Received: 19 May 2021 | Revised: 25 May 2021 | Accepted: 27 May 2021

DOI: 10.1111/ejn.15336

EDITORIAL

EJN European Journal of Neuroscience FENS WILEY

Brain extracellular matrix: An upcoming target in neurological and psychiatric disorders

Neurons and glial cells in the central nervous system (CNS) are embedded in a dense and dynamic meshwork of extracellular matrix (ECM). ECM components, which are synthesized and secreted by both neurons and glial cells, co-aggregate and form highly organized extracellular structures around cell somata, axon initial segments, dendrites and synapses, in particular, in the form of so-called perineuronal nets (PNNs). The brain ECM plays multiple roles in development (e.g., regulating closure of critical periods in brain areas), adulthood (e.g., shaping synaptic plasticity and stability, cognitive flexibility and context discrimination) and generally in physiology and pathology of the CNS. Recent data point to substantial alterations and functional impact of the ECM composition and integrity in aging, epilepsy, neurodegeneration and dementia, depression, bipolar disease, and schizophrenia. This special issue comprises a series of articles that lay out the latest understanding of cellular and molecular mechanisms by which diverse forms of ECM are changed in CNS diseases and how these alterations may affect synaptic and cognitive functions. Emphasis is put on the mechanisms regulating proteolytic remodeling of neural ECM under different (patho)physiological conditions, the ECM-mediated signaling in major neurological and psychiatric disorders, and emerging tools and strategies for analysis and therapeutic targeting of the neural ECM. This Special Issue comprises 13 articles, five of which are original research reports, four reviews, and four methodological studies.

The review of Ulbrich et al. (2020) provides an overview of major neurological and psychiatric diseases in terms of remodeling of neural and perivascular ECM. It puts forward the concept of biphasic dysregulation of local balance between extracellular proteases and the ECM in brain diseases: the initial phase is characterized by degradation of ECM due to high levels of expression and activity of extracellular proteases, such as matrix metalloproteinases (MMPs), while the recovery/chronic phase is accompanied by the upregulated expression of ECM molecules due to changes in their synthesis, or increased expression/activities of tissue inhibitors of metalloproteinases (TIMPs). The initial downregulation of ECM opens a window of pathophysiological plasticity to remodel neural networks, while upregulation of ECM during the chronic phase would impair neuroplasticity and stabilize the diseased state. An additional level of complexity is related to the leakage of blood plasma proteins, such as fibrinogen, and the diffusion of perivascularly overproduced MMPs, TIMPs and ECM molecules into the CNS parenchyma, leading to diverse effects on neurons.

Besides extracellular proteolysis, signaling triggered via receptors for ECM components, such as integrins, is a key topic to understand the role of ECM in the etiology of brain disorders. The review by Fanny Jaudon and co-workers focuses on common mechanisms and signaling pathways mediated by integrins, such as regulation of trafficking and activities of AMPA and NMDA subtypes of glutamate receptors and activation of microglia, attempting to bring together data from studies on the genetics and molecular structure of integrins with those on synaptic physiology and brain pathology (Jaudon et al., 2020). Importantly, diverse integrin-targeting strategies have been developed in the cancer field and for non-neuronal tissues. The review provides insights into their potential benefits for the treatment of neuropsychiatric disorders.

In their systematic review paper, Hall et al. (2020) provide a comprehensive summary and interpretation of the mechanobiology of aging and degenerating brain with a special emphasis on the ECM and neurodegenerative disorders. They expound the important role and the possibilities of neuro-mechanobiology research for the understanding of the complex interplay between the extracellular environment and intracellular domain. Finally, they formulate key questions to be answered to understand the influence of

Abbreviations: 3D, three-dimensional; ADAM10, a disintegrin and metalloproteinase domain-containing protein 10; ADAMTS1, ADAM metallopeptidase with thrombospondin type 1 motif 1; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BCAN, brevican; CD44, cluster of differentiation 44; ChABC, chondroitinase ABC; CNS, central nervous system; ECM, extracellular matrix; MMP, matrix metalloproteinase; NCAN, neurocan; NMDA, N-methyl-D-aspartate; PNN, perineuronal net; Poly I:C, polyinosinic-polycytidylic acid sodium salt; SEMA4G, semaphorin 4G; SNP, single nucleotide polymorphism; SRGN, serglycin; TIMP, tissue inhibitor of metalloproteinases.

neuro-mechanobiology on CNS development and during physiological as well as pathological aging.

In their review paper, Ismary Blanco and Katherine Conant give a comprehensive and timely overview of the relationship between gamma-oscillations and ECM restructuring upon conditions of stress and depression, from fish to humans. They conclude that ECM changes as a consequence of stress, in particular manifested in PNN alterations, can be a promising readout in depression models to test the effectiveness of antidepressants (Blanco & Conant, 2020).

The complex interplay between the extracellular environment and neuroprotective signaling pathways is only partially understood. It is important to characterize the mutual interactions of the ECM with the surrounding cells in the CNS in development and during physiological as well as pathological aging. In their research report, Schmidt et al. (2020) from the Morawski group provide further evidence of the neuroprotective action of the perineuronal ECM against the formation of pathological forms of Tau. They provide insights into the interplay between the major ECM proteins and the intracellular Tau levels, and demonstrate a direct effect of aggrecan on Tau expression and phosphorylation.

Kalpachidou et al. (2020) describe the behavioral phenotype of mice deficient in Fras1, an extracellular protein of the basement membranes that surround embryonic epithelia, choroid plexuses and meninges in fetal mouse brain. Mutations in human Fras1 are responsible for the Fraser Syndrome with brain deformities and mental impairments occasionally observed in patients. The ECM of PNNs was found to be disorganized in cortical and subcortical areas in *Fras1*-deficient mice, which exhibit many behavioral defects, including impaired egocentric spatial memory and aberrant olfactory learning and memory.

Wegrzyn et al. (2020) from the Faissner group provide insights into the ECM and cellular mechanisms of the maternal immune system during gestation, which is well known to be linked to neuropsychiatric diseases like schizophrenia. By using behavioral tests, primary astrocytic and neuronal cell cultures, immunocytochemistry and electrophysiological recordings, the researchers observed that treatment with polyinosinic-polycytidylic acid sodium salt (Poly I:C), a model of viral infection, resulted in impairment of prepulse inhibition, a significantly reduced axonal complexity and a significant reduction of the major ECM molecule aggrecan with regard to staining intensity, area and soma size.

Assmann et al. (2020) studied the significance of a single nucleotide polymorphism (SNP) in the human NCAN gene encoding the neuronal chondroitin sulphate proteoglycan neurocan, which is known as a risk factor for psychiatric disorders like schizophrenia and bipolar disorder, in a cohort of young healthy humans. The researchers report that this SNP correlates with reduced verbal memory, hippocampal overactivation during novelty encoding and reduced prefrontal grey matter density, pointing to an intermediate phenotype.

Pantazopoulos et al. (2020) focus on characteristic molecular ECM signatures in the brains of schizophrenic patients. They employed gene expression profiling of parceled cortical and subcortical areas to demonstrate complex patterns of dysregulation of ECM elements. The most robust alterations in gene expression were detected for SRGN, CD44, ADAMTS1, ADAM10, BCAN, NCAN and SEMA4G. Moreover, changes in ECM-related genes correlated with cognitive performance of patients.

Also, analysis of ECM changes in animal models of schizophrenia points to dysregulation of ECM, in particular in the prefrontal cortex. A methodological study by Kaushik et al. (2020) describes a semiautomatic method suitable for fine structural analysis of PNN units, i.e. ECM "holes" in which synaptic boutons are located and the ECM "barriers" around them. Application of this method to high-resolution images of PNNs obtained in the subchronic ketamine model of schizophrenia revealed that PNN units are smaller, less circular but more numerous than in control animals.

Another methodological study introduces a new approach for targeted digestion of neural ECM using the enzyme chondroitinase ABC (ChABC). Carstens et al. (2020) designed an adeno-associated virus encoding ChABC under the control of the Cre-LoxP system. In addition to the expression of ChABC in cell types of interest, this approach is advantageous to avoid potential impurities of commonly used bacterially produced and purified ChABC and to provide persistent long-lasting attenuation of ECM.

Freitas et al. (2021) present data mining and bioinformatics as powerful tools to an unbiased approach towards unraveling disease-characteristic ECM proteomic patterns. They integrated data from 16 reports demonstrating changes in ECM components in human post mortem brains of Alzheimer's, Parkinson's and Huntington's disorder patients and concluded that this approach allows generating new hypotheses about common and specific denominators, thus opening avenues for designing new ECM-targeting regenerative therapies. A systematic comparison of molecular changes in brain regions resilient to a disease or strongly affected by it may be instrumental to dissect new therapeutic targets.

For the more efficient study of neuro-mechanobiology in the CNS, Fruhauf et al. (2020) introduce a biomimetic 3D in vivo culture system for co-cultivation of microglia and T cells to investigate and characterize the activation of brain-resident microglia cells and the infiltration of peripheral T cells in neuroinflammatory conditions. Their findings indicate that biomimetic 3D matrices allow for co-cultivation and activation of primary microglia and T cells and provide useful tools to study and search for new drugs to manipulate their interaction in the context of neurodegeneration.

In summary, the content of this Special Issue extends our understanding of complex disease stage- and brain region-specific dysregulations of ECM in the CNS and provides new tools and stimulating examples of research suggesting that targeting the neural ECM, ECM receptors and extracellular proteases could be beneficial in a broad range of neurological and psychiatric conditions.

KEYWORDS

dementia, depression, ECM, perineuronal net, schizophrenia

ACKNOWLEDGEMENTS

A.D. and C.S. are supported by Deutsche Forschungsgemeinschaft (DFG Project-ID 362321501—GRK SynAge 2413/1; Project-ID 425899996—SFB 1436) and by Federal state Saxony-Anhalt and the European Structural and Investment Funds (ABINEP grant ZS/2016/08/80645). M.M. is supported by the DFG, PP 2041 Computational Connectomics (MO 2249/3-1 and MO 2249/3-2) and the Alzheimer Forschung Initiative (AFI#18072).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors wrote and edited the manuscript.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.15336.

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