ECM and to the structural organization of the matrix. They are also involved in neuronal migration, axon guidance, and synapse formation.
Matrisome-associated	Regulators	ADAMTs, MMPs	Regulators are enzymes essentially involved in major CNS functions. They degrade ECM components and cell surface proteins, act as receptors and cytokines, and thus contribute to ECM remodeling. Their activity should be tightly regulated by their inhibitors.
	Affiliated	Semaphorins, Plexins, Galectins.	These molecules interact closely with the ECM and have functions in migration, synapse formation, and cell homeostasis by regulating the immune response.
	Secreted Factors	GDNF, BDNF, IGF, Interleukins, WNT family	This heterogeneous group interacts extensively with structural components of the ECM. For example, the interaction of these growth factors with GAGs regulates cell growth, cell survival, and tissue repair. Other secreted factors are more involved in brain patterning during early stages of brain development and in immune cell responses.

The *core matrisome* consists of three subcategories of proteins defined by their domain structures: collagens, proteoglycans, and glycoproteins.

Collagens are large trimeric proteins containing at least one triple-helical domain that are secreted into the extracellular space, where they are the most abundant ECM protein in tissues throughout the body. While GAGs resist compressive forces, collagens form structures that resist tensile forces in multiple directions. Although it was thought that collagens were rarely present in the adult CNS, recent evidence has shown the expression of several types of collagens in different locations of the nervous tissue (Hubert et al., 2009). Collagens are a major component of the basement membrane in the CNS, which is composed of several different types of collagens, including collagen I, IV, and VI (Hall et al., 2021). Abnormal expression of collagens located in the BM and BBB have been implicated in several neurological disorders, including Alzheimer's disease (AD), multiple sclerosis, spinal cord injury (SCI), or stroke (Bhowmick et al., 2019; Knox et al., 2022; Michalski et al., 2020; Sweeney et al., 2019; van Vliet et al., 2020; Wang & Shuaib, 2007). Collagens have also been observed in the IM of the gray and white matter in the brain and spinal cord, and even in some neuronal PNNs (Gregorio et al., 2018; Su et al., 2017).

Proteoglycans are a diverse family of large molecules composed of GAGs covalently attached to a core protein (Beller & Snow, 2014; Fawcett & Kwok, 2022; Frantz et al., 2010; Maeda, 2015) that help to maintain the structure of the ECM and play important roles in cell signaling. Proteoglycans are produced by various neural cells in the CNS (Carulli et al., 2005; Siebert et al., 2014) and undergo multiple and specific post-translational modifications before and after reaching the ECM (Yu et al., 2017). Common modifications occur at the sulfation sites in their GAG chains, which can affect their binding properties and function (Fawcett & Kwok, 2022). Depending on the subtype of GAGs attached, proteoglycans differ in size and function (Cui et al., 2013; Zimmermann & Dours-Zimmermann, 2008). Two major subtypes of proteoglycans found in the CNS ECM are detailed as follows:

Chondroitin sulfate proteoglycans (*CSPGs*), the most abundant proteoglycans in the CNS, are ubiquitously distributed in the diffuse IM but are also a major component of PNNs (Fawcett & Kwok, 2022; Hayes & Melrose, 2021). CSPGs exert a variety of functions in neural cells, directly or indirectly through their interactions with various growth factors and secreted molecules in the extracellular environment (Fawcett & Kwok, 2022; Wang et al., 2008). Some of the most relevant CSPGs in the CNS are *Phosphocan*, which plays a role in cell adhesion, migration, and axon guidance (De Luca & Papa, 2017; Melrose et al., 2021); *Aggrecan*, which is the major CSPG found in the adult brain, and has been implicated in the regulation of synaptic plasticity and memory formation (Dauth et al., 2016); *Versican*, widely distributed in the CNS and peripheral nervous system (PNS), where it is involved in cell adhesion, proliferation, migration, myelin formation, and tissue development and repair (Melrose et al., 2021); *Neurocan* involved in axon growth and guidance and neural circuit formation. It is upregulated in response to injury and contributes to glial scar formation (Asher et al., 2000; Deguchi et al., 2005; Harris et al., 2009; Hayes & Melrose, 2021; Tang et al., 2003).

Heparan sulfate proteoglycans (*HSPGs*) are found primarily on the cell surface of neurons and glia, and act as co-receptors for several signaling molecules, including growth factors, morphogens, and other ECM proteins (Melrose et al., 2021; Tang et al., 2003; Yu et al., 2017). They play a number of important roles in development, regulating cell migration, axon growth, synaptogenesis, growth factor signaling, and as a component of the stem cell niche. Agrin, syndecan, and glypican are examples of HSPGs (Long & Huttner, 2022; Tang et al., 2003; Yu et al., 2017); *Agrin* is thought to stabilize the interaction between laminin and integrin which is critical for neurogenesis, neurite outgrowth, synapsis formation (Barros et al., 2011; Shabani et al., 2021). *Syndecan* is involved in intercellular signaling that modulates developmental processes such as neural progenitor proliferation or neuronal migration through the interaction with several morphogens such as Wnt or GDNF (Bespalov et al., 2011; Wang, Forsythe, et al., 2012). The bioactivity of important morphogens for CNS development, such as fibroblast growth factor (FGF) and the WNT family, is regulated by *glypican* (Jen et al., 2009; Pan & Ho, 2021; VeneroGalanternik et al., 2015).

Glycoproteins are a class of proteins with one or more oligosaccharide chains attached and multiple domains, each with specific binding sites for other ECM molecules and for cell receptors. They contribute to both matrix organization and cell attachment to the ECM. Some of the major glycoproteins in the CNS ECM include:

Laminin, a heterotrimeric protein composed of three distinct subunits, α, β, and γ chains, which combine to form a cross-shaped structure (Chavda et al., 2022; Durbeej, 2010; Miner & Yurchenco, 2004; Nirwane & Yao, 2019). Laminin is one of the major components of the BM (Barros et al., 2020; Nirwane & Yao, 2019). There are several types of laminins in the CNS (Minton, 2009), each type has specific binding properties and functions in the CNS, such as contributing to the structural integrity and function of the BM, function and cell fate modulation of neural stem cell (NSC), cell adhesion, neurogenesis, neuronal migration, axon guidance, and synapse formation, among others (Barros

et al., 2020; Guldager Kring Rasmussen & Karsdal, 2016; Jucker et al., 1996; Long & Huttner, 2022; McClenahan et al., 2016; Nirwane & Yao, 2019, 2022).

Fibronectin (*FN*) is a structural protein composed of a dimer of two very large subunits linked by disulfide bonds at their C-terminal ends, that supports the entire ECM meshwork and contributes to the development, maintenance, and plasticity of the nervous system (Pankov & Yamada, 2002; Singh et al., 2010; Wang et al., 2013). FN is found in a soluble form in body fluids and as insoluble FN fibrils, in which FN dimers are cross-linked by an additional disulfide bond at the BM around blood vessels. It also assembles in the ECM on the cell surface of neurons and their processes, where it can influence the growth and directionality of neuronal processes (Wierzbicka-Patynowski & Schwarzbauer, 2003). FN can directly contact integrin receptors and activate intracellular pathways that promote neuronal survival, proliferation, and neurite outgrowth (Tonge et al., 2012; Wang et al., 2011). FN can also exert other functions indirectly, by assembling with proteoglycans, such as syndecans, which induce the clustering of integrins in the membrane (Bonneh-Barkay & Wiley, 2009; Schwarzbauer & DeSimone, 2011; Singh et al., 2010). This process leads to activation of kinases, actin organization, and strengthening of focal adhesions (Wierzbicka-Patynowski & Schwarzbauer, 2003).

Tenascins (*Tn*) are a family of ECM glycoproteins that are expressed in various tissues, including the CNS (Tucker & Chiquet-Ehrismann, 2009; Wang et al., 2013). In the CNS, TnC and TnR, are of particular interest because of their distinct, but also overlapping dual functions in inhibiting and promoting mechanisms of cell proliferation and migration, fate determination, axonal pathfinding, myelination, and synaptic plasticity (Jakovcevski et al., 2013; Vecino & Kwok, 2016). TnC is primarily found in the ECM of areas undergoing active morphogenesis, such as the developing cortex and cerebellum, and can either promote or inhibit neurite outgrowth (Faissner & Reinhard, 2015; Götz, 1997). TnR, on the other hand, is exclusively and widely expressed in the adult CNS and is involved in ECM assembly and synaptic plasticity at the PNNs (Barros et al., 2011; Fawcett et al., 2019; Suttkus et al., 2014).

The *ECM-associated matrisome* includes proteins known to associate and interact with the assembled ECM.

ECM-affiliated proteins are a list coined by Naba and colleagues (Naba et al., 2012) that refers to proteins that are not commonly considered to be ECM components but are plausible to interact with them (Morawski et al., 2014). It includes secreted factors that associate with solid-phase complexes (e.g., semaphorins, plexins) and some protein families that are consistently identified by proteomic readouts in ECM-enriched samples for yet unknown reasons (e.g., annexins, galectins). Some important roles of ECM-affiliated proteins in the CNS are exerted by semaphorins, present either in the IM or in the PNNs, where they act as guidance cues for axonal and neurite growth, and also in other developmental processes including neuronal proliferation, migration, neurogenesis, and synapse formation (Carulli et al., 2021; Limoni & Niquille, 2021). Other relevant ECM-affiliated proteins in the CNS are Galectins, which are lectins that bind to galactosamine residues present in the ECM throughout the CNS, and play relevant roles during development in modulating neurite outgrowth and myelination, as well as in response to injury by participating in the inflammatory response, and immune modulation (Martin-Saldana et al., 2022; Nio-Kobayashi & Itabashi, 2021).

ECM regulators refer to ECM-remodeling enzymes such as matrix metalloproteinases, cross-linkers, proteases, regulators, and so forth (Naba et al., 2012). These secreted enzymes are important during CNS development for neural differentiation, cell migration, and synaptic plasticity, but also for repair and injury in neurodegenerative disorders (Behl et al., 2021; Melrose et al., 2021). The major players are the metalloprotease (MMP) family, A disintegrin and metalloproteinases (ADAMs), and A disintegrin and metalloproteinases with thrombospondin motifs (ADAMTs). The MMPs are the primary metalloproteases responsible for tissue remodeling by degrading ECM components, such as collagens, proteoglycans, and glycoproteins such as laminins. They are highly expressed during the developing CNS when there is a high ECM remodeling activity, and their expression levels decrease in adulthood (Cabral-Pacheco et al., 2020). ADAMs, are transmembrane enzymes with proteolytic and adhesive functions. By cleaving cell surface proteins, including receptors, cytokines, and cell adhesion proteins, they can modulate neurodevelopmental mechanisms, including axonal guidance, neurogenesis, myelination, and synaptic plasticity (Hayes & Melrose, 2021; Hsia et al., 2019). The activities of these metalloproteinases are tightly regulated by their inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). They inhibit all MMPs but have a higher degree of specificity and selectivity for ADAM and ADAMTs (Jackson et al., 2017).

ECM secreted factors are a heterogeneous group of proteins including cytokines, chemokines, and growth factors that are released into the extracellular space and are known or expected to interact with structural components of the ECM. For example, most of the growth factors bind to GAGs, but also to specific domains of other ECM proteins (Fawcett & Kwok, 2022; Hynes & Naba, 2012). ECM secreted factors promote a variety of functions in the CNS, including cell survival, cell growth, and differentiation, as well as effectors of tissue repair and immune cell responses (Deverman & Patterson, 2009; Mousa & Bakhiet, 2013).

2.2 | Biophysical properties of the ECM

In addition to signals derived from the biochemical composition of the ECM, its biophysical properties can modulate cell responses by tuning gene expression profiles, which subsequently trigger phenotypic changes. In turn, different cell types and cell states produce, secrete, degrade, and remodel ECM components, thereby modifying both the composition and topography of the ECM, which in turn affects cell behavior (Bonnans et al., 2014). The dynamic changes in physicochemical properties through this cell-ECM feedback loop are known to have a relevant influence on processes such as cell migration, proliferation, differentiation, and maturation (Figure 2; Urbanczyk et al., 2020). Recent studies have specifically focused on the importance of studying the biophysical properties of the CNS ECM to construct new and more translational in vitro and in vivo models by better mimicking the physicochemical properties of the native CNS. Key biophysical properties of the CNS ECM include mechanical strength, elasticity, hydration, porosity, adhesive properties, and biochemical signaling (Hall et al., 2021; Tonti et al., 2021; Urbanczyk et al., 2020).

2.2.1 | Mechanical properties

The composition of proteins in the ECM, as well as their spatial orientation and degree of cross-linking, affect the mechanical properties of the ECM (Javier-Torrent et al., 2021). The dense network of extracellular proteins and polysaccharides in the CNS ECM confers a high degree of *mechanical strength*, allowing the tissue to resist compressive and tensile forces (Melrose et al., 2021; Padhi & Nain, 2020). In addition, the high *elasticity* of the ECM contributes to the structural integrity of the CNS tissue and allows for the transmission of mechanical forces (Javier-Torrent et al., 2021). The *stiffness* of CNS tissue varies with region, age, and context (e.g., disease or injury vs. healthy tissue) (Antonovaite et al., 2018; Bartlett et al., 2020; Hall et al., 2021; Murphy et al., 2016; Segel et al., 2019). The stiffness of the ECM is

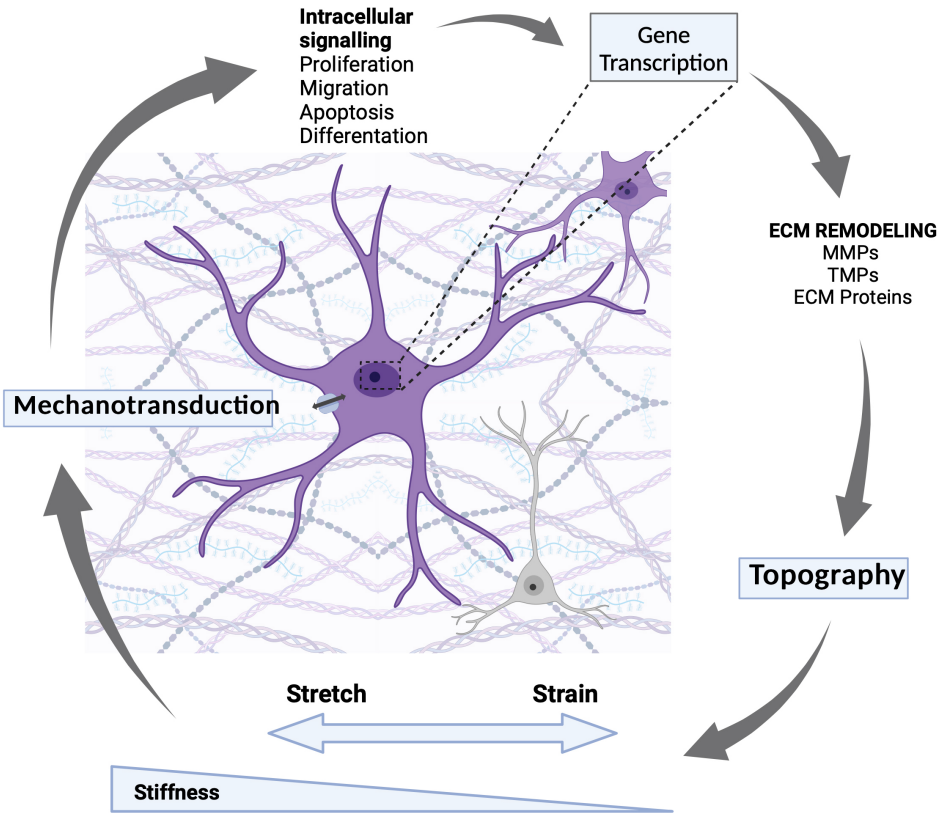

FIGURE 2 The feedback loop between cells and the ECM environment in the CNS. Schematic representation of the loop in which neural cells produce and secrete ECM components, and ECM components in turn influence cell behavior by providing mechanical support, adhesive surfaces, and signaling cues. Neural cells can also degrade and remodel the ECM, which can further influence cell behavior. This dynamic process creates a feedback loop in which neural cells and the ECM continuously interact and influence each other.

governed by the interplay between ECM proteins and the residing cells (Javier-Torrent et al., 2021). Changes in ECM stiffness can have significant effects on cell behavior, including migration, proliferation, and differentiation (Hall et al., 2021; Long & Huttner, 2022; van Essen, 2020). In general, brain tissue is softer than spinal cord tissue, with a typical stiffness of 90–110 Pa during development, 0.2–8.0 kPa in adulthood, and 2.6–30 kPa in spinal cord tissue (Bartlett et al., 2020; Cooper et al., 2020; Karimi et al., 2017). The interaction between the ECM and the cells also regulates the *porosity* of the CNS ECM. Porosity is a structural feature that is crucial for regulating molecule transport, including nutrients, oxygen, and signaling molecules, between the blood and the CNS (Chan & Leong, 2008; Comellas et al., 2020; Nicolas et al., 2020). It can range from low porosity in the brain, associated with tight junction formation, to high porosity in the spinal cord, associated with increased permeability (Akhmanova et al., 2015). The porosity of the CNS ECM can be affected by disease, aging, injury, and inflammation, as well as by the presence of ECM-degrading enzymes (Akhmanova et al., 2015).

2.2.2 | Mechanotransduction

The process by which cells sense and respond to mechanical forces in their environment, such as stretch, compression, bending, and shear stress, is called mechanotransduction (Urbanczyk et al., 2020). The mechanobiology of the ECM is mediated by interactions between the ECM and the cytoskeleton of cells (Hall et al., 2021; Kim & Nelson, 2012; Procès et al., 2022; Tyler, 2012). The cytoskeleton of neural cells connects to the ECM at focal adhesion complexes via transmembrane integrin receptors, which transmit forces from the ECM to the interior of the cell and vice versa (Dobrynina et al., 2020; Grillo et al., 2022; Schwanstecher & Schwanstecher, 2015) (Figure 2). Through this pathway, mechanical stimuli can modulate a variety of functions in neurons and glia, including growth cone mechanosensing, traction force generation, axon guidance, stem cell differentiation, and synapse maintenance (Hall et al., 2021; Martino et al., 2018; Procès et al., 2022; Tyler, 2012). Thus, all these functions are finely regulated by the balance established between the cytoskeletal tension within the cell and the forces generated by the surrounding ECM, and its alteration has been implicated in several neurological disorders. For example, alterations in the stiffness and composition of the ECM have been implicated in the progression of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Barnes et al., 2017; Hall et al., 2021; Hebisch et al., 2023). In AD, alterations in the composition and organization of the ECM have been shown to contribute to the formation and deposition of amyloid-beta plaques and neurofibrillary tangles, which are hallmark pathological features of the disease (Simpson et al., 2020; Sun et al., 2021). Similarly, in PD, changes in ECM stiffness and composition have been linked to the loss of dopaminergic neurons in the substantia nigra (Surmeier et al., 2010).

2.2.3 | Topography

Topography defines the macroscale architecture of the ECM by integrating properties related to shape, organization, geometry, and size, as well as the orientation, texture, and nanoscale patterns of the fibrils that constitute the ECM (Oldham et al., 2022; Paul et al., 2019). Topography is determined by several factors, including mechanical forces, and biochemical composition (Kim et al., 2016; Urbanczyk et al., 2020; Yang et al., 2021). Topographical changes induced by ECM remodeling, such as changes in fiber orientation, can influence multiple cell behaviors in the nervous tissue, including cell shape, axon guidance, migration, or cell differentiation (Oldham et al., 2022; Zhang et al., 2009). The topographical and mechanical properties of the ECM are discussed in detail elsewhere (Janson & Putnam, 2015; Young et al., 2016).

3 | TEMPORAL AND CONDITION-SPECIFIC DYNAMICS OF THE CNS ECM

The rapid development of omic technologies have allowed obtaining spatiotemporally resolved data of ECM expression profiles, which will help to better understand the importance of the microenvironment in complex biological systems such as the CNS. It is clear that when the composition, organization, and dynamics of the ECM are perturbed, the behavior of resident cells is drastically altered (Tonti et al., 2021). Subtle changes in the biochemical signals and mechanical properties during development, aging, disease, or injury, can force a cell to exhibit either stage-specific

homeostatic or condition-specific behaviors (Sheppard et al., 1991; Tonti et al., 2021). In the next section, we will discuss several examples of changes in the chemical and biophysical properties of the ECM, ranging from development to aging within the CNS ECM.

3.1 | ECM dynamics during development and maturation

3.1.1 | Changes in the ECM composition profiles during development and aging

During development, the ECM in the CNS undergoes significant remodeling as the brain and spinal cord form and grow (Burnside & Bradbury, 2014). This remodeling process involves changes in the composition and organization of ECM molecules, as well as changes in the mechanical properties of the tissue (Urbanczyk et al., 2020). The ECM of the embryonic brain and spinal cord is largely dominated by HA and an extensive extracellular space, occupying up to 40%–50% of the volume of the early CNS. However, other ECM proteins, including collagens, proteoglycans, and glycoproteins, are also critical for proper CNS development. For example, several collagens are involved in cell migration, axon growth and guidance, synapse formation, and BBB function (Limoni & Niquille, 2021; Onursal et al., 2021; Vecino & Kwok, 2016). Proteoglycans, such as CSPGs, interact with various signaling molecules and cell surface receptors, such as integrins, to regulate proliferation, neural differentiation, and neuronal growth among other functions (Avram et al., 2014; Carulli et al., 2005; Mencio et al., 2021; Miyata & Kitagawa, 2017; Mizumoto et al., 2015). Glycoproteins, particularly laminins, are highly expressed in the BM of neural niches during CNS development, where they promote both the proliferation of NSCs and their differentiation into distinct neuronal lineages (Hall et al., 2008; Ma et al., 2008). TnC is another important glycoprotein that is expressed in regions of the CNS that are undergoing growth and remodeling, influencing the self-renewal and differentiation of NSC into distinct neural cell lineages. TnC is also involved in many other processes related to CNS development, including cell adhesion, migration, and axonal growth and pathfinding (Faissner, 1997; Tucić et al., 2021).

As the CNS develops, the neural microenvironment matures through protein expression (Figure 3a) and structural changes in the ECM (Barros et al., 2011; Mouw et al., 2014). Expression of ECM proteins characteristic of the fetal or immature stages remains concentrated in specific neurogenic areas in the adult CNS, such as the dentate gyrus in the hippocampus or the central canal in the spinal cord (Zimmermann & Dours-Zimmermann, 2008). A gradual increase in the glial contribution to the maturing CNS ECM allows the generation of specialized extracellular structures in the form of PNNs, perinodal, and perisynaptic matrices (Fawcett et al., 2019; Kwok et al., 2010; Mouw et al., 2014; Rhodes & Fawcett, 2004; Testa et al., 2019). For example, during myelination, oligodendrocytes around the nodes of Ranvier and PNNs begin to express versican V2, TnR, and phosphocan (Zimmermann & Dours-Zimmermann, 2008). This is accompanied by a corresponding increase in the synthesis of more mature-associated ECM components, including a truncated form of neurocan, increased levels of aggrecan and phosphacan (Fawcett et al., 2019; Galtrey et al., 2008; Meyer-Puttlitz et al., 1996), as well as high production of link proteins, such as the HAPLN1, which will indicate a full maturation state of specialized ECM such as PNNs (Kwok et al., 2010). Accordingly, PNN maturation has recently been shown to coincide with myelination, synaptogenesis, and voltage-dependent regulation of ion channels, ultimately leading to more mature neuronal circuit function (Carulli & Verhaagen, 2021; Testa et al., 2019).

Later, age-specific changes in the expression of ECM components occur (Figure 3b). Although our knowledge of how the ECM is altered during aging is still limited, recent studies by Ewald (2020a, 2020b) in the C. elegans model system have allowed the identification of age-dependent changes in the ECM-related genes, showing a general decrease in most of ECM components with longevity (Ewald, 2020a). However, other ECM components increase with age, such as the pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNFα), which contribute to the chronic low-grade inflammation that characterizes aging (Franceschi & Campisi, 2014). The expression of CSPGs also increases with age in the CNS. Since CSPGs are potent inhibitors of axonal growth and neuroplasticity after injury, their age-dependent expression is likely related to the limited regenerative potential of the aged CNS (Grumet et al., 1996).

Other age-related changes in the ECM proteome compromise the biophysical integrity and function of the ECM. Long-lived proteins in the ECM have been shown to accumulate multiple modifications with age that affect their function and the ECM structure (Ewald, 2020b). For example, collagens or FN undergo fragmentation due to the increased protease activity in the extracellular milieu, and the accumulation of advanced glycation end products leads to aberrant protein cross-linking in the ECM network, both of which affect cell sensitivity to environmental stimuli (Kular et al., 2014; Mutalik & Gupton, 2021; Rebelo et al., 2022; Scott & Panin, 2014). Additionally, changes in protein folding

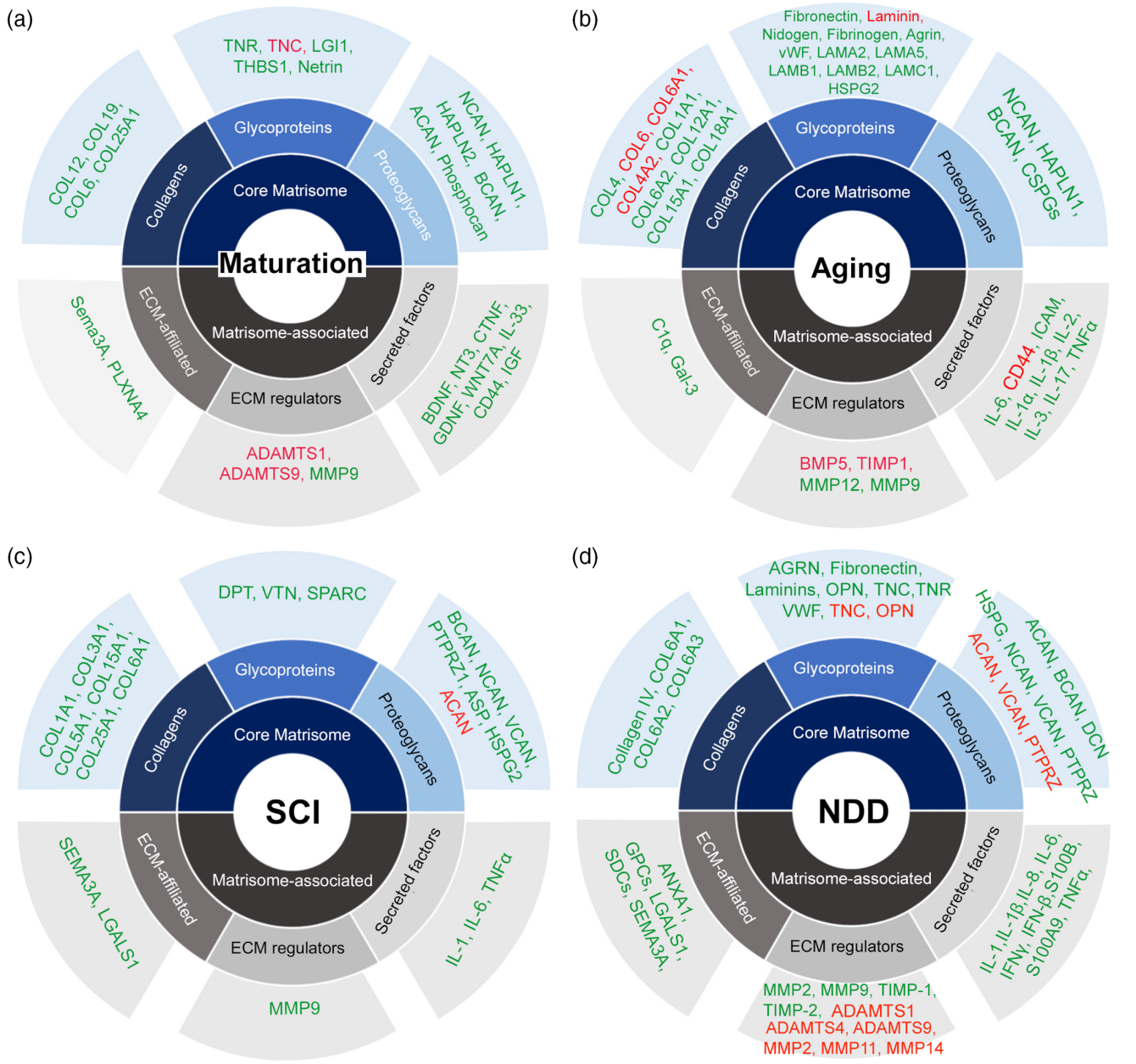

FIGURE 3 Matrisome changes during CNS development, aging, injury, and disease. The graphs show some examples of changes in the expression of different ECM components observed during (a) development/maturation (Bonansco et al., 2023; Bondy & Lee, 1993; Carulli & Verhaagen, 2021; Cerpa et al., 2008; Chopra et al., 2019; Christopherson et al., 2005; Dono, 2003; Emsley & Hagg, 2003; Glasgow et al., 2021; Godbout & Johnson, 2004; Gregorio et al., 2018; Günther et al., 2005; Gutekunst et al., 2010; Hubert et al., 2009; Kowiański et al., 2018; Lovero et al., 2015; Melrose et al., 2021; Monavarfeshani et al., 2017; Nguyen et al., 2020; Pintér et al., 2020; Pochon et al., 1997; Roszkowska et al., 2016; Seppänen et al., 2006; Shimazu et al., 2006; Song & Dityatev, 2018; Su et al., 2017; Xu et al., 2010; Yoo et al., 2017) and (b) aging (Chandra et al., 2022; Clarke et al., 2018; Ewald, 2020b; Godbout & Johnson, 2004; Kular et al., 2014; Nguyen et al., 2020; Nguyen et al., 2021; Piekarz et al., 2020; Porcher et al., 2021; Reichwald et al., 2009; Shobin et al., 2017; Silva-Vargas et al., 2016; Végh et al., 2014; Wang et al., 2020; Yin et al., 2016) of the CNS, as well as (c) in spinal cord injury (SCI), and (d) neurodegenerative disorders (NDD) such as AD (Berzin et al., 2000; Cheng et al., 2009; Downs et al., 2022; Hondius et al., 2016; Kalaria & Pax, 1995; Lendvai et al., 2013; Lorenzl et al., 2003; Lorenzl et al., 2004; Muenchhoff et al., 2014; Perlmutter et al., 1991; Snow et al., 1990; Verbeek et al., 1999), PD (Iczkiewicz et al., 2006; Liu et al., 2005; Lorenzl et al., 2003; Verbeek et al., 1999), and ALS (Fang et al., 2010; Forostyak et al., 2020; Kaplan et al., 2014; Korner et al., 2016; Lorenzl et al., 2003; Mizuno et al., 2008; Morisaki et al., 2016; Ono et al., 1998; Rabin et al., 2009; Satoh et al., 2014). Increased or decreased expression of ECM components are shown in green and red, respectively.

and degradation pathways, can lead to the accumulation of misfolded or aggregated proteins in the ECM and contribute to age-related diseases such as AD and PD (Fontaine et al., 2016; Hartl et al., 2011; Sun et al., 2021).

3.1.2 | The changing biophysical properties in the developing CNS

During development, the ECM undergoes dynamic changes in its biophysical properties that have important implications for cell behavior and tissue morphogenesis (Kim & Nelson, 2012; Sheppard et al., 1991; van Essen, 2020). In the early stages of neural development, patterning, and organogenesis are influenced by low mechanical forces (Vining & Mooney, 2017) that make it relatively soft and flexible, allowing for rapid growth and development of the brain and spinal cord (Javier-Torrent et al., 2021). A major change in the biophysical properties of the ECM during development is an increase in stiffness (Dufort et al., 2011; Lu et al., 2012; Segel et al., 2019), which is known to affect cell attachment, growth, and differentiation (Dufort et al., 2011; Iwashita et al., 2014; Vining & Mooney, 2017). In addition to changes in stiffness, the topography, porosity, and spatial organization of the ECM also change during development (Akhmanova et al., 2015). The ECM in the fetal CNS is highly porous, facilitating the diffusion of nutrients and other molecules to the developing tissues (Abuwarda & Pathak, 2020). As the CNS develops, the ECM becomes less porous and more organized and structured, affecting the diffusion of small molecules such as growth factors and creating a physical and chemical barrier that shapes regeneration and tissue morphogenesis (Iwashita et al., 2014; Sheppard et al., 1991). During aging, the ECM undergoes other changes that contribute to the decline of neural function in the CNS. One notable change is the accumulation of cross-linked collagen and elastin, which increases the stiffness of the ECM and decreases its elasticity (Phillip et al., 2015; Segel et al., 2019). This decrease in elasticity can restrict the movement of cells and limit their ability to migrate or differentiate, contributing to age-related changes in tissue architecture and function (Hall et al., 2021).

3.2 | ECM changes during injury and disease

The normal function of the nervous system can be compromised not only by the improper wiring between neural cells, but also by the perturbed interactions of these cells with their surrounding ECM. As described above, the organization of the large variety of extracellular signals present in the ECM is critical for maintaining the homeostatic neural function. Its alteration upon injury or disease can trigger dyshomeostatic and toxic effects on surrounding cells (Bonneh-Barkay & Wiley, 2009). Numerous studies in postmortem patient tissues, in vivo animal models, and in vitro human models have shown that the neural ECM composition is profoundly altered in injury and neurodegeneration (Aronica et al., 2015; Freitas et al., 2021; Rabin et al., 2010; Satoh et al., 2014; Vargas et al., 2008; Wong & Venkatachalam, 2019). In this section, we will summarize some of the most relevant perturbations of the CNS ECM in injury and disease.

3.2.1 | ECM alterations in response to injury in the CNS

After CNS injury, the composition of the ECM undergoes significant changes that may affect tissue repair and regeneration (Bonnans et al., 2014; Kjell & Götz, 2020). Major changes in ECM composition after CNS injury include the following changes (Figure 3c).

(a) Increased expression of matrix MMPs

MMPs are produced by a variety of cell types, including astrocytes, microglia, and infiltrating immune cells (Page-McCaw et al., 2007; Tewari et al., 2022), and their increased expression after CNS injury is a double-edged sword (Cabral-Pacheco et al., 2020; Chopra et al., 2019). On the one hand, MMPs are required for ECM degradation and remodeling during tissue repair (Cabral-Pacheco et al., 2020). On the other hand, excessive MMP activity can lead to the degradation of abnormally large amounts of ECM, resulting in tissue damage and impaired regeneration. In addition, the degradation products of the ECM can have detrimental effects on neurons and other cells in the injured area (Brkic et al., 2015; Cabral-Pacheco et al., 2020).

(b) Altered proteoglycan expression

Proteoglycans can be upregulated or downregulated after CNS injury (Siddiqui et al., 2022). CSPGs are often upregulated in glial scars and act as barriers to axon regeneration and plasticity, preventing the growth and remodeling of neural circuits (Buescher et al., 2015; Mencio et al., 2021; Sirko et al., 2010). CSPGs contribute to the inhibitory environment in the CNS after injury in several ways (Siddiqui et al., 2022; Siebert et al., 2014): (1) forming a dense matrix around the site of injury, creating a physical barrier to axon growth and regeneration; (2) binding to and inhibiting the function of growth factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), which are important for axon growth and plasticity (Kurihara & Yamashita, 2012); (3) interacting with receptors on the surface of neurons, such as the receptor protein tyrosine phosphatase sigma (RPTPσ), which inhibits axon growth and guidance (Kurihara & Yamashita, 2012; Tran et al., 2018).

(c) Altered growth factor expression

Growth factors such as NGF, BDNF, and GDNF, are important in promoting neuronal survival and regeneration and are upregulated in the early stages of injury to promote neuronal survival and regeneration (Aloe et al., 2015). Other growth factors, such as insulin-like growth factor (IGF), may also be upregulated to support tissue growth and repair. However, there may also be changes in the expression of growth inhibitory factors, such as myelin-associated inhibitors, which may limit the regenerative potential of the CNS after injury (Geoffroy & Zheng, 2014). The exact pattern of growth factor expression may depend on several factors, including the type, severity, and location of the injury, and the stage of recovery (Aloe et al., 2015; Logan et al., 1994).

(d) Increased expression of fibrous ECM proteins is associated with increased stiffness of the CNS ECM after injury

In response to injury, the ECM can become stiffer due to the deposition of scar tissue and increased cross-linking of ECM components (Kjell & Götz, 2020). This is due to a profound remodeling of the ECM in which there is an increased production of ECM proteins such as collagen and FN, and a decrease in the activity of enzymes that degrade and remodel the ECM (Tewari et al., 2022). This results in a stiffer and more fibrotic ECM that contributes to glial scar formation and inhibits axonal growth, thereby limiting tissue repair (Kjell & Götz, 2020; Moeendarbary et al., 2017).

3.2.2 | Perturbations of the ECM in neurodegeneration

During neurodegeneration, several changes occur in the ECM that affect its function and contribute to the pathogenesis of the disease:

(a) ECM remodeling

Changes in the expression, organization, and degradation of ECM components influence the physical properties of the ECM, such as its stiffness and permeability, which in turn affect the behavior of cells that interact with it (Bonneh-Barkay & Wiley, 2009; Sun et al., 2021).

(b) Increased deposition of ECM proteins

In many neurodegenerative diseases, there is an abnormal accumulation of disease-specific ECM proteins, such as amyloid-beta and tau in AD. Aggregates, such as senile plaques, have been associated with the accumulation of core structural components of the CNS ECM, including collagen IV or glycoproteins such as laminin, elastin, or FN (Freitas et al., 2021; Ma et al., 2020; Perlmutter et al., 1991). These aggregates could disrupt the structure and function of the ECM and cause toxicity to surrounding cells. In patients with AD, accumulation of Aβ protein is observed in the vascular BM, which also changes its composition and thickness (Thomsen et al., 2017). However, direct evidence linking these events to neurodegenerative outcomes is lacking.

(c) Impaired ECM signaling

During neurodegeneration, alterations in the expression and signaling of ECM components (Figure 3d) can disrupt normal cellular processes such as cell migration, proliferation, survival, or connectivity. For example, decreased expression of laminins, tenascins, and integrins, is associated with impaired ability of neurons to form synapses and promote survival (Hondius et al., 2016; Stern et al., 2022; Sun et al., 2021).

(d) Activation of reactive glial states and immune responses

Several studies have described non-cell autonomous mechanisms of neuronal degeneration triggered by astrocytes, which acquire a more reactive cellular state in degenerative diseases such as amyotrophic lateral sclerosis (ALS) or AD (Ilieva et al., 2009; Izrael et al., 2020; Philips & Robberecht, 2011). In AD patients and animal models, reactive astrogliosis has been observed in early stages, associated with altered expression of metalloproteinases and other extracellular proteins that may affect the amyloid transport and amyloid plaque formation (Preman et al., 2021). Reactive astrocytes are known to remodel the CNS ECM by expressing specific ECM proteins, including CSPG, versican, TnC, thrombospondins, or aggrecan (Jones & Bouvier, 2014; Sofroniew, 2005; Wiese et al., 2012). They are also thought to exert deleterious effects on surrounding neurons by releasing toxic factors into the ECM, including inflammatory cytokines, prostaglandins, and reactive oxygen species among others (de Boer et al., 2014; di Giorgio et al., 2007; Drachman et al., 2002; Haidet-Phillips et al., 2011; Marchetto et al., 2008; Nagai et al., 2007). The ECM can also modulate immune responses in the affected CNS areas in response to neurodegeneration by microglia. In several neurodegenerative diseases, the status of microglia is altered, changing their sentinel or housekeeping functions and promoting proinflammatory responses (Hickman et al., 2018). The increase in activated microglia leads to an abnormal secretion of inflammatory and immune-related proteins, which can have both protective and detrimental effects on neurons (Clarke & Patani, 2020; Li & Barres, 2018; McGeer & McGeer, 1995). Thus, the extracellular space should be contextualized as a reservoir of molecules secreted by resident and relatively distant cells that can have relevant effects on neural cells.

It is worth noting that in addition to biochemical changes in the ECM caused by the progressive neuronal and myelin loss, the increase in the number and reactive state of astrocytes and microglia in several neurodegenerative diseases or after injury may also be accompanied by changes in the mechanical properties of the neural microenvironment (Hall et al., 2021; McGeer & McGeer, 1995). Unfortunately, the experimental and technical hurdles to measure and to functionally validate the mechanical changes, have not allowed reliable determination of the contribution of mechanotransduction to the physiopathogenesis of these neurological conditions (Bonneh-Barkay & Wiley, 2009; Hall et al., 2021). Furthermore, the limited availability of models that can reproduce disease- and injury-related ECM changes, undermines our ability to directly assess the biological relevance of ECM changes to the pathophysiology of these conditions. By linking context-specific ECM changes to specific cellular behavioral responses, it may contribute to the understanding of neuropathogenesis as well as to the identification of reliable biomarkers and effective therapeutic targets (Bonneh-Barkay & Wiley, 2009; Hall et al., 2021).

4 | MATRICES FOR NEURAL APPLICATIONS

The development of matrices for neural applications has been an active area of research in recent years. These matrices, which can be natural or synthetic, are used in a variety of applications including in vitro modeling, tissue engineering, as well as cellular and drug therapeutics. The goal of using matrices in these approaches is to provide a suitable microenvironment for cells to grow, differentiate, and function, as well as to enhance regeneration and promote drug delivery. The design and development of matrices for neural applications is a complex process that involves consideration of the biocompatibility, mechanical properties, and bioactivity of the matrix material. In this review, we will explore the use of decellularized extracellular matrices as well as other natural and synthetic matrices for the study of neural regeneration and disease.

4.1 | Decellularized extracellular matrices

In recent years, tissue engineering has made significant progress, with biological scaffolds gaining attention for their biocompatibility and bioactivity. Among these scaffolds, decellularized extracellular matrix (dECM), which are biomaterials derived from human or animal organs/tissues after the removal of cellular components by decellularization techniques, are attracting the interest of multiple biomedical fields (Xu et al., 2021; Zhang, Du, et al., 2021). The decellularization process preserves the physicochemical signals and biological performance of the dECM, making it a suitable substrate for mechanical support and 3D biological scaffold for cell seeding (Yaldiz et al., 2022; Yao et al., 2019). Once seeded with cells, dECM scaffolds can be used in tissue engineering for in vitro cell regrowth, repair of damaged tissues, and replacement of missing organs (Abaci & Guvendiren, 2020; Cho et al., 2021; Cornelison

et al., 2018a; de Waele et al., 2015; Harting et al., 2009; Simsaid et al., 2021; Zhang, Zhang, et al., 2021). dECM can also be further processed into dECM hydrogels, which have multiple tissue engineering applications. For example, they can be used as the primary component of a delivery system for cells, growth factors, or genes in the treatment of various diseases; they can serve as bioinks for 3D tissue constructs; or they can be used as 2D and 3D platforms for in vitro modeling (Abaci & Guvendiren, 2020; Boso et al., 2020; Taylor et al., 2018; Xu et al., 2021). In this section, we will describe the current state of decellularized matrix protocols, verification methods, and post-processing protocols (Gu et al., 2017; Guo et al., 2010; Harris et al., 2017; Heng et al., 2017; Moura et al., 2022; Reginensi et al., 2020; Simsaid et al., 2021).

4.1.1 | Decellularization protocols

Ideal decellularization refers to the complete removal of cellular components while preserving the original architecture, composition, biochemical, and mechanical properties of the native tissue. Decellularization protocols for the CNS present significant challenges due to the intricate architecture and extensive vascularization of the brain and spinal cord. Currently, there is no gold standard method for decellularization of neural tissue as it is highly dependent on factors such as animal species, age, anatomical location, and size of the source tissue (Zhang et al., 2022). A variety of decellularization protocols have been developed in recent years, including physical (Rabbani et al., 2021), chemical (Ghuman et al., 2016), biological treatments (Sood et al., 2016), and combinations of these approaches (Baiguera et al., 2014; Buckenmeyer et al., 2020; Crapo et al., 2012; Gilpin & Yang, 2017; Mendibil et al., 2020; Nellinger et al., 2022) (Figure 4a and Table 2 summarize the major decellularization methods, their mechanisms of action, and outcomes). *Physical protocols* remove cellular material or disrupt myelin content using mechanical or sonic energy (Hussey et al., 2020). This can be accomplished using equipment such as homogenizers, sonicators, agitation, or high-pressure systems. While these methods are effective and speed up the decellularization process, they can also damage the ECM and alter its properties. *Chemical-based protocols* involve the use of alcohol, acid or base solutions, that solubilize lipids and help sterilize the ECM, which can be useful for in vivo applications. Surfactants are also included in this group and act by disrupting protein and/or lipid interactions in the cell membrane. For nervous tissue, the detergents sodium dodecyl sulfate (SDS) and sodium deoxycholate (SDC) are typically used in combination with other chemical agents such as Triton X-100 or ethylenediaminetetraacetic acid (EDTA), to enhance decellularization. This protocol is effective in removing cellular material but can also compromise the integrity of the ECM and the loss of bioactive molecules. Finally, many biological protocols are based on enzymatic treatments, particularly with trypsin, which facilitate the incorporation of detergents or DNase to remove DNA content, thereby reducing the immunogenicity of the ECM (Suss et al., 2022). Apoptotic or cytotoxic drugs, such as camptothecin, can also be used prior to the decellularization protocol to help eliminate immunogenic components (Cornelison et al., 2018b). These biological protocols are generally less aggressive than detergent-based protocols, but require the combinatorial use of chemical or physical agents to efficiently remove the resulting cellular debris (Akbari Zahmati et al., 2017; Keane et al., 2015; Mendibil et al., 2020; Nellinger et al., 2022). More detailed information on these decellularization methods can be found in the following references (Buckenmeyer et al., 2020; Mahdian et al., 2023; Moffat et al., 2022; Rabbani et al., 2021; Zhang et al., 2022).

Each method has its own limitations, and the appropriate combination for decellularization of CNS tissue remains to be optimized. Obtaining appropriate protocols for decellularization of neural tissues from different spatiotemporal and condition-specific contexts requires an iterative process, where protocol adaptations and systematic comparative analysis between them will allow to exploit the full potential of decellularized scaffolds in CNS applications.

4.1.2 | Decellularization verification methods

The verification techniques can be broadly categorized into several key areas, each addressing a distinct aspect of the dECM quality and suitability for its intended use (Figure 4b).

(a) Efficacy of cell removal and cytocompatibility

Various tests evaluate the effectiveness of the decellularization method, including quantitative analyses to measure DNA, myelin, and phospholipid content within the dECM. The complete removal of antigens and nucleic acids along with other cellular components ensures the biocompatibility of the scaffold. The presence of residual DNA derived from nuclear or mitochondrial sources are endogenous danger signals, also known as damage-associated molecular patterns

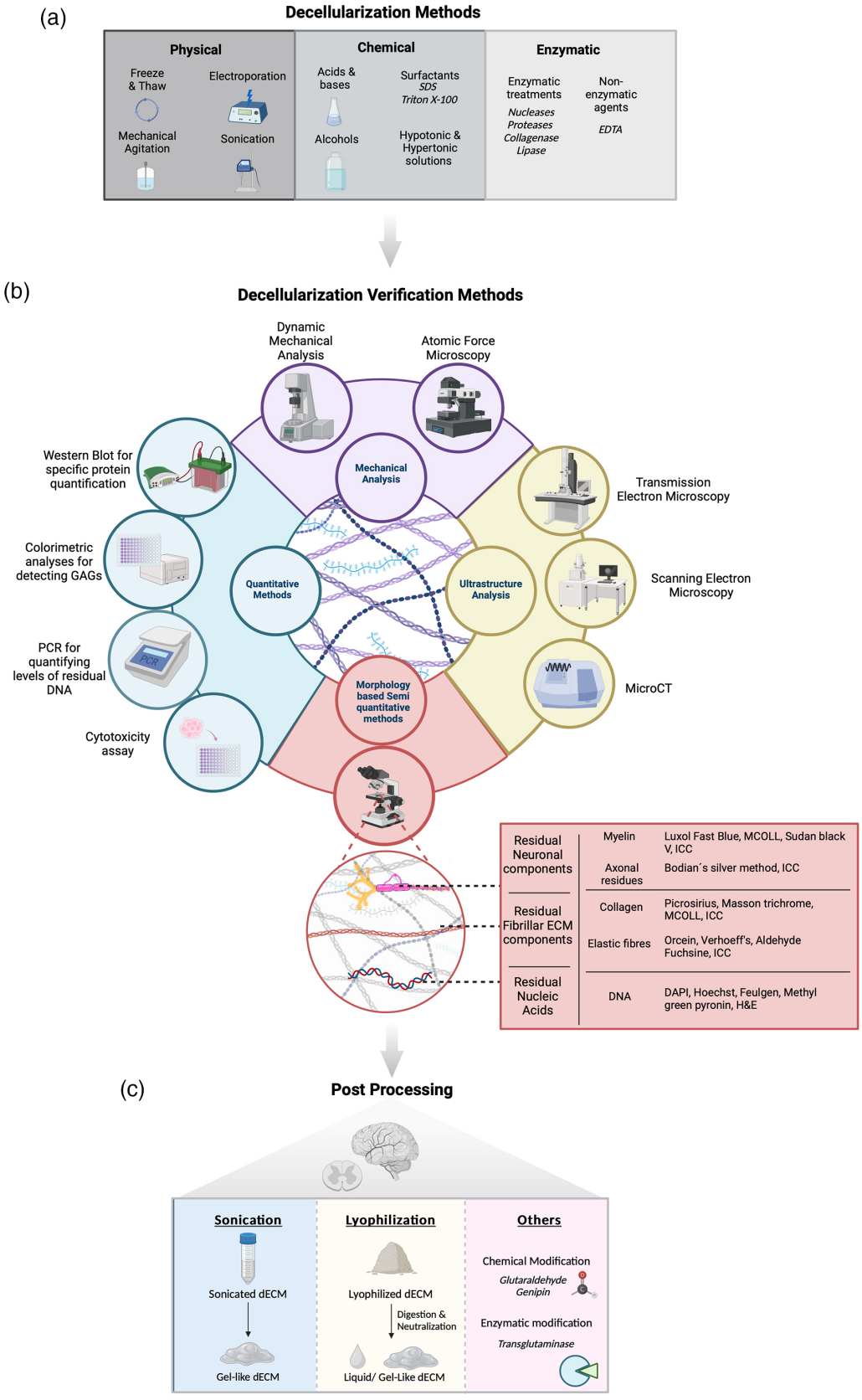

FIGURE 4 Legend on next page.

(DAMPs), which can activate the innate immune system and potentially trigger an inflammatory response after dECM-based implantation therapies (Wood & Goto, 2012). Accordingly, exacerbated proinflammatory responses have been correlated with increased accumulation of DNA, mitochondria, and cell membrane debris within ECM scaffolds, underscoring the need for careful evaluation and elimination of cellular components during decellularization (Londono et al., 2017). Crapo's criteria, which propose a threshold of less than 50 ng/mg dsDNA with less than 200 base pairs and the absence of nuclear material when stained with nucleic acid-specific dyes such as DAPI, serve as benchmarks for effective decellularization (Crapo et al., 2011). Semi-quantitative staining-based methods, complemented by quantitative approaches such as PCR, immunofluorescence, and PicoGreen™ assays, are commonly used for comprehensive assessment (Bible et al., 2012; el Soury et al., 2021).

(b) Ultrastructure evaluation

Scanning and transmission electron microscopy (SEM and TEM) provide valuable insight into various ultrastructural metrics, including porosity, fiber bundle structure, and density of dECM. In addition, microcomputed tomography imaging allows comprehensive visualization of the entire dECM. An example of the potential of this approach was demonstrated by Wüthrich and colleagues, who provided unprecedented insight into the vascular architecture within perfusion-based decellularized peripheral nerves (Wüthrich et al., 2020). It is noteworthy that preservation of the native ECM microstructure significantly influences cellular regeneration and activity (Philips et al., 2018).

(c) Biochemical analysis

Histological staining techniques are adept at identifying fibrillar structures such as collagen, myelin, and elastin, while quantitative methods such as colorimetric analysis, Western blotting, or mass spectrometry-based analysis, facilitate the detection of key ECM components such as GAGs, collagen, FN, and laminin, which are critical for modulating regeneration, promoting cell survival after injury, and mitigating apoptosis (Huang et al., 2023).

(d) Mechanical testing

Mechanical testing provides valuable insight into the presence, distribution, and integrity of key structural proteins, such as collagen and elastin fibers, within the dECM. Techniques such as atomic force microscopy and both uniaxial and biaxial mechanical testing are widely used to evaluate and compare the mechanical properties of decellularized tissues with their native counterparts (Peng et al., 2019).

4.1.3 | Postprocessing protocols

After decellularization, the ECM can be processed by a variety of methods, including sonication, lyophilization, chemical modification, and functionalization. Sonication is a process that uses high-frequency sound waves to break up and disperse any remaining cellular debris or components within the decellularized tissue (Hussey et al., 2020). This can improve the homogeneity and consistency of the decellularized tissue, making it more suitable for use in tissue engineering and other applications. Lyophilization, also known as lyophilization, is a process in which water is removed from the tissue by sublimation under vacuum. This can help to stabilize the tissue and increase its shelf life, making it easier to store and transport. The resulting dECM powder can be solubilized by digestion in a pepsin solution, in an acidic environment, and then re-equilibrated to physiological conditions (Abaci & Guvendiren, 2020; Buckenmeyer et al., 2020; Crapo et al., 2012; Medberry et al., 2013; Saldin et al., 2017). The solubilized ECM can be self-assembled into a nanofibrous hydrogel at physiological temperature. It is worth noting that during the solubilization process, pepsin can disrupt the collagen fibers and alter the composition, structural integrity, and mechanical properties of the resulting dECM (Figure 4c; Pouliot et al., 2020; Yaldiz et al., 2022).

FIGURE 4 Overview of major decellularization, verification, and postprocessing techniques. (a) Table detailing the physical (Rabbani et al., 2021), chemical (Ghuman et al., 2016), and enzymatic (Sood et al., 2016) decellularization methods for CNS tissues. (b) Diagram illustrating the verification methods for decellularization efficacy, categorized into quantitative, morphology-based semi-quantitative assessments, mechanical, and ultrastructural analyses. (c) Table summarizing postprocessing approaches for CNS applications, including sonication (Hussey et al., 2020), lyophilization (Abaci & Guvendiren, 2020), chemical modification, and functionalization (Buckenmeyer et al., 2020).

TABLE 2 Summary of decellularization protocols for CNS applications.

Decellularization method		Effect	Pros	Cons	Reference
Chemical	Surfactants (SDS, SDC, Triton X-100) Acids and/or bases Hypo or Hypertonic solutions Alcohol	- Disrupt protein and lipid interactions and cell membranes. - Hydrolytic degradation of biomolecules and solubilization of cytoplasmic components. - Cause osmotic shock, dehydration, and cell lysis.	- Remove the cellular components and maintain less amount of DNA. - Preserve the highest sulfated GAGs contents. - Retention of growth factors. - Remove axon-inhibitory proteins.	- Protein denaturation. - The concentration of surfactant should be balanced to avoid loss of functional proteins or impairment in the proteomic analysis. - It can modify the ECM stiffness.	Cho et al., 2021; DeQuach et al., 2011; Hong et al., 2020b; Jin et al., 2018; Lam et al., 2019; Nieto-Nicolau et al., 2021; Simsaid et al., 2021; Sood et al., 2019; Sun et al., 2020
Physical	Freeze–thaw Mechanical agitation Sonication	- Disrupt cell membrane, mechanically or via ice crystal formation.	- Remove cellular components in an efficient manner. - Reduce the time of decellularization protocols.	- It might destroy ECM network, therefore affecting the mechanical properties.	Cho et al., 2021; Crapo et al., 2012; DeQuach et al., 2011; Hong et al., 2020b; Jin et al., 2018; Lee et al., 2019; Nieto-Nicolau et al., 2021; Simsaid et al., 2021; Sood et al., 2019; Sun et al., 2020
Biological	Enzymatic (Nucleases, proteases, collagenase, lipase) Cytotoxic/ apoptotic drugs	- Catalyze the cleavage of phosphodiester bonds of nucleotides, fragmenting DNA and RNA for inactivation. - Cleave lysine and Arginine residues. - Commonly used in combination with chelating agents, such as EDTA.	-High amount of neurotrophins and growth factors preserved. - Sterilizing agents.	- It requires the combination with physical or chemical methods. - Implicated in the loss of glycosaminoglycans (GAGs).	Cho et al., 2021; Cornelison, Gonzalez-Rothi, et al., 2018; DeQuach et al., 2011; Hong et al., 2020b; Jin et al., 2018; Lam et al., 2019; Nieto-Nicolau et al., 2021; Simsaid et al., 2021; Sood et al., 2019

After the initial post-processing steps such as sonication and lyophilization, advanced methods including chemical and enzyme-mediated modification, further refine the functionality and suitability of dECM for CNS-related applications. Post-processing *chemical modifications* can introduce functional groups into the tissue to enable specific interactions with cells or other materials (Xue et al., 2018). For instance, cross-linking with glutaraldehyde or genipin can improve the mechanical strength and stability of the decellularized tissue by forming covalent bonds between the tissue components (Baiguera et al., 2014; Jiang et al., 2013; Keane et al., 2012). Incorporation of bioactive molecules, including neurotrophins and other growth factors, directly into the dECM provides a supportive environment that mimics the native CNS milieu and promotes neural regeneration and functional recovery (Aubin et al., 2016; Ventura et al., 2020). *Enzyme-mediated modification*, such as the use of transglutaminase, can selectively modify ECM proteins and subsequently alter the structure of the ECM to enhance bioactivity to promote neural cell attachment, and differentiation (Zhang et al., 2022).

Given the complex challenges and innovative solutions presented in the field of decellularization, particularly in CNS applications, the trajectory of this field is toward refining and tailoring protocols to achieve more precise and beneficial results. The current trajectory, characterized by innovative postprocessing techniques such as chemical and enzyme-mediated modifications, is promising. These methods not only refine the structural and functional integrity of dECM, but also enrich it with bioactive signals essential for tissue-specific regeneration. As the field moves forward, a major focus will be on overcoming the limitations of current protocols, with respect to batch variability, residual DNA content, and loss of critical ECM components. The future direction appears to be driven by a dual emphasis on innovation and verification, that is, the development of new techniques that are both effective in decellularization and capable of preserving or even enhancing the native properties of the ECM, coupled with rigorous verification methods to ensure the safety and efficacy of dECM-based therapies.

4.2 | Decellularized extracellular matrix technologies for CNS regeneration

The application of ECM strategies for tissue repair spans multiple disciplines. In the quest to advance CNS regeneration, the choice of ECM scaffolds plays a critical role in creating a provisional microenvironment conducive to tissue repair. Because of its biological activity, tissue specificity, tolerability, and minimal immunogenicity, dECM provides an effective platform for both in vitro studies and therapeutic interventions in the CNS (Xu et al., 2021). The wide range of dECM-based applications includes its use as a delivery system, transplantation matrix, preseeded scaffolds, and injectable solutions. In this section, we will review the regenerative potential of several of these methods.

4.2.1 | dECM-based delivery systems

Advances in biomaterials science have greatly enriched the development of new technologies tailored for controlled drug delivery (Shan & Wu, 2024). Among these innovations, the use of ECM-based carriers for minimally invasive delivery injections represents a significant leap forward, offering targeted treatments for injury and disease. ECM-based delivery systems have been developed to precisely control the localized release of encapsulated therapeutic agents such as cells (Bae et al., 2021; Cerqueira et al., 2018; Jiang et al., 2020; Liu et al., 2017; Marquardt et al., 2020; Wang et al., 2012a; Yang et al., 2010), growth factors (Angelova et al., 2013; Xu et al., 2016; Xu et al., 2018), or other substances (Faust et al., 2017; Tsintou et al., 2021) in localized manner at the site of injury or disease. These systems are intended to overcome the limitations of conventional drug delivery methods with respect to efficacy and toxicity (Li & Mooney, 2016). Conventional delivery systems often require either high doses or frequent administration, which can compromise the efficacy of treatments and pose a higher risk of side effects and toxicity, highlighting the importance of advances in delivery system technology for safer and more effective therapeutic applications. An illustrative case of therapeutic agents embedded in dECM-based delivery systems is extracellular vesicles (EVs). EVs are natural nano-sized carriers that can be derived from a variety of cultured cells. This method takes advantage of the inherent regenerative cues found in EVs to potentially streamline the regeneration and repair of neuronal pathways (Bahram Sangani et al., 2021; Moore et al., 2019). In particular, Tsintou and colleagues highlighted the efficacy of EVs, particularly those derived from mesenchymal stem cells (MSC), when combined with ECM-based injectable hydrogels (Figure 5a). This strategy was designed to enhance neural recovery mechanisms, particularly after stroke in nonhuman primates, by prolonging the presence of EVs at the site of injury and amplifying their targeted effects (Tsintou et al., 2021;

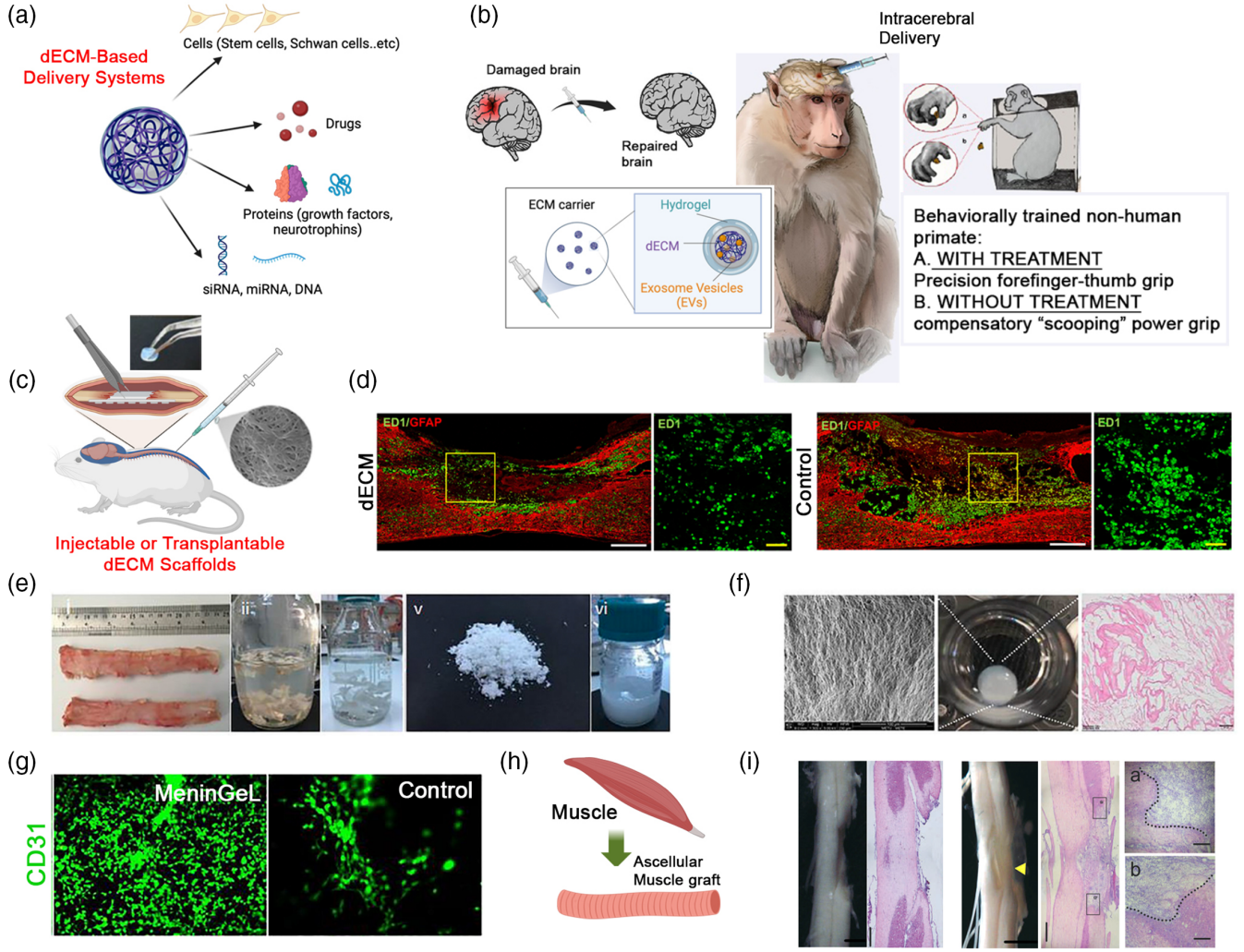

FIGURE 5 Decellularized extracellular matrix (dECM) strategies for CNS regeneration. (a) Schematic representation of dECM as a multifunctional carrier for targeted delivery of cells, drugs, proteins, and/or nucleotides to the CNS. (b) Illustration of strategies based on extracellular vehicles (EVs) encapsulated within dECM-based injectable hydrogel particles designed for in situ injection at brain lesion sites to facilitate repair after stroke in nonhuman primates. The inset shows the syringe loaded with the hydrogel mixture enriched with dECM and EVs, with the dECM serving as a sustained release system for the EVs. This arrangement minimizes clearance from the body and maximizes the targeted therapeutic effects of the EVs. Panels (a) and (b) were adapted with permission from (Tsintou et al., 2021). (c) Schematic representation of dECM as an injectable or transplantable therapy for SCI. (d) Histological section of the injured spinal cord tissue samples treated with dECM hydrogels after implantation for 8 weeks. Representative immunofluorescence images of ED1 positive cells (macrophages in green) and GFAP (astrocytes in red). Collagen hydrogel served as a control. Panels (c) and (d) were adapted with permission from (Hong et al., 2020b) under Creative Commons (CC) license number: 5750221418334. (e) Image showing the process of decellularization of spinal meninges. (f) Scanning electron microscopy micrograph (left) and histological image of hematoxylin and eosin (H-E) staining (right) obtained from meninges-derived hydrogel sections. (g) Immunofluorescence images of CD31 cells in MeninGel and control (Matrigel). Panels (e)–(g) were adapted with permission from (Ozudogru et al., 2021) under CC license number: 5750240819585. (h) Schematic representation of acellular scaffolds for SCI repair. (i) Photographs and H-E stained sections showing ventral views of the spinal cord without (left) or with (right) chemically extracted acellular muscle scaffold at 4 weeks after implantation. Panels (h) and (i) were adapted with permission from (Zhang et al., 2012) under license number: 5750241337916. The rest of the figure was originally created by the authors of this article.

Figure 5b). A study by Faust and colleagues found that the combination of nonhomologous ECM hydrogels with EVs significantly increased neuronal cell survival and neurite outgrowth after SCI, surpassing the effects observed with EVs alone (Faust et al., 2017). Hernandez et al. explored the use of decellularized porcine tissue-derived ECM hydrogels as delivery systems for miRNA and EVs. Their research showed that these hydrogels can encapsulate and preserve the

bioactivity of miRNA and EVs, provide controlled and prolonged release, and protect them from rapid degradation (Hernandez et al., 2018).

ECM-based strategies have also proven useful for modulating morphogen delivery as a therapeutic approach. In a study by He-Lin et al., an acellular spinal cord scaffold (ASC) embedded in a thermosensitive hydrogel was designed to overcome the barriers associated with short-term stability and delivery of bFGF in the treatment of SCI. Integration of the ASC was critical in facilitating sustained and controlled release of bFGF, which significantly enhanced functional recovery in rat models after SCI. This recovery was characterized by stimulated axonal regeneration and neural stem cell differentiation, results not achieved by the thermosensitive hydrogel alone (Xu et al., 2016).

4.2.2 | Injectable and transplantable dECM scaffolds

dECM scaffolds, which can be either injectable or transplantable, are designed to create a physical and chemical structure that mimics the native extracellular environment (Yaldiz et al., 2022). Compared to solid dECM, injectable strategies, particularly ECM-based hydrogel scaffolds and bioinks, have shown considerable potential by providing an optimal mix of native extracellular signals that promote cellular ingrowth. This approach allows for minimally invasive injection, making it suitable for accessing deep or more diffusely damaged areas of the CNS that are not easily accessible by surgery. Once injected, the hydrogel conforms to the shape of the lesion, filling irregular spaces and creating a scaffold that supports cellular infiltration and tissue regrowth (Hasanzadeh et al., 2023). On the other hand, transplantable acellular scaffolds offer a different approach to CNS repair by providing a preformed, bioengineered environment that can be implanted directly into the lesion site. Unlike injectable hydrogels, which shape are highly malleable to the lesion space upon injection, transplantable scaffolds are designed and shaped ex vivo prior to placement in the damaged area. This strategy allows precise control over the physical properties of the scaffold, including shape, size, and mechanical strength, which can be tailored to the specific needs of the injury site (Shafiee et al., 2020; Zhang et al., 2022). Transplantable dECM scaffolds are particularly useful in cases where substantial structural support is needed to bridge large gaps or cavities in CNS tissue. Next, we will review some examples of injectable and transplantable dECM technologies, highlighting their successful integration with CNS tissues, and their subsequent impact on regeneration and healing.

Many approaches to enhance CNS regeneration have used decellularized tissue from either the CNS or PNS. Spinal cord dECM is increasingly being used in traumatic spinal cord injury (SCI) and offers several advantages that are only beginning to be explored in the treatment of traumatic brain injury (TBI; Jiang et al., 2023). Wu and colleagues have shown that brain-derived dECM hydrogels provide sustained protection of structural and functional brain integrity after TBI. This was evidenced by improved neurobehavioral outcomes, reduced glial scar formation, and decreased microglial pro-inflammatory responses (Wu et al., 2017). Similarly, Hong et al. investigated the use of porcine brain dECM hydrogels to influence macrophage behavior and promote neuronal regeneration in an SCI model (Figure 5c,d). The dECM hydrogels, at various concentrations, were found to induce macrophages to adopt an anti-inflammatory M2 phenotype and enhance neurite outgrowth, leading to significant improvements in locomotor function when applied to rat SCI models (Hong et al., 2020). Many other biological functions with regenerative potential have been attributed to brain dECM: it promotes significant angiogenic responses (Ribatti et al., 2003), enhances neural lineage differentiation from MSC and induced pluripotent stem cells (iPSC) in vitro (DeQuach et al., 2011), promotes the formation of neural network brain architecture (Sood et al., 2016), has the ability to increase cellular adhesion and proliferation in culture (He et al., 2015), and maintains neural differentiation phenotypes upon the introduction of mitogenic stimuli (de Waele et al., 2015).

Recent research highlights the importance of neural dECM-based treatments in reducing inflammation, promoting neural regeneration, and facilitating functional recovery after traumatic injury. For example, the work of Ozudogru and Arslan (2021) and Ozudogru et al. (2021) describe the creation of a hydrogel derived from decellularized bovine spinal cord meninges, which they named MeninGEL, that retains the original biochemical structure and matrix components for use in SCI repair (Figure 5e–g). MeninGEL forms a self-supporting hydrogel at body temperature and exhibits excellent cell compatibility, promoting the differentiation of human MSC into neural cells and inducing endothelial cells to form vascular structures without the need for additional growth factors, thereby improving functional recovery (Ozudogru et al., 2021; Ozudogru & Arslan, 2021). Another example comes from a study by Cerqueira et al. demonstrating the regenerative efficacy of peripheral nerve matrix in spinal cord contusion lesions. Transplantation of decellularized nerve grafts effectively bridged the injury gap, established immune tolerance, and supported spinal cord cell

survival and axonal growth in treated rats (Cerqueira et al., 2018). Similarly, Cornelison et al. observed that transplanted decellularized nerve grafts, helped modulate the immune response by reducing the M1:M2 macrophage ratio in a rat cervical contusion model (Cornelison et al., 2018).

There are also documented cases of the use of decellularized tissues of non-neural origin for CNS applications. Zhang et al. demonstrated the potential of acellular muscle grafts as scaffolds for spinal cord injury repair (Figure 5h,i). Their study found that these scaffolds not only integrated well with the host tissue, but also promoted significant axon sprouting and led to increased neuron survival in treated rats (Zhang et al., 2012). Tukmachev et al. and Crapo et al. developed injectable hydrogels using spinal cord-derived dECM (SC-dECM) and urinary bladder-derived dECM (UBM) to investigate whether tissue-specific ECM had an advantage over ECM from other tissue sources (Crapo et al., 2012; Tukmachev et al., 2016). Tukmachev's study showed no significant differences between SC-dECM and UBM in rat spinal cord injury. However, they reported that both SC-dECM and UBM had increased vascularization, neurite outgrowth, and macrophage polarization capabilities compared to the control group (Tukmachev et al., 2016). Exploring innovative treatments for stroke, recent studies by Ghuman et al. also utilized UBM hydrogel for regenerative purposes (Ghuman et al., 2016; Ghuman et al., 2017). In these studies, Ghuman and colleagues observed that injection of UBM hydrogel into the affected stroke area resulted in increased cellular proliferation, particularly around the rim of the cavity and to a lesser extent within the core of the hydrogel itself. The presence of UBM hydrogel was also associated with an increase in M2 macrophage polarization, an indication of beneficial tissue remodeling. However, further research in animal models showed that although the UBM hydrogel reduced the size of the cavity created by the stroke, it did not significantly alter the formation of scar tissue (Ghuman et al., 2017). Collectively, these studies provide insight into the diversity of ECM-based approaches and their regenerative potential for traumatic CNS injury.

Recent studies have also demonstrated the ability of dECM in neurodegenerative disease applications. For example, an in vitro study by Bae et al. highlighted that laminin-supplemented porcine brain dECM can regulate human neurons, astrocytes and microglia offering a viable method to mimic humanized brain environment for neurological studies (Bae et al., 2023). In addition, dECM was shown to be neuroprotective against amyloid beta-induced toxicity in vitro, suggesting its potential as a therapeutic agent for AD (Zhang et al., 2019). Another promising application of dECM is in the treatment of PD, where Lin and team have pioneered the development of a specialized brain dECM hydrogel that was carefully engineered to meet the therapeutic needs of this disease (Lin et al., 2017). The study showed that the rat brain dECM scaffolds functionalized with bFGF not only promoted cell survival in vitro, but also significantly enhanced behavioral recovery in a PD rat model, lasting up to 20 days after treatment (Lin et al., 2017).

Among these examples, precision engineering of dECM is emerging as a key area of focus, with advanced biofabrication techniques, including 3D bioprinting (Liu, Gong, et al., 2023; Tang et al., 2021; Wang et al., 2022) and electrospinning (Mungenast et al., 2023), on track to accelerate the development of dECM therapeutic solutions. These methods will enable the creation of patient-specific dECM scaffolds that precisely replicate the complex architecture and composition of individual CNS tissues.

4.3 | Advanced matrices for CNS regeneration: Natural, synthetic, and combinatorial approaches

While dECM provides an environment that closely mimics biological conditions, it faces obstacles such as limited availability, batch-to-batch inconsistencies, and scalability issues. To address these challenges, scientists have explored the use of both natural and synthetic ECM matrices. Natural matrices offer high biocompatibility and can be tailored to specific needs. Conversely, synthetic matrices offer consistency, scalability, and customizable physical and chemical properties, but sometimes lack the full biological complexity of natural matrices. The decision to use natural, synthetic, or/and dECM matrices thus depends on balancing biological relevance with practical considerations such as reproducibility and availability, tailored to the unique requirements of each CNS application.

4.3.1 | Natural matrices

An alternative to the whole ECM-derived matrix is the use of purified ECM proteins from animals (e.g., fibrin, laminin, collagen, FN, HA) and plants (including alginate, agar, carrageenan, and fucoidan; Catoira et al., 2019; Li et al., 2014) (Figure 6). These approaches fail to replicate the morphologic structure of the native ECM, but retain other properties

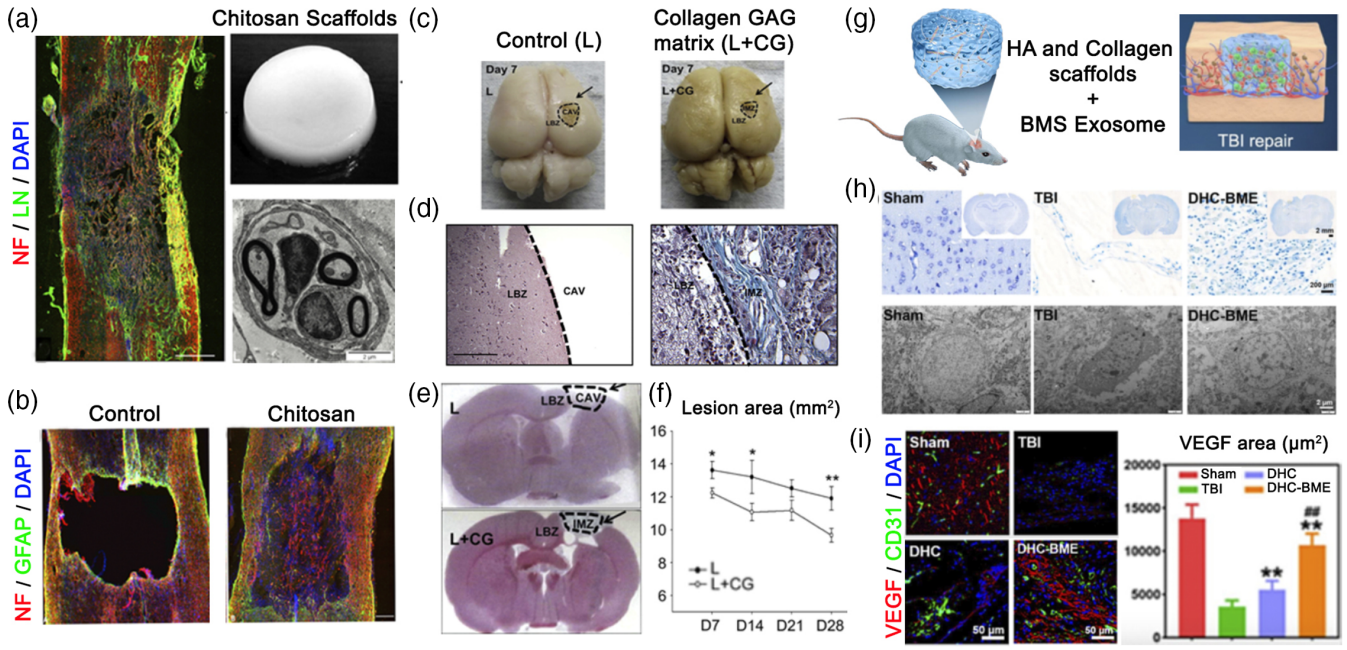

FIGURE 6 Examples of natural matrices for CNS applications. (a-b) Chitosan-FPHS implantation results in reduced astrocytic response and robust axon regrowth. (a) Fluorescence micrograph (left) showing a correlation of the distribution of axons (NF, red) with laminin (LN, green) within the lesion-Chitosan-FPHS implantation site. Insets show chitosan-FPHS photograph (top right) and electron microscopy image showing a tubule containing axons myelinated by Schwann cells (bottom right). (b) Fluorescence micrographs of longitudinal spinal cord sections in sham and chitosan-FPHS groups 4 weeks after lesion; GFAP astrocytes (green), NF-labeled axons (red), and DAPI nuclei (blue). Panels (a) and (b) were adapted with permission from (Chedly et al., 2017) under CC license number: 5750680382756. (c–f) Morphologic evidence of tissue repair in the lesion area associated with CG matrix implantation. (c) Photograph of the whole brain 7 days after unilateral surgical brain lesion in the right hemisphere with implantation of a CG matrix in the lesion area (L + CG) (right) compared to that without implantation (L) (left). (d) Representative micrographs of H-E stained coronal sections from an L brain showing the presence of cells in the lesion boundary zone (LBZ) adjacent to the cavity (CAV) (left) or cells + collagen fibers surrounding the CG scaffold in the intra-matrix zone (IMZ) previously devoid of cells (right). (e) Images of H-E stained coronal sections of an L or L + CG brain. Black arrows indicate the location of the lesion in L and the CG matrix is shown as a gray insertion in the L + CG brain. (f) Line graph showing lesion areas in the same injured section (2.0 mm anterior to the bregma). Panels (c)–(f) were adapted with permission from (Huang et al., 2012) under CC license number: 5750690829586. (g) Schematic illustration of the biomimetic construction of BME-incorporated HA-Col hybrid hydrogel (DHC) and the co-effect on the recruitment and differentiation of endogenous NSC and angiogenesis in TBI rats. (h) Nissl staining images to assess neuronal regeneration at 14 days postinjury (dpi; top) and TEM images to observe the structures of neurons in the lesions at 28 dpi (bottom). (i) Immunofluorescence staining images of CD31/VEGF double staining showing the angiogenic potential of HA-Col hybrid hydrogel (left). Bar graph of area occupied by VEGF+ vessels per field in Sham, TBI, DHC, and BME-DHC hydrogels (right). Panels (g)–(i) were adapted with permission from (Liu, Wu, et al., 2023) under CC license number: 5750680988451.

such as high biocompatibility, low toxicity, biodegradability, and the ability to bind water. In recent years, these natural matrices have been explored for their potential in CNS applications (Cao et al., 2009; Fan et al., 2017; Gros et al., 2010; Zeng et al., 2011; Zhang et al., 2022; Zhang, Liu, et al., 2021). A selection of examples is presented below to illustrate their use and efficacy.

Chitosan is a degradable cationic polysaccharide with excellent biocompatibility and low immune rejection. Chitosan degradation products can be metabolized and easily made into hydrogels (Delmar & Bianco-Peled, 2016). Chitosan and other polymers have been widely used in nerve tissue regeneration. Chedly et al. demonstrated that a chitosan hydrogel scaffold, when implanted in the rat spinal cord after injury, significantly promoted tissue repair by directing astrocyte processes toward the lesion to promote axonal growth into and beyond the injury site (Figure 6a,b). It also modulated the inflammatory response, resulting in significant improvements in motor function (Chedly et al., 2017).

Collagens and *FN* are other natural matrices used as backbone hydrogels for CNS applications. King et al. evaluated the potential of four injectable biomaterials: collagen, viscous FN, fibrin, and a mixture of fibrin and FN (FB/FN). They gelled in situ for repair after SCI, avoiding the need for tissue excision required by preformed devices. Their results

indicated that while all materials supported axonal growth and integration with the host spinal cord, the FB/FN mixture showed superior properties in handling, integrating, and promoting robust axonal growth, making it a promising candidate for filling injury-induced cavities in the spinal cord (King et al., 2010). Huang et al. investigated the use of collagen-glycosaminoglycan (CG) scaffolds to evaluate their efficacy in promoting neural regeneration after surgical brain trauma. Their results showed that CG scaffold implantation significantly improved functional recovery by facilitating the proliferation, differentiation, and migration of endogenous neural progenitor cells and increasing the tissue concentration of neurotrophic factors (BDNF and GDNF), suggesting its potential as a clinical strategy for tissue regeneration and recovery after brain injury (Huang et al., 2012) (Figure 6c–f).

HA has been widely used in TBI and SCI applications to reduce inflammation, by inhibiting fibrotic scar formation after SCI, while promoting angiogenesis and improving recovery of nerve function (Meng et al., 2014). A recent study proposed a novel method of incorporating bone marrow mesenchymal stem cell (BMSC)-derived exosomes (BME) into hyaluronan-collagen hydrogel (DHC-BME) to achieve both brain matrix mimicry and sustained release of exosomes for TBI healing. The results showed that DHC-BME induced neurogenesis and angiogenesis by recruiting endogenous NSCs. In addition, this approach enhanced remyelination, axonal regeneration, synapse formation, glial scar inhibition, brain structural remodeling, and remarkable functional recovery (e.g., motor, sensory, reflex, balance, and spatial learning and memory) in a TBI rat model (Liu, Wu, et al., 2023) (Figure 6g–i).

Plant-derived matrices, such as fucoidan, have been investigated for their potential to promote neural tissue regeneration (Nascimento et al., 2021; Yao et al., 2021). A study by Kim and co-authors demonstrated the ability of fucoidan-based hydrogels to promote the differentiation of NSCs into functional neurons (Kim et al., 2020). The use of these natural matrices, particularly in neural tissue engineering, highlights their potential to mimic the complex environment of the CNS, facilitating not only cell growth but also specific functional outcomes.

Combinations of multiple natural ECM components and novel methods have recently been used to reverse neural dysfunction following traumatic injury. For example, Liu et al. used 3D printing technology to create scaffolds composed of collagen, chitosan, and exosomes derived from human umbilical cord MSC stimulated with brain-derived neurotrophic factor (BMExos). Their results showed that this 3D-CC-BMExos therapy not only enhanced the recovery of neuromotor and cognitive functions in a TBI rat model, but also promoted the remodeling of neural networks, indicating significant improvements in nerve fiber regeneration, synaptic connections, and myelin sheath reconstruction (Liu, Zhang, et al., 2023).

4.3.2 | Synthetic and semi-synthetic materials

Semi-synthetic and synthetic materials (Figure 7) have emerged as an alternative to dECM and natural matrices due to the scalability and reproducibility of these materials (Lin & Anseth, 2009; Rubert Pérez et al., 2015). Here, we will describe some examples of these materials and their potential for use in in vivo and in vitro CNS studies:

Water-soluble synthetic polymers such as poly (ethylene glycol) (PEG) or poly(ethylene glycol) diacrylate (PEGDA), are widely used in tissue engineering applications due to their tunable mechanical strength, excellent biocompatibility, and minimal immunogenicity. However, their chemical nature can result in reduced cell viability and adhesion compared to natural matrices (Hoffman, 2012). The use of short bioactive peptide sequences for surface modification or as part of the material, have improved the bioactivity of these polymers. For example, short peptide-functionalized PEG hydrogels have been shown to support neural stem cell growth and differentiation (Ali et al., 2013; Chapla et al., 2020; Li et al., 2018; Mosley et al., 2017). Functionalized PEGDA and GelMA have also been shown to not only improve cell viability and cell migration, but also to allow tuning of mechanical properties (Chapla et al., 2020; Hu et al., 2022; Lim et al., 2017; Mosley et al., 2017; Shahidi et al., 2021; Ye et al., 2020).

Synthetic polymers, such as the polyionic complex (PIC), formed by the electrostatic interaction of oppositely charged polyelectrolytes, have been investigated for their potential use in neural tissue engineering. In particular, Pratt et al. (2004) have successfully cultured Schwann cells in a three-dimensional, functionalized PIC polymer, achieving high cell viability. Similarly, poly(acrylic acid) (PAA) hydrogels have been successfully used as substrates for neural cell culture, with promising results in terms of both biocompatibility and support for neural electrode applications (Lu et al., 2009).

The use of *injectable self-assembling peptide* (*SAP*) *hydrogels* in brain and spinal cord tissue engineering has also been highlighted in recent years (Hong et al., 2019; Rubert Pérez et al., 2015). These hydrogels are formed through noncovalent interactions to produce structures with the high molecular mass typically associated with covalent

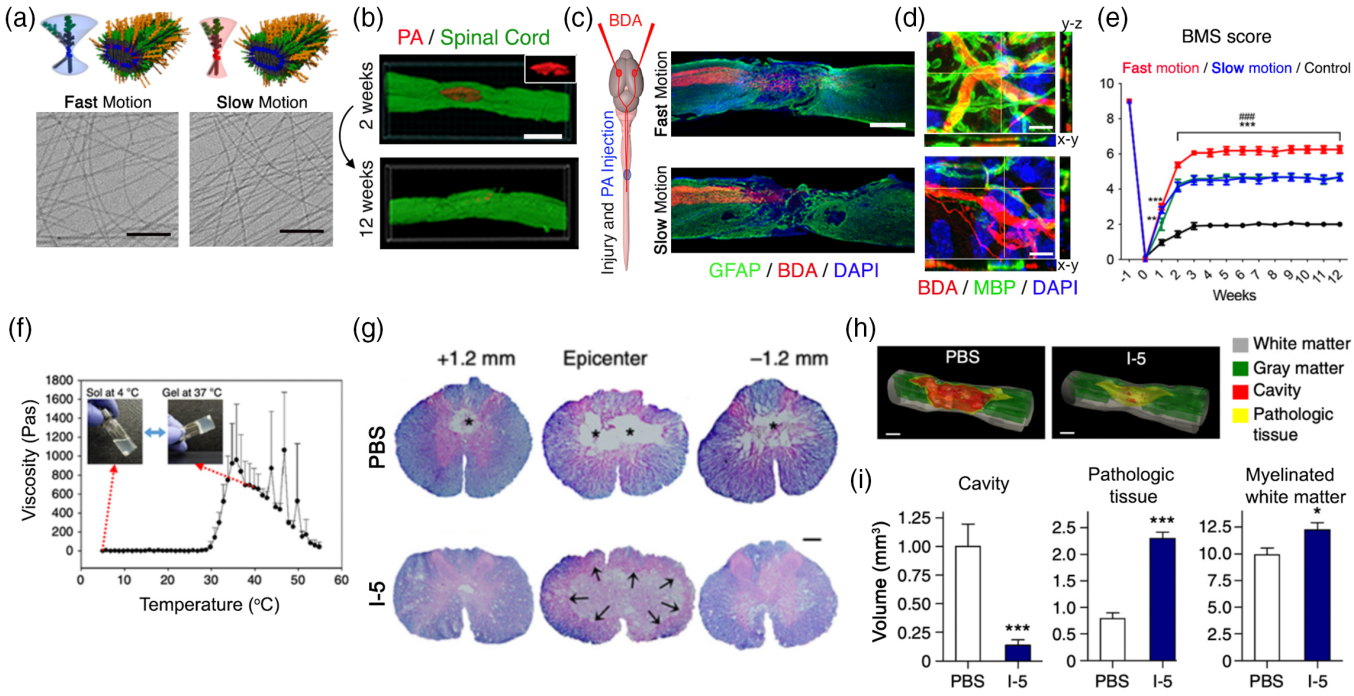

FIGURE 7 Examples of synthetic matrices for CNS applications. (a–e) Two chemically different peptide amphiphile scaffolds with two identical bioactive sequences reveal differences in the growth of corticospinal axons and functional recovery after SCI. (a) Molecular graphics representation of a supramolecular nanofiber showing two bioactive signals with different molecular motions (top); cryo-TEM micrographs of IKVAV PA2 co-assembled with FGF2 PAs (FGF2 PA1 fast motion and FGF2 PA2 slow motion) (bottom). (b) Fluorescence micrographs of spinal cords (green) injected with PA (red) covalently labeled with Alexa 647 show the degradation of the material 12 weeks after injection. (c) Fluorescence micrographs of longitudinal spinal cord sections in fast- and slow-motion PA hydrogel groups; GFAP astrocytes (green), BDA-labeled axons (red), and DAPI nuclei (blue). (d) Representative 3D fluorescence micrographs of BDA-labeled axon regrowth (red) and myelin basic protein (MBP, green). (e) Basso Mouse Scale (BMS) for locomotion. Panels (a)–(e) were adapted with permission from (Álvarez et al., 2021). (f–i) Imidazole poly(organophosphazenes) (I-5) injectable hydrogel for SCI repair in a rat with spinal contusion injury. (f) Graph showing viscometer measurements of temperature-dependent sol–gel transition and viscosity changes. Demonstration of rapid gelation of I-5 polymer solution at 4C and 37C. (g) Coronal sections of spinal cord treated with PBS or I-5 injection stained with eriochrome cyanine. There are no cystic cavities in the I-5 injections. (h) Three-dimensional reconstruction of spinal cords treated with PBS and I-5. (i) Bar graphs showing volume of postinjury cavity, pathological tissue, and myelinated white matter. Panels (f)–(i) were adapted with permission from (Hong et al., 2017). The rest of the figure was originally created by the authors of this article.

macromolecules, and allow the incorporation of distinct bioactive epitopes. These versatile hydrogels have been used primarily as injectable systems in models of stroke or traumatic CNS injury to improve cell survival and functional outcomes (Edelbrock et al., 2018; Hlavac et al., 2020; Hong et al., 2019; Pavlović et al., 2023; Tysseling-Mattiace et al., 2008). In a recent example, Alvarez et al. designed and characterized an injectable peptide amphiphile (PA) supramolecular polymer displaying two distinct signals for the treatment of severe SCI in mice. One signal activates the transmembrane receptor β1-integrin, and a second signal activates the basic fibroblast growth factor 2 receptor. In addition, this PA-based system was designed to have tunable supramolecular motion, which is critical for achieving optimal bioactivity. PAs with high molecular motion enhanced the activation of specific cellular receptors in neurons and blood vessels promoting tissue regeneration and reversing paralysis (Álvarez et al., 2021) (Figure 7a–e). The authors also took advantage of this new phenomenon and reported that the laminin-derived IKVAV sequence displayed by the supramolecular polymers with greater motion significantly enhanced the maturation of human iPSC-derived motor neurons (Álvarez et al., 2023). These studies demonstrated the potential of dynamic supramolecular polymers for CNS tissue repair and regeneration and highlighted the importance of recapitulating multiple properties of the physiological ECM in in vitro systems to overcome the limitations of human stem cell-based models.

SAP hydrogels have also been combined with stem cell therapies for CNS repair (Cheng et al., 2013; Peressotti et al., 2021; Tatman et al., 2016). As a recent example, Ohno et al. developed a self-assembled mRADA hydrogel incorporating the mRADA-tagged extracellular domain of N-cadherin as a scaffold for transplanted neuroblasts to treat TBI

in mice. When the hydrogel was injected into deep brain tissue, it facilitated the migration of implanted neuroblasts to the injured sites, promoting neuronal regeneration and functional recovery (Ohno et al., 2023). In another study, magnetically responsive SAP hydrogels (RADA-16) were used to transplant human MSC into a SCI rat model. When injected into injured rats, axon growth and alignment were achieved at the injury site, providing a novel method for scaffold topology regulation in the context of CNS regeneration (Tran et al., 2022). Other PA hydrogel strategies have been extensively reviewed elsewhere (Cui et al., 2010; Gelain et al., 2021; Hendricks et al., 2017).

Thermoresponsive hydrogels have the unique ability to undergo physical changes in response to temperature variations, making them particularly suitable for minimally invasive procedures in the CNS. They allow precise control of the release of therapeutic agents and support neuronal growth and repair in targeted areas of the CNS. Hong et al. demonstrated that injection of the thermosensitive hydrogel imidazole poly(organophosphazenes) (I-5) significantly reduced cystic cavities in a rat model of SCI, facilitating tissue repair. This hydrogel promoted FN-rich ECM bridging mediated by macrophage-expressed matrix MMP9 and enhanced functional recovery by preserving myelinated white matter and motor neurons and increasing axonal regrowth (Figure 7f–j). The study highlights the critical role of dynamic interactions between inflammatory cells and biomaterials in stimulating beneficial ECM remodeling after injury in the CNS (Hong et al., 2017, 2020).

While both natural and synthetic matrices offer distinct advantages, challenges remain in optimizing these materials for CNS regeneration. Ongoing research focuses on the dilemma of achieving biocompatibility without compromising mechanical properties in synthetic materials, as well as the challenges of scalability and consistency in the production of natural matrices. Future advances may focus on the development of hybrid materials that combine the best features of natural and synthetic matrices, as well as exploring novel functionalization techniques to enhance the bioactivity and mechanical properties of these scaffolds.

4.3.3 | Combinatorial approaches

An active line of research in the field of CNS regeneration is exploring the effect of combining dECM, natural and/or synthetic matrices to integrate multiple and complementary properties that could improve regenerative outcomes (Hasanzadeh et al., 2023; Tan et al., 2020; Volpato et al., 2013; Xu & Hsu, 2023). One example is the combination of synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA) with dECM to enhance the mechanical robustness of the decellularized matrix, providing a stable structure for neural tissue growth while maintaining the biological signaling of dECM. Ma et al. investigated this by electrospinning PLGA onto spinal cord dECM to create a scaffold that closely matches the mechanical properties required for neural repair. This PLGA-coated dECM scaffold (PLGA-DSC) was significantly more robust than the uncoated dECM scaffold and provided excellent mechanical support and cytocompatibility. This environment was conducive to the migration, growth, and differentiation of NSCs and promoted functional recovery after SCI (Ma et al., 2021). Hu et al. developed a self-healing hydrogel composed of phenylboronic acid-grafted hyaluronic acid (HA-PBA) and dopamine-grafted gelatin (Gel-Dopa) specifically designed to mimic the composition, stiffness, and viscoelasticity of brain parenchyma for the treatment of brain lesions. This HA-PBA/Gel-Dopa hydrogel exhibited shear-thinning properties for injectability, rapid hemostasis, and high tissue adhesion, facilitating efficient self-healing and supporting neural cell infiltration. In a mouse model of brain injury, this hydrogel reduced astrogliosis, prevented glial scar formation, and promoted lesion closure, highlighting its potential to advance the treatment of traumatic injury in the CNS (Hu et al., 2023).

More recently, researchers have also explored the blending of synthetic and natural electrically conductive matrices for spinal cord repair. They have used a mixture of borax-functionalized chondroitin sulfate, polypyrrole, and gelatin to develop a hydrogel that not only conducts electricity but also has self-healing properties (Figure 8a). This innovative material was formed by a combination of electrostatic and covalent bonding and offered promising potential for spinal cord repair applications (Luo et al., 2022). This hydrogel has been shown to promote axonal growth and neuronal differentiation, reduced astrocyte differentiation in vitro, and enhanced neurogenesis, axon myelination, and motor recovery in rats after SCI (Luo et al., 2022) (Figure 8b–d). Another example is Ru-Siou's research that developed a conductive microporous hydrogel infused with electromagnetized gold nanoyarn-balls (GYBs)-coated injectable microbeads (MBs) to enhance angiogenesis and neurogenesis after TBI (Figure 8e–g). This hydrogel used its unique surface roughness and remote electrical stimulation via the GYBs to enhance healing processes, specifically increasing BDNF production and calcium ion permeability. This strategy not only promoted cell migration and penetration, but also significantly

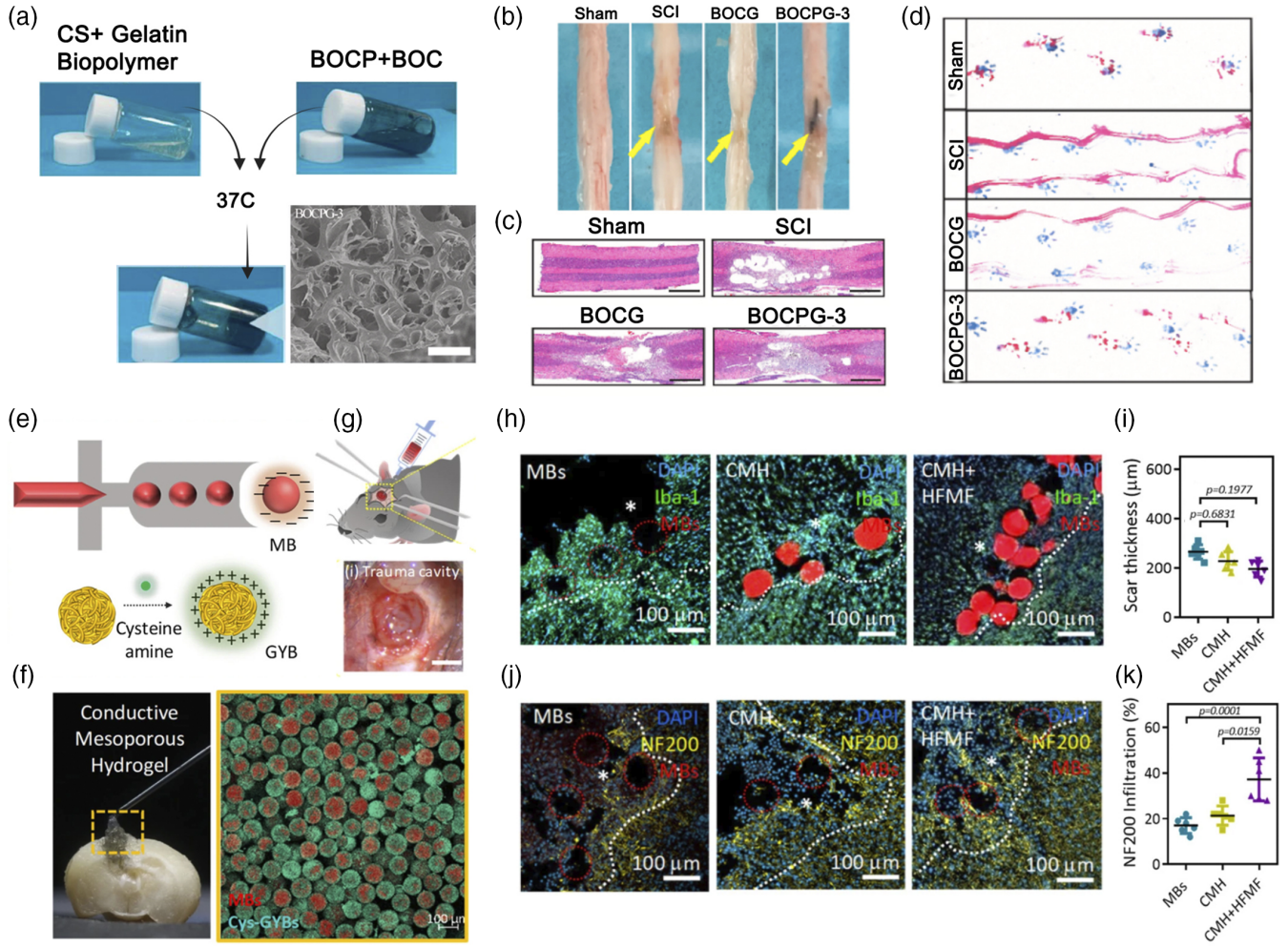

FIGURE 8 Combinatorial Approaches for CNS Uses. (a) Photographs showing the mixtures used to obtain an electroconductive BOCPG hydrogel. SEM image showing the ultrastructure of the electroconductive ECM-based hydrogels. (b) Representative images of the spinal cord after SCI repair in the different experimental groups. Yellow arrows indicate the site of injury. (c) Representative images of Masson's trichrome staining show the morphology of the spinal cord in the different experimental groups. (d) The recovery of hind limb motor function in rats of different groups was analyzed using representative footprints. The forepaw was stained with red ink and the hind paw was stained with blue ink. Panels (a)–(d) were adapted with permission from (Luo et al., 2022). (e–k) Formation of an adaptable conductive microporous hydrogel (CMH) for TBI. (e) Schematic illustration of the formation of monodispersed gelatin methacrylamide (GelMA) injectable building blocks (microbeads, MBs) (top); the process of synthesizing cys-GYB (bottom). (f) Image showing that CMH was modulable to macroscale shapes in a TBI cavity. (g) Images of the TBI cavity after implantation of the CMH scaffold (bottom). (h) Fluorescence images of Iba-1 immunostaining after treatment with MB, CMH, and CMH + HFMF. (i) Analysis of scar thickness in peri-trauma areas. (j) Fluorescence images of NF200 immunostaining after MB, CMH and CMH + HFMF treatment. (k) Analysis of NF200-positive responses at peri-trauma areas. Panels (e)–(k) were adapted with permission from Hsu et al. (2022).

enhanced functional recovery in brain tissue by exploiting the synergistic effects of electrical stimulation and the microporous structure of the scaffold (Hsu et al., 2022) (Figure 8h–k).

Pei et al. developed a novel therapeutic approach for CNS recovery after stroke, using rigid-flexible composite scaffolds loaded with bone marrow mesenchymal stem cells (BMSCs). These scaffolds, combining electrospun nanofibres and an injectable hydrogel, significantly enhanced the therapeutic outcomes induced by implanted BMSCs, leading to improved cell viability, migration, neurite outgrowth, angiogenesis, and paracrine effects. In particular, this approach reduced brain edema and infarct volume, improved neurological function, and promoted neuronal and vascular growth (Pei et al., 2023). Xu and colleagues developed an injectable bioactive hydrogel using an oxidized tannic acid-modified gold nano-crosslinker and demonstrated its effective crosslinking with chitosan. This hydrogel demonstrated self-healing properties, excellent injectability, and the ability to promote NSC proliferation and differentiation, along with

strong anti-inflammatory and antioxidant properties. In studies using a PD rat model, the hydrogel significantly improved motor function, electrophysiological performance, and cell survival (Xu et al., 2023).

The integration of decellularized, natural, and synthetic matrices in CNS regeneration represents a transformative advance, that bridges the gap between biological compatibility and structural functionality, providing tunable scaffolds for neural tissue repair and functional restoration.

5 | CONCLUSIONS AND FUTURE PERSPECTIVES

The rapid development of biomaterial-based technologies for the generation of rationally designed matrices leads us to believe that it will be possible to design context-specific ECM mimetic matrices for multiple applications. The CNS ECM is particularly complex, due to its high dynamics during development and in response to injury and disease. The characterization of these constant changes in the ECM is experimentally challenging and requires the use of biochemically adapted profiling methods. However, it is crucial to understand context-specific changes in the composition and structure of the ECM, as this may have implications for current modeling, diagnostic, and therapeutic strategies in several neurological disorders.

Decellularized matrices have shown great promise in various in vitro modeling applications and in vivo studies. However, there are associated challenges that must be addressed to realize their full potential: (1) The spatiotemporal characteristics of the tissues used to create dECM materials have a significant impact on their properties and efficacy. Tissues from specific regions have unique microenvironments tailored to support specific cellular functions, resulting in differences in mechanical, biochemical, and topographic properties. These differences can result in different cellular responses. In addition, the age of the source tissue affects the ECM, altering its composition and properties over time, such as increased fibrosis and stiffness, and higher levels of inflammation in older tissues; (2) The use of nonhuman tissues introduces additional hurdles, such as species-specific discrepancies that can impede material integration, including the risk of immune rejection in the case of xenogeneic transplantation; (3) The decellularization technique, choice of reagents, and subsequent treatments can also alter the biological properties of the material, potentially affecting the presence of tissue-specific growth factors and hormones. The conversion of tissue into hydrogel-based dECM materials by enzymatic digestion can alter ultrastructural and mechanical properties, such as stiffness and ECM fiber arrangement, which may differ significantly from those of the native tissue. After implantation, dECM materials degrade naturally, and this degradation rate-dependent on concentration and composition must be optimized, especially considering that scarring is a major obstacle in CNS repair; (IV) Scaling up the production of decellularized matrices to meet the demand for in vitro and in vivo studies can also be challenging, especially given the variability in tissue quality, from batch to batch, and availability. In addition, the use of decellularized matrices in neurological applications requires regulatory approval, which can be a lengthy and costly process.

Thus, future development of dECM materials for nervous system repair will require a deep understanding of the target tissue and the optimal conditions for initiating effective tissue repair. This knowledge should then be used to develop biomaterials that accurately mimic the ECM of healthy or pro-regenerative stage neural tissue. This includes careful tissue selection and the decellularization method to preserve the structural and biochemical integrity of the original tissue, as well as the isolation of soluble elements from the decellularized tissue or the addition of growth factors and stem cells to the dECM, to enhance functional regeneration. Advances in technologies such as crosslinking and 3D printing offer opportunities to fine-tune the mechanical, topographical, and structural properties of dECM materials, including precise micropatterning and porosity adjustments, to more effectively direct the fate of neural cells.

The development of future biomaterial-based technologies for CNS modeling and regeneration, will require the integration of the latest advances in biomedical research. The focus will likely shift to the creation of ECM-mimetic matrices that mimic not only the physical structure of the CNS ECM, but also its dynamic functional properties. Innovations such as the incorporation of bio-responsive materials capable of adapting to physiological changes could provide targeted healing in response to specific CNS conditions. The integration of artificial intelligence and machine learning for predictive modeling and design optimization of these matrices, could further enhance their efficacy. Similarly, exploration of the interface between neuroscience and nanotechnology could lead to the development of nanoscale delivery systems for therapeutic agents that precisely target damaged or diseased areas within the CNS. In addition, the exploration of synergistic therapies that combine biomaterial-based technologies with advanced drug delivery systems and neuromodulation techniques could provide comprehensive solutions to complex neurological disorders. This could include the integration of bioelectric interfaces with ECM mimetic matrices to enhance neural connectivity and

functional recovery. Finally, the use of patient-specific data, including genetic and proteomic profiles, could enable the creation of customized ECM mimetic matrices that address individual pathological conditions. In this line, advances in tissue engineering and stem cell technology could enable the creation of personalized and more sophisticated neural tissue constructs. This level of personalization could have a dramatic impact on the efficacy of neurological treatments.

Overcoming all these challenges and harnessing the potential of these futuristic strategies will require a multidisciplinary approach that combines expertise from materials science, neuroscience, engineering, and medicine. Moreover, the lack of companies currently exploiting ECM for CNS applications presents a significant opportunity for innovation and development in regenerative medicine. Recognizing the immense potential of ECM technologies in addressing complex neurological conditions underscores the importance for companies to pioneer in this area. This collaborative effort will be crucial in translating these innovations from research to clinical applications, ultimately fulfilling the vision of CNS regeneration and providing new hope in the treatment of neurological disorders, in which most of them still have no cure. Santiago Ramon y Cajal said, "After development, the sources of growth and regeneration of axons and dendrites dried up irrevocably. In the adult centers, the neural pathways are something fixed and unchangeable: everything can die, nothing can regenerate" (Y Cajal, 1928). However, he also wrote that "it is the duty of future generations to find a way to overcome the intrinsic failure of the adult brain to regenerate". In this sense, the clinical potential of continuously evolving biomaterial-based strategies, such as those reviewed here, leads us to believe that they will evolve into effective therapeutic strategies for the treatment of multiple neurological conditions.

AUTHOR CONTRIBUTIONS

J. Alberto Ortega: Conceptualization (lead); funding acquisition (lead); supervision (lead); writing – original draft (lead); writing – review and editing (lead). **Gisele P. Soares de Aguiar:** Writing – original draft (equal). **Palash Chandravanshi:** Writing – original draft (equal). **Natacha Levy:** Writing – original draft (equal). **Elisabeth Engel:** Conceptualization (lead); supervision (lead); writing – original draft (lead); writing – review and editing (lead). **Zaida Álvarez:** Conceptualization (lead); funding acquisition (lead); investigation (lead); supervision (lead); writing – original draft (lead); writing – review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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