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Extracellular Matrix Abnormalities in Schizophrenia

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Abstract

Emerging evidence points to the involvement of the brain extracellular matrix (ECM) in the pathophysiology of schizophrenia (SZ). Abnormalities affecting several ECM components, including Reelin and chondroitin sulfate proteoglycans (CSPGs), have been described in subjects with this disease. Solid evidence supports the involvement of Reelin, an ECM glycoprotein involved in corticogenesis, synaptic functions and glutamate NMDA receptor regulation, expressed prevalently in distinct populations of GABAergic neurons, which secrete it into the ECM. Marked changes of Reelin expression in SZ have typically been reported in association with GABA-related abnormalities in subjects with SZ and bipolar disorder. Recent findings from our group point to substantial abnormalities affecting CSPGs, a main ECM component, in the amygdala and entorhinal cortex of subjects with schizophrenia, but not bipolar disorder. Striking increases of glial cells expressing CSPGs were accompanied by reductions of perineuronal nets, CSPG- and Reelin-enriched ECM aggregates enveloping distinct neuronal populations. CSPGs developmental and adult functions, including neuronal migration, axon guidance, synaptic and neurotransmission regulation are highly relevant to the pathophysiology of SZ. Together with reports of anomalies affecting several other ECM components, these findings point to the ECM as a key component of the pathology of SZ. We propose that ECM abnormalities may contribute to several aspects of the pathophysiology of this disease, including disrupted connectivity and neuronal migration, synaptic anomalies and altered GABAergic, glutamatergic and dopaminergic neurotransmission.

Keywords

extracellular matrix; chondroitin sulphate proteoglycans; perineuronal nets; astrocytes; schizophrenia; Reelin

1. INTRODUCTION

Recent years have seen remarkable progress in the identification of neuronal and glial abnormalities in schizophrenia (SZ) (e.g. Reynolds et al., 1990, Benes, 2000, Boksha, 2004, Stewart and Davis, 2004, Heckers and Benes, 2005, Mitterauer, 2005, Carter, 2006, Harrison and Law, 2006, Beneyto et al., 2007, Berretta et al., 2007, Kondziella et al., 2007, Pantazopoulos et al., 2007, Tamminga et al., 2010, Volk and Lewis, 2010, Miyake et al.,

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2011, Takahashi et al., 2011b). Emerging evidence suggests a key role for a third, until recently unsuspected, player: the extracellular matrix (ECM) (Impagnatiello et al., 1998, Guidotti et al., 2000a, Eastwood et al., 2003, Zaharieva et al., 2008, Pantazopoulos et al., 2010, Takahashi et al., 2011a). Decreased expression of the ECM glycoprotein Reelin represents one of the most solid findings in SZ (Guidotti et al., 2000a, Guidotti et al., 2000b, Costa et al., 2004, Dong et al., 2005). Recent findings from our group point to substantial abnormalities affecting chondroitin sulfate proteoglycans (CSPGs), a key component of the brain ECM, in subjects with SZ but not bipolar disorder (Pantazopoulos et al., 2010). Marked increases in the number of glial cells expressing CSPGs, not accompanied by astrogliosis, suggest anomalous regulation of CSPG expression. Concurrent reductions of CSPG-positive perineuronal nets (PNNs) point to altered CSPG content in the ECM. Evidence for genetic vulnerability related to some ECM molecules and abnormalities affecting ECM and ECM-related factors, further supports ECM abnormalities in SZ (Vawter et al., 2000, Vawter et al., 2001, Eastwood et al., 2003, Buxbaum et al., 2008, Shifman et al., 2008, Zaharieva et al., 2008, Pisante et al., 2009, Liu et al., 2010, Dow et al., 2011, Kahler et al., 2011).

In this review, we summarize basic current knowledge on the composition and functions of the brain ECM, with particular emphasis on CSPGs and Reelin and their relevance to the pathophysiology of SZ, and discuss evidence for the involvement of ECM in SZ and its implications with respect to current knowledge on the pathophysiology of this disease (for more comprehensive reviews on ECM structure and functions, please see Tissir and Goffinet, 2003, Dityatev and Schachner, 2006, Viapiano and Matthews, 2006, Galtrey and Fawcett, 2007, Dityatev et al., 2010a, Faissner et al., 2010, Gundelfinger et al., 2010). We put forth that interactions between ECM, neuronal and glial cell populations may be disrupted in SZ, potentially affecting key developmental and adult brain functions (Oohira et al., 2000, Yamaguchi, 2000, Pizzorusso et al., 2002, Carulli et al., 2005, Viapiano and Matthews, 2006).

1.1 Distribution of the ECM in the central nervous system (CNS)

The ECM occupies approximately a volume fraction of 20% of the normal adult brain (Sykova and Nicholson, 2008). It wraps tightly around synapses and completely surrounds all brain cells, separating them from each other by gaps spanning approximately 38-64 nm in width (Chvatal et al., 1999, Thorne and Nicholson, 2006, Sykova and Nicholson, 2008). The ECM also fills the synaptic cleft, although its biochemical composition within this specialized space is different, and less well known, with respect to the rest of the brain ECM (Zuber et al., 2005). In addition to the loosely organized ECM surrounding all cells, highly organized pericellular ECM aggregates, i.e. PNNs, ensheath the cell body, dendrites and proximal portion of the axon of distinct neuronal subpopulations (Fig. 1) (Hartig et al., 1995, Celio et al., 1998, Hartig et al., 1999, Wegner et al., 2003, Alpar et al., 2006, John et al., 2006, Pantazopoulos et al., 2006). PNNs represent the most well studied form of neural ECM; described by Camillo Golgi as early 1893, their molecular composition and functions have only recently come to the forefront of neuroscience research (Golgi, 1893, 1898, Celio et al., 1998, Spreafico et al., 1999, Pizzorusso et al., 2002, Dityatev and Schachner, 2003, Hensch, 2005, Carulli et al., 2006, Fawcett, 2009, Gogolla et al., 2009, Pizzorusso, 2009).

1.2 ECM molecular composition and structure in CNS

The brain ECM has a unique molecular composition, based on aggregates of hyaluronan and CSPGs connected by glycoproteins (e.g. tenascins) (Fig. 2) (Bandtlow and Zimmermann, 2000, Yamaguchi, 2000, Rauch, 2004, Rauch et al., 2005, Viapiano and Matthews, 2006). Hyaluronan represents the backbone of the brain ECM, while CSPGs, in particular those belonging to the lectican family (aggrecan, versican, brevican and neurocan), are thought of

as the ‘organizers of the brain ECM’ (Yamaguchi, 2000). A broad variety of other constituents, including the CSPG phosphacan, tenascins, heparan sulfate proteoglycans, Reelin, laminins, thrombospondins, hyaluronidases and proteases, add to this basic lattice and contribute to the structure and function of the ECM (Ruoslahti, 1996, Dityatev and Fellin, 2008, Frischknecht and Seidenbecher, 2008). ECM components are anchored to cell membranes through a variety of cell surface molecules, including the cell adhesion molecule (CAM) superfamily, membrane bound proteoglycans and hyaluronan synthase (Galtrey and Fawcett, 2007).

The composition and structure of the ECM undergo substantial changes during CNS development. A juvenile form of ECM present in late embryonic life and early postnatal life does not organize into PNNs and supports neurogenesis and gliogenesis, cell migration, axonal outgrowth, synaptogenesis and synaptic rearrangement (Bandtlow and Zimmermann, 2000, Vitellaro-Zuccarello et al., 2001, Carulli et al., 2007, Zimmermann and Dours-Zimmermann, 2008, Maeda, 2010). In contrast, adult ECM is, in general, non-permissive for axonal outgrowth and regeneration (Rhodes and Fawcett, 2004, Galtrey and Fawcett, 2007, Fawcett, 2009); PNN maturation occurs late in postnatal development (Carulli et al., 2006, Gundelfinger et al., 2010). The functional specialization of these ECM structures is reflected in their distinct molecular composition, which includes link proteins, is enriched in particular CSPGs and is specific to distinct neuronal populations (Lander et al., 1997, Hagihara et al., 1999, Matthews et al., 2002, Wegner et al., 2003, Fawcett, 2009).

1.3 Cellular sources of ECM molecules

Several types of neurons and glial cells contribute to the synthesis of ECM molecules and their secretion into the extracellular space in a cell- and development stage- specific manner (Bandtlow and Zimmermann, 2000, Ogawa et al., 2001, Carulli et al., 2006, Viapiano and Matthews, 2006). Recent findings also suggest species differences. For instance, CSPG detection by histochemical *Wisteria Floribunda* agglutinin (WFA) labeling, a method widely used for CSPG detection, labels exclusively PNNs in rodents and non-human primates (Hartig et al., 1992, Bruckner et al., 1994, Celio et al., 1998, Pizzorusso et al., 2002, Murakami and Ohtsuka, 2003, Wegner et al., 2003, Baig et al., 2005, Carulli et al., 2006, Deepa et al., 2006, Viapiano and Matthews, 2006). In contrast, WFA-CSPG detection in the normal human amygdala, reveals not only PNNs but also intense intracellular CSPG labeling in a subpopulation of astrocytes (Pantazopoulos et al., 2008). The highly segregated distribution of CSPG-positive astrocytes within the human amygdala is consistent across subjects, suggesting association with specific neurochemical and/or anatomical features. These findings suggest an intriguing specie-specific role for astrocytes as CSPG sources in the human CNS.

Cell sources of Reelin also vary during development. During early stages, Reelin is synthesized and secreted by Cajal-Retzius cells, located in the marginal zone of the developing cortex. These cells almost completely disappear by the time migration of cortical neurons is completed (D’Arcangelo et al., 1995, Alcantara et al., 1998, Drakew et al., 1998, Forster et al., 2010, Meyer, 2010). Throughout adulthood, Reelin is expressed prevalently by GABAergic neurons not typically associated with PNNs, such as those expressing neuropeptide Y and somatostatin, and to a lesser extent by some calretinin- and calbindin-positive neurons (Pesold et al., 1999, Ramos-Moreno et al., 2006, Campo et al., 2009). Neurons expressing parvalbumin (PVB), typically associated with PNNs, do not contain Reelin (Pesold et al., 1999, Campo et al., 2009).

2. EVIDENCE FOR ECM ABNORMALITIES IN SZ

Growing evidence from postmortem investigations points to ECM abnormalities in SZ. Abnormal expression of ECM glycoprotein Reelin is one of the most solid findings in this disorder (Impagnatiello et al., 1998, Guidotti et al., 2000a, Costa et al., 2001). Marked increase of CSPG-positive glial cells and reduction of CSPG-positive PNNs were detected in the medial temporal lobe of subjects with SZ (Pantazopoulos et al., 2010). Current knowledge on the involvement of CSPGs and Reelin, and other ECM and ECM-related factors, in SZ is briefly reviewed below.

2.1 CSPG-glial abnormalities in SZ

Mounting evidence suggests that astrocytes play a key role in regulating ECM properties, synthesizing CSPGs, and building PNNs (Faissner et al., 2010, Gundelfinger et al., 2010). In the amygdala and entorhinal cortex (ECx) of subjects with SZ, glial cells expressing CSPGs were found to be massively increased (Pantazopoulos et al., 2010) (Fig. 3). These cells were morphologically identified as astrocytes, consistent with the exclusive co-localization of WFA-CSPG with glial fibrillary acidic protein (GFAP), a marker typically used to label astrocytes, in the normal human amygdala (Pantazopoulos et al., 2008). Expression of genes encoding for five major CSPGs in the brain, i.e. versican, aggrecan, neurocan, brevican and phosphacan, was tested in the basal nucleus of the amygdala and found to be increased by 1.3 to 2.03 folds (significant for versican; qRT-PCR) in subjects with SZ, supporting histochemical results. These changes were not accompanied by astrogliosis, as shown by normal numbers of cells expressing GFAP. Increased numbers of CSPG-positive glial cells in the absence of astrogliosis may reflect induction of CSPG expression in cells that do not express these molecules constitutively and/or increased expression in astrocytes normally containing them at low levels, perhaps as a consequence of overproduction, increased internalization and/or impaired secretion. We hypothesized that such dysregulation may in turn affect CSPG expression in the ECM. Indeed, significant PNN reductions were detected in lateral nucleus of the amygdala and layer II of lateral ECx. Notably, in healthy human subjects, these subregions contain by far the highest densities of PNNs (Bruckner et al., 1999, Pantazopoulos et al., 2006). Normal numbers of PVB-positive neuron numbers within these same regions in SZ (Pantazopoulos et al., 2007, Pantazopoulos et al., 2010) point to reduced CSPG levels in the ECM of SZ, rather than loss of PNN-associated neurons. No CSPG-related changes were detected in bipolar disorder, suggesting pathophysiological differences between this disease and SZ with regard to ECM abnormalities.

These results point to substantial anomalies affecting CSPG expression in glial cells and ECM perineuronal aggregates in SZ. Importantly, these changes were not affected by pharmacological treatment, such as exposure to antipsychotics (chlorpromazine-equivalent dose) or lithium salt throughout lifetime or during last six months' of life, and other therapeutic drugs (e.g. serotonin-reuptake inhibitors and valproic acid), or other therapeutic intervention such as electroconvulsive therapy (for more details see Pantazopoulos et al., 2010). The only exception was a significant negative effect of lifetime exposure to antipsychotics on numbers of CSPG-positive glial cells in the basal nucleus of the amygdala in subjects with SZ, confirmed by negative correlation, indicating that antipsychotic exposure tend to decrease CSPG-positive glial cells in this nucleus. Given the direction of this effect, antipsychotics are unlikely to be responsible for the observed increase. Drugs of abuse, e.g. cocaine, marijuana, alcohol, nicotine, and a number of other potential confounds including age, gender, cause of death, brain weight, hemisphere etc., were not found to account for the abnormalities observed. Finally, these changes did not vary with duration of illness or age at onset of illness suggesting that they may be inherent to the disease (Pantazopoulos et al., 2010). If CSPG abnormalities in SZ were present during development, CSPG dysregulation may interfere with neuronal migration, axon outgrowth and synaptic

maturation within the amygdala and ECx of subjects with SZ. Disruption of PNNs formation during later stages of development may lead to failure to stabilize successful sets of neural connections, complete maturation of selective neuronal populations, including those expressing PVB, and transition to an adult form of plasticity (see also 3.3.1). Such ECM/PNN defects in the amygdala may affect the ability to attribute appropriate emotional valence to sensory inputs and form stable, contextualized memories (Gloor, 1986, LeDoux, 1992, Gogolla et al., 2009, Pizzorusso, 2009). In the ECx, ECM/PNN abnormalities may impair the establishment and consolidation of long-term declarative memory and perceptual processing, that may be relevant to the impairment of learning, memory, and executive functions typically described in subjects with SZ (e.g. Kuperberg and Heckers, 2000, Riley et al., 2000). Overall, set in the context of medial temporal lobe role in emotion and perceptual processing, social behavior and affect regulation, a disruption of ECM functions has strong potential to contribute to the pathophysiological underpinnings of some of the main symptoms of SZ, such as flat affect, social and cognitive impairment, delusional thinking and anxiety. Preliminary results suggest that ECM abnormalities in SZ may not be unique to the medial temporal lobe, but instead involve other cortical and subcortical regions (Guillin et al., 2007, Murray et al., 2008). It is therefore possible that ECM changes affecting key regions in the pathophysiology of SZ may contribute to different aspects of functional impairment observed in this disease.

2.2 Reelin abnormalities in SZ

Reelin abnormalities have been extensively reported in SZ (see Fatemi et al., 2000, Guidotti et al., 2000a, Costa et al., 2001, Torrey et al., 2005, Eastwood and Harrison, 2006, Costa et al., 2007, Guidotti et al., 2010). In brief, downregulation of the reelin gene has been detected in several brain regions, including the hippocampus, prefrontal and temporal cortex, cerebellum, and caudate nucleus of subjects with SZ (Impagnatiello et al., 1998, Costa et al., 2001, Maloku et al., 2010). Aberrant epigenetic mechanisms as well as genetic abnormalities have been invoked to account for reelin downregulation. Epigenetic pathology is supported by findings of over-expression of DNA methyltransferases, enzymes that catalyze promoter methylation, in association with reelin downregulation, increased expression of methyl donor molecules, and increased methylation of reelin (Veldic et al., 2004, Abdolmaleky et al., 2005, Veldic et al., 2005, Costa et al., 2007, Guidotti et al., 2007, Guidotti et al., 2010). These findings may not exclude the possibility that polymorphisms of the reelin gene may represent a vulnerability factor for SZ, at least in specific subpopulations (Shifman et al., 2008, Wedenoja et al., 2008, Gregorio et al., 2009, Liu et al., 2010). Reelin downregulation is typically accompanied by decreased expression of glutamic acid decarboxylase 67 (GAD₆₇; one of the two synthetic enzymes for GABA), suggesting a strong functional link between Reelin expression and GABAergic neurotransmission (Guidotti et al., 2000a, Veldic et al., 2004). Notably, Reelin downregulation was also detected in manic bipolar disorder subjects, leading to the suggestion that they may represent a shared molecular mechanism contributing to psychosis (Guidotti et al., 2000a, Costa et al., 2001). In light of the role of Reelin in corticogenesis, synaptic maturation and stabilization, and PNNs formation, it has been proposed that downregulation of reelin gene expression may contribute to neuropil hypoplasticity, decrease of dendritic spines and reduction of GAD₆₇ expression (Costa et al., 2001). Similar Reelin-related findings in SZ and bipolar disorder with psychosis led to the suggestion that these mechanisms may represent a shared vulnerability to psychosis (Costa et al., 2001).

2.3 Other ECM molecules found to be involved in SZ

In addition to CSPGs and Reelin, several other ECM components, and ECM-interacting factors, have been found altered in SZ, further supporting the involvement of ECM in this disease. Recent results point to **ADAMTSL3** gene (a disintegrin-like and metalloprotease

domain with thrombospondin type I motifs-like-3) as a candidate gene for SZ (Need et al., 2009, Dow et al., 2011). This secreted enzyme is a member of the ADAMTS family, known for its role in cell-matrix interactions, ECM assembly and, specifically, CSPG proteolysis (Hall et al., 2003). **Chondrex gene** (YKL-40), which encodes for an extracellular matrix glycoprotein involved in cell growth and migration, was found to be significantly increased in the hippocampus of subjects with SZ (Chung et al., 2003). **Semaphorin 3A**, an ECM molecule with key developmental and adult functions (see 3.1) was reported to be increased in the cerebellum of subjects with SZ (Eastwood et al., 2003, Ben-David and Shifman, 2010, Zimmer et al., 2010, Kabayama et al., 2011, Nishiyama et al., 2011, Piaton et al., 2011). Notably, this increase was negatively correlated with Reelin expression and associated with downregulation of genes involved in synaptic formation and maintenance, suggesting that semaphorin 3A may contribute to the synaptic pathology of SZ. Further evidence comes from studies showing altered expression of **neural cell adhesion molecules** (N-CAM) in SZ (Vawter et al., 2000, Vawter et al., 2001). These molecules play key roles in neural development, signal transduction, synaptic stabilization establishing structural linkages to extracellular and intracellular proteins. Notably N-CAMs represent one of the main CSPG cell surface receptor, raising the possibility that abnormalities affecting these two families of molecules may be linked. Gene expression and genetic studies support the idea that **neuregulin 1** contributes directly to SZ (Corfas et al., 2004, Hahn et al., 2006, Harrison and Law, 2006, Alaerts et al., 2009). This molecule was found to interact with ECM components and to share many of the CSPG functions (Corfas et al., 2004). Growth factors transforming growth factor beta (**TGF-beta**) and epidermal growth factor (**EGF**), shown to stimulate CSPGs synthesis in astrocytes (Smith and Strunz, 2005), are thought to play a role in the pathogenesis of SZ (Futamura et al., 2002, Kim et al., 2004, Benes et al., 2007, Ikeda et al., 2008, Zaharieva et al., 2008).

3. ECM FUNCTIONS BEAR DIRECT RELEVANCE TO THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

ECM functions during development and adulthood are highly reminiscent of those disrupted in SZ. Below, we focus in particular on those involving CSPGs and Reelin and place them in the context of known pathological findings in SZ.

3.1 Axonal pathfinding, neuronal differentiation and migration

Growing evidence supports the idea that neurodevelopmental processes such as neuronal differentiation and migration, and neuronal network formation may be disrupted in SZ (Akbarian et al., 1993a, Arnold and Trojanowski, 1996, Reif et al., 2006, Benes et al., 2009, Connor et al., 2010, Deutsch et al., 2010). Convergent findings point to abnormal distribution of interstitial white matter neurons (IWMNs) within the frontal, parietal and temporal lobes (Akbarian et al., 1993a, Akbarian et al., 1993b, Akbarian et al., 1996, Anderson et al., 1996, Kirkpatrick et al., 1999, Eastwood and Harrison, 2003). The majority of these results show an increase of IWMNs within the superficial white matter, interpreted as failure of these neurons to migrate into the cortical white matter. Interestingly, reelin mRNA expression in IWMNs was also decreased (Eastwood and Harrison, 2003), consistent with its potential contribution to a failure of neuronal migration from the white matter into the cortex. Aberrant IWMNs may originate from the cortical subplate and/or from the ganglionic eminence. A contribution from the latter is suggested by the fact that at least a portion of IWMNs increased in SZ is represented by interneurons expressing Reelin and/or somatostatin-neuropeptide Y (Eastwood and Harrison, 2003, Yang et al., 2011). Yang et al. have recently reported that an increase of IWMNs in the superficial layer of the prefrontal cortex in SZ was accompanied by a decrease of somatostatin mRNA expression, a peptide typically expressed in interneurons, in the gray matter, and an increase of somatostatin-

positive neurons in the superficial white matter (Yang et al., 2011). Together, these findings suggest that migration of interneurons arising from the ganglionic eminence and traveling through the white matter to reach the cortex may be disrupted in SZ (Yang et al., 2011).

Within the ECx of SZ subjects, abnormal cytoarchitecture and heterotopic displacement of the cell clusters in layer II have been reported by several groups and attributed to anomalous neuronal migration (Jakob and Beckmann, 1986, Arnold et al., 1991, Jakob and Beckmann, 1994, Falkai et al., 2000, Kovalenko et al., 2003). Increases of CSPG-positive glial cells in the ECx were highly selective for layer II cell clusters (Pantazopoulos et al., 2010)(Fig. 2), matching the distribution of cytoarchitectonic abnormalities and raising the possibility that abnormal CSPG expression during development may have contributed to neuronal migration disturbances. Furthermore, increases of small caliber vertical axons in these layers (Longson et al., 1996) are consistent with a disruption of axonal guidance, another key CSPG function. These fibers were proposed to originate from the amygdala (Longson et al., 1996, Benes and Berretta, 2000), a possibility consistent with the idea that concurrent CSPG abnormalities in the amygdala and ECx may lead to miswiring of their reciprocal connections.

The ECM plays a key role in the regulation of cell differentiation and migration and axonal outgrowth and guidance (Bandtlow and Zimmermann, 2000). The structure of CSPGs changes throughout development, modulating chemical properties required for traction or repulsion of migrating cells and growing axons, and dictating which growth factors, chemokines, axon guidance molecules and other ECM factors they bind to (Maeda, 2010). During development, CSPGs are found to concentrate within areas of active cell proliferation such as the ventricular zone of the ganglionic eminence and dorsal telencephalon and ependymal layer of the spinal cord (Bandtlow and Zimmermann, 2000, Zimmer et al., 2010). Phosphacan, and its membrane-bound splice variant receptor-type tyrosine phosphatase- β (RPTP β), localize along radial glial fibers and migrating neurons in the developing cortex (Maeda et al., 1995, Ishii and Maeda, 2008). A compelling example of the role played by CSPGs in neuronal migration is reported in a study by Zimmer et al. (Zimmer et al., 2010). These authors showed that CSPGs, linked to semaphorin 3A, guide cortical interneurons migrating from the ganglionic eminence to the cortex, preventing them from entering the striatal mantle zone. Experimental disruption of this combined CSPG-semaphorin 3A effect led to migrating ganglionic eminence cortical interneurons to inappropriately invade the striatal cortical mantle (Zimmer et al., 2010).

Reelin regulation of cerebral cortex neuronal migration is well documented. It affects both somal translocation during early corticogenesis and, later, radial glia-guided locomotion. It provides a complex set of instructions, as it attracts migrating neurons toward the pial surface and acts as a positional cue, causing neurons to detach from their guiding glial fibers and terminate migration (for reviews see Tissir and Goffinet, 2003, Forster et al., 2010, Zhao and Frotscher, 2010). Similar functions are postulated in several other brain regions, including the hippocampus, cerebellum, olfactory bulb and thalamus (for review see Tissir and Goffinet, 2003, Forster et al., 2006).

3.2 Axon myelination

Myelin abnormalities in SZ, first suggested in 1992 (Hyde et al., 1992), include reduction of myelin compactness and increased density of concentric lamellar bodies, altered expression of key myelin components such as sphingomyelin, galactocerebrosides, myelin-associated glycoprotein and reduction of oligodendrocytes and clusters of oligodendrocyte-related genes (Hakak et al., 2001, Uranova et al., 2001, Hof et al., 2002, Flynn et al., 2003, Hof et al., 2003, Tkachev et al., 2003, Schmitt et al., 2004, Uranova et al., 2004, Dwork et al., 2007, Le-Niculescu et al., 2007, Sokolov, 2007, Konrad and Winterer, 2008, Dean et al., 2009, English et al., 2009, Martins-de-Souza et al., 2009, Chan et al., 2010, Martins-de-

Souza, 2010). Abnormalities affecting the nodes of Ranvier have been recently reported (Haroutunian et al., 2010).

ECM molecules, and CSPG in particular, are involved in several aspect of the myelination process. During early postnatal life, the CSPG brevican is expressed by immature oligodendrocytes in coincidence with the phase in which these cells extend membrane processes to ensheath axon fibers (Ogawa et al., 2001). During adulthood, brevican, tenascin-R and phosphacan are present at the nodes of Ranvier on myelinated axons with a particularly large diameter in the CNS (Bekku et al., 2009). Brevican deficiency was found to cause a reorganization of the ECM composition around the nodes, suggesting that this CSPG dictates the specialization of the hyaluronan-binding nodal matrix assemblies in large diameter nodes (Bekku et al., 2009). Together, these considerations support the hypothesis that a disruption of ECM composition in SZ may contribute to myelin defects reported in this disease.

3.3 Synaptic functions

Synaptic defects are arguably one of the most well studied abnormality in SZ. Synaptic structural and ultrastructural changes, altered expression of presynaptic proteins, reduction of dendritic spine density, fewer synaptic vesicles and shrinkage of axon boutons have been reported in several brain regions (Eastwood and Harrison, 1995, Perrone Bizzozero et al., 1996, Uranova et al., 1996, Glantz and Lewis, 1997, Garey et al., 1998, Harrison, 1999, Glantz and Lewis, 2000, Mirnics et al., 2000, Rosoklija et al., 2000, Prabakaran et al., 2004, Clark et al., 2006, Camargo et al., 2007, Le-Niculescu et al., 2007, Sweet et al., 2007, Pennington et al., 2008, Smalla et al., 2008, Sweet et al., 2009, Chan et al., 2010, Chu and Liu, 2010, English et al., 2011). Importantly, synaptic abnormalities have been detected in the entorhinal and perirhinal cortices, regions where CSPG changes were also found (Eastwood and Harrison, 1995, Arnold, 1997, Harrison, 1999, Hemby et al., 2002, Law et al., 2004, Beneyto et al., 2007, Pantazopoulos et al., 2010).

Synaptic regulation is a prominent ECM function. Several ECM molecules, such as Reelin, CSPGs, pentraxins, thrombospondins, tenascins and laminins, together with the main group of ECM receptors, integrins, act in concert to regulate synaptogenesis, synaptic stabilization, maintenance, plasticity and homeostasis (Dityatev and Schachner, 2006, Dityatev et al., 2010a, Faissner et al., 2010). Interactions between ECM, glial and neuronal elements are key to these functions, leading to the suggestion of a ‘quadripartite’ synapse, with the addition of ECM to the ‘tripartite’ constituted by pre- and postsynaptic elements and astrocytes (Sykova, 2004b, Dityatev and Schachner, 2006, Halassa et al., 2007, Frischknecht et al., 2009, Dityatev et al., 2010a, Faissner et al., 2010). Interactions between ECM, astrocytes and glutamatergic transmission, and their effects on synaptogenesis and synaptic stabilization/maturation, are highlighted here as particularly relevant to the pathophysiology of SZ.

3.3.1 Synaptogenesis, synaptic stabilization/maturation—Direct involvement of astrocyte-derived CSPG and other ECM molecules in synaptogenesis is broadly supported by cell-insert co-culture system experiments showing that perturbations of CSPGs synthesis or integrity significantly alter the number of newly-formed synapses (Faissner et al., 2010, Pyka et al., 2011). Indirect mechanisms, through ECM regulation of glutamatergic transmission vary across development. In early developmental stages, the extracellular concentration of glutamate regulates the motility of dendritic spine (elongation/retraction) and axonal filopodia, and thus their chances of finding a synaptic partner (Tashiro et al., 2003, Segal et al., 2010). Once a synapse is formed, its stabilization and maturation depends on glutamate concentration within the synaptic cleft, as well as on the availability of

glutamate receptors to individual synapses (Hashimoto and Kano, 2003, Frischknecht et al., 2009, Dityatev, 2010). CSPG/hyaluronan-based ECM affects these parameters in several ways. First, the degree of ECM viscosity and the interactions between the negatively charged glycosaminoglycan proteoglycan chains and glutamate, which is itself negatively charged, control glutamate diffusion in the extracellular space (Sykova, 2004b, a, Sykova and Nicholson, 2008, Hrabetova et al., 2009). Second, later in postnatal development, hyaluronan/CSPG-based ECM in the form of PNNs, compartmentalizes the neuronal surface, restricting the surface mobility of integral membrane proteins, including glutamate AMPA receptors (Frischknecht et al., 2009, Dityatev et al., 2010b). This function defines the reservoir of receptors available to each synapse, an important determinant for the capability of high frequency firing (Frischknecht et al., 2009). Synergistic interactions between AMPA and NMDA receptors are needed to maintain overall integrity of glutamate synapses. In this regard, it is noteworthy that Reelin contributes to the regulation of NMDA receptors and thus strongly affects synaptic maturation and stabilization. Reelin postsynaptic membrane binding sites mediate its interactions with NMDA receptors, which have been shown to affect LTP induction (reviewed in Dityatev et al., 2010a). Reelin has also been shown to mediate a switch in the subunit composition of NMDA receptors (from accumulation to lack of the NR2B subunit) considered to be the hallmark of synaptic maturation (Sinagra et al., 2005). Thus, pathologies affecting ECM composition may affect several key aspects of glutamate transmission and, consequently, synaptic functions. Together, these considerations indicate that ECM abnormalities related to disease states may profoundly affect synaptogenesis and synaptic stabilization/maturation both directly and through glutamate-mediated mechanisms.

3.3.2 PNNs, PVB-positive neurons and adult synaptic plasticity—PNNs develop late in postnatal life, as they gradually mature into stable, dense ECM perisynaptic aggregates enveloping somata, dendrites and the initial axonal segment, and surrounding successful synaptic contacts, thus stabilizing successful neuronal connections and restricting further plasticity (Pizzorusso et al., 2002, Galtrey and Fawcett, 2007). This process occurs in an experience-driven manner, regulated by both excitatory glutamatergic inputs and inhibition mediated by GABA-A receptors, and coincides with the closure of critical developmental periods, and PVB-positive neurons maturation (Koppe et al., 1997, Vitellaro-Zuccarello et al., 2001, Pizzorusso et al., 2002, Dityatev and Schachner, 2003, Hensch, 2005, Dityatev and Schachner, 2006, Pizzorusso et al., 2006, Dityatev et al., 2007, Sugiyama et al., 2008, Balmer et al., 2009, Gogolla et al., 2009, Dityatev et al., 2010a). For instance, in the visual cortex maturation of PNNs around PVB-positive neurons is a key determinant for the establishment of ocular dominance, culminating in the closure of the critical period (Saghatelian et al., 2001, Pizzorusso et al., 2002, Sugiyama et al., 2008). Similar findings in other brain regions suggest that this PNN role may not be specific to the visual cortex (Balmer et al., 2009, Gogolla et al., 2009). Particularly relevant to mental illnesses, a study by Gogolla et al. shows a similar mechanism in the amygdala (Gogolla et al., 2009). This region plays a key role in emotion processing and is necessary for fear memory acquisition and extinction (LeDoux et al., 1989, LeDoux, 2003, Akirav and Maroun, 2007, Myers and Davis, 2007). Gogolla et al. show that formation of PNNs in the amygdala marks the closure of a developmental period during which fear memories can be fully erased by fear extinction training (i.e. repeated exposure to the conditioned stimulus in absence of unconditioned reinforcement). Once this period is closed, the ability of creating erasure-resilient, contextualized, fear memories is instated (Bouton, 2004, Kim and Richardson, 2008, Gogolla et al., 2009). Thus, PNN maturation in the amygdala may be necessary for the transition to an adult form of emotion-related learning that allows the formation of erasure-resistant fear memories. Notably, abnormal fear conditioning and extinction has been observed in subjects with SZ (Holt et al., 2009). Together with our

findings of decreased PNNs in the amygdala of subjects with SZ, these results suggest that, in this disease, ECM abnormalities may cause failure of key emotion-related circuitry to mature during late postnatal developmental stages. It is important to note that although the association between PNNs and PVB-positive neurons has been detected consistently (Fig. 1) (Celio, 1993, Hartig et al., 1994, Pantazopoulos et al., 2006), PNNs have been shown to be associated with a number of neuronal populations, including excitatory projection neurons and inhibitory interneurons, several of which express the voltage gated K^+ channel Kv3.1b subunit, critical for high-frequency firing (Perney et al., 1992, Lenz et al., 1994, Weiser et al., 1995, Gan and Kaczmarek, 1998, Hartig et al., 1999, Murakami and Ohtsuka, 2003, Wegner et al., 2003, Bruckner et al., 2004, McDonald and Mascagni, 2006, Vitellaro-Zuccarello et al., 2007). It is therefore plausible to postulate that ECM abnormalities in SZ may affect the development and functions of both excitatory and inhibitory neuronal populations.

3.4 Neurotransmission and growth factor regulation

Abnormalities affecting growth factors and main neurotransmitters have been detected consistently in SZ. Cytokines/growth factors thought to be involved in SZ include brain derived neurotrophic factor (BDNF), transforming growth factor $\beta 1$ (TGF $\beta 1$), neuregulin1 (NRG1), epidermal growth factor (EGF) (Takahashi et al., 2000, Futamura et al., 2002, Hahn et al., 2006, Harrison and Law, 2006, Dean et al., 2009, Jaaro-Peled et al., 2009, Kalkman, 2009, Sun et al., 2010, Watanabe et al., 2010). The role of TGF $\beta 1$ is particularly intriguing in the context of ECM abnormalities. On the one hand, growing evidence supports the involvement of TGF $\beta 1$ in SZ. Increases of TGF $\beta 1$ expression have been detected in the serum and several brain regions, together with anomalies of its signaling pathways (Kim et al., 2004, Benes et al., 2007, Kalkman, 2009, Mauney et al., 2011). Emerging evidence for TGF $\beta 1$ as a potential candidate gene for SZ suggests that these abnormalities may be, at least in part, related to genetic vulnerability (Zaharieva et al., 2008, Pantazopoulos et al., 2011). On the other hand, TGF $\beta 1$ powerfully stimulates CSPG synthesis in astrocytes and, in general, plays a key role in regulating ECM formation and astrocytic functions (Baghdassarian et al., 1993, Lawrence, 1996, Asher et al., 2000, Sometani et al., 2001, Hyttiainen et al., 2004, Gomes et al., 2005, Smith and Strunz, 2005, Vivien and Ali, 2006, Wilkins-Port and Higgins, 2007). Taken together, these observations suggest that increased TGF- $\beta 1$ expression may contribute to CSPG upregulation in astrocytes from subjects with SZ. In turn, the ECM controls the access of growth factors/cytokines to their cellular targets. CSPGs concentrate a range of active molecules, including BDNF, in PNNs and present them to membrane receptors (Galtrey and Fawcett, 2007, Fawcett, 2009). A reduction of CSPG-positive PNNs in SZ may thus further disrupt BDNF, and other cytokine/growth factor, signaling in SZ (Takahashi et al., 2000, Futamura et al., 2002, Hahn et al., 2006, Harrison and Law, 2006, Jaaro-Peled et al., 2009, Kalkman, 2009, Pantazopoulos et al., 2010, Watanabe et al., 2010).

Strong evidence supports abnormalities affecting glutamate, GABA and dopamine in SZ (Olney, 1990, Coyle, 1996, Laruelle, 1998, Benes and Berretta, 2001, Goff and Coyle, 2001, Prabakaran et al., 2004, Lewis et al., 2005, Carlsson and Carlsson, 2006, Clark et al., 2006, Novikova et al., 2006, Yu et al., 2006, Le-Niculescu et al., 2007, Lo et al., 2007, Dean et al., 2009, Gupta et al., 2009, English et al., 2011). Abnormalities affecting glutamate ionotropic and metabotropic receptors have been reported in several brain regions (Meador-Woodruff and Healy, 2000, Harrison et al., 2008, Ghose et al., 2009, Javitt, 2010). Altered expression of GAD₆₇, and several presynaptic and postsynaptic GABA-related factors are thought to reflect dysfunction of distinct subpopulations of GABAergic interneurons, including PNN-associated PVB-expressing neurons and somatostatin/NPY-expressing neurons, which synthesize and secrete Reelin (Woo et al., 1997, Guidotti et al., 2000a, Zhang and Reynolds,

2002, Woo et al., 2004, Lewis et al., 2005, Torrey et al., 2005, Benes et al., 2007, Huang and Akbarian, 2007, Hashimoto et al., 2008, Morris et al., 2008, Fung et al., 2010). In particular, abnormalities affecting neurons expressing PVB have been detected in several brain regions in subjects with SZ, and are thought to represent a key element of this disease (Lewis et al., 2004, Lewis et al., 2005, Pantazopoulos et al., 2007, Fung et al., 2010, Woo et al., 2010). Current views on a disruption of dopaminergic functions in SZ postulate combinations of factors affecting its release, uptake, receptor expression and responsivity and intracellular signal transduction, that may lead to altered dopaminergic tone (Grumet et al., 1996, Laruelle and Abi-Dargham, 1999, Laruelle et al., 1999, Svensson, 2000, Syed et al., 2011).

Several aspects of the complex interactions between ECM regulation of glutamate, GABA and dopamine neurotransmission have surfaced in the previous paragraphs. As discussed, the ECM controls the reservoir of AMPA receptors available to individual synapses, and modulates NMDA receptor subunit composition leading to maturation of excitatory synapses (Sinagra et al., 2005, Pizzorusso et al., 2006, Frischknecht et al., 2009). ECM abnormalities causing dysregulation of glutamate receptor availability at the synaptic site may compound the effects of altered expression of these receptors in SZ (Meador-Woodruff and Healy, 2000, Huerta et al., 2006, Beneyto et al., 2007, Hammond et al., 2010). As mentioned, PNNs are predominantly associated with neurons expressing GABAergic inhibitory interneurons expressing PVB in cortical and subcortical brain regions (Hartig et al., 1992, Seeger et al., 1996, Celio et al., 1998, Pizzorusso et al., 2002, Pantazopoulos et al., 2006, Pizzorusso et al., 2006, Sugiyama et al., 2008). PNNs abnormalities may impair the maturation and normal functions of PVB-expressing neurons, in turn affecting adult synaptic plasticity and gamma oscillatory activity (McRae et al., 2007, Gogolla et al., 2009, Woo et al., 2010). Furthermore, CSPGs have been shown to control the development of dopaminergic innervation (Gates et al., 1996, Charvet et al., 1998, Moon et al., 2002, Li et al., 2007). ECM abnormalities may disrupt dopaminergic innervation of key regions such as the striatum and amygdala.

In addition, the ECM plays a key role in modulating volume transmission, i.e. cell communication mediated by signal diffusion within the extracellular space (Agnati et al., 2006). Physical signals, e.g. electrotonic currents, as well as a broad variety of chemical signals, such as neurotransmitters (extrasynaptic release or synaptic spill-over and cross-talk), growth factors, ions, gases and enzymes, are transmitted through the ECM. Variations of ECM composition affect its viscosity and electrical charge, and thus signal diffusion (Sykova and Nicholson, 2008). For instance, the high content of negatively charged CSPGs is likely to affect local ion concentrations, as demonstrated by increased diffusion coefficient of Ca^{++} following enzymatic chondroitin sulfate chain removal, as well as diffusion of charged neurotransmitters such as glutamate (Hrabetova et al., 2009, Gundelfinger et al., 2010). Thus, pathological CSPG expression variations may profoundly affect volume transmission, altering a broad range of signals linking cellular networks (Sykova, 2004a, Agnati et al., 2006). In the amygdala, where reduced dopamine reuptake is suggested by findings of increased dopamine concentrations and decreased dopamine transporter expression in the amygdala of subjects with SZ (Reynolds, 1983, Berretta et al., manuscript in preparation), altered ECM composition may lead to excessive diffusion of dopamine in the extracellular space, with overstimulation of extrasynaptic dopamine D2 receptors (Agnati et al., 2006, Carlsson and Carlsson, 2006).

4. PHARMACOLOGICAL MANIPULATION OF ECM COMPONENTS

Investigations on pharmacological manipulation of proteoglycans have focused mostly on the treatment of brain injury, neurodegenerative disorders and cancer (Viapiano and Matthews, 2006). CSPGs are enriched in glial scars, such as those that develop following

brain injury, and have strong inhibitory effects on axonal re-growth (Davies et al., 1997, Fawcett and Asher, 1999, Morgenstern et al., 2002, Fawcett, 2009). Proteoglycans, and CSPGs in particular, are also upregulated in advanced stages of at least some neurodegenerative diseases, such as amyloidopathies, and are thought to contribute to the pathophysiology of these diseases (DeWitt and Silver, 1996, Castillo et al., 1999, McLaurin and Fraser, 2000, Sobel and Ahmed, 2001, van Horssen et al., 2003, Rhodes and Fawcett, 2004). Malignant gliomas and other cancers alter the normal ECM composition and rely on overexpression of CSPGs to promote tumor growth, vascularization and invasiveness (Paulus et al., 1996, Nutt et al., 2001, Viapiano and Matthews, 2006, Cattaruzza et al., 2008). Pharmacological tools to address these effects have been developed in recent years, and include use of the enzyme chondroitinase ABC, which removes chondroitin sulfate chains from the core proteins, and ECM regulatory factors, in some cases secreted by cell transplants (Raisman, 2004, Chiu et al., 2009, Garcia-Alias et al., 2009, Hyatt et al., 2010, Lindsay et al., 2010, Jefferson et al., 2011, Mackay-Sim and St John, 2011, Tan et al., 2011, Wang et al., 2011). Interestingly, lithium inhibits factors impairing axon outgrowth, and was found to induce marked axon sprouting following brain injury (Dill et al., 2008). Furthermore, chlorpromazine affects ECM availability of biglycan and decorin, leucine-rich small proteoglycans known to transduce signals through several growth factor receptors and to affect CSPG synthesis (Stichel et al., 1995, Oohira et al., 2000, Gotte et al., 2004, Feugaing et al., 2007, Galtrey and Fawcett, 2007).

Promising advances have been made toward pharmacological correction of Reelin abnormalities in SZ (Guidotti et al., 2009, Guidotti et al., 2011). As discussed, strong evidence points to epigenetic mechanisms as a causal factor in Reelin reduction in this disease (Veldic et al., 2004, Abdolmaleky et al., 2005, Veldic et al., 2005, Costa et al., 2007, Guidotti et al., 2007, Guidotti et al., 2010). In an elegant series of studies, Costa, Guidotti and co-workers have shown that co-administration of valproate and atypical antipsychotics facilitates chromatin remodeling, which in turn might contribute to reelin- and GAD(67)-promoter demethylation. By counteracting altered epigenetic mechanisms in SZ, this pharmacological strategy may contribute to bringing Reelin expression toward normal levels (Guidotti et al., 2009, Guidotti et al., 2011).

5. CONCLUSIONS

On the basis of the considerations discussed above, we put forward that ECM/glial abnormalities may represent a unifying factor contributing to disturbances of neuronal migration, synaptic connectivity and plasticity, and GABAergic, glutamatergic and dopaminergic neurotransmission in SZ. Interestingly, at least four genes potentially involved in ECM-glial-neuronal interactions, i.e. PTPRZ1, the gene encoding for phosphacan, reelin, ADAMTSL3, and TGF- β 1 have been recently identified as potential SZ susceptibility genes (Buxbaum et al., 2008, Shifman et al., 2008, Wedenoja et al., 2008, Zaharieva et al., 2008, Gregorio et al., 2009, Liu et al., 2010) (Dow, 2011 #11264) (Need et al., 2009), suggesting that ECM abnormalities in this disease may be, at least in part, linked to genetic factors and present during development. In the long term, knowledge of the pathophysiological mechanisms involved in ECM abnormalities in SZ, and their consequences at the cellular, neural circuit and functional levels, may allow our field to benefit from advanced therapeutic approaches targeting ECM components, and CSPGs in particular, in the context of research on brain injury, Alzheimer's disease and cancer (DeWitt and Silver, 1996, Davies et al., 1997, Viapiano and Matthews, 2006, Cattaruzza et al., 2008, Kwok et al., 2008, Li et al., 2008, Yang and Schnaar, 2008).

Abbreviations

CSPGs	chondroitin sulfate proteoglycans
EGF	epidermal growth factor
ECM	extracellular matrix
ECx	entorhinal cortex
GAD₆₇	67 kDa isoform of glutamic acid decarboxylase
GFAP	glial fibrillary acid protein
PNN	perineuronal net
PVB	parvalbumin
SZ	schizophrenia
TGF-beta	transforming growth factor beta
WFA	wisteria floribunda agglutinin

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Highlights

The brain extracellular matrix may play a key role in schizophrenia.

Solid evidence supports the involvement of extracellular matrix glycoprotein Reelin

Emerging findings point to chondroitin sulfate proteoglycans/glial interactions

Extracellular matrix functions are relevant to the pathophysiology of schizophrenia

Figure 1. PNNs predominantly surround neurons expressing parvalbumin
Confocal photomicrograph showing PNNs (green) enveloping PVB-positive neurons (red).
Scale bar =100 μ m. *Modified from* (Pantazopoulos et al., 2006).

Figure 2. Simplified diagram depicting CSPG synthesis and their secretion into the ECM, and interaction with other ECM molecules

CSPGs are formed by a core protein and a glycosaminoglycan component consisting of chondroitin sulfate chains (versican is represented here as an example). The core protein is synthesized in cytoplasmic ribosomes and then transferred to the Golgi apparatus for glycosylation. Several enzymes concur in adding repeating disaccharide units to form linear polysaccharide chains, which are then polymerized through the activity of chondroitin synthase and chondroitin polymerizing factor. Glycosaminoglycan chains are modified by sulfation, packed into secretory vesicles, and released into the ECM, where they interact with a number of other components, such as hyaluronan and tenascins. Denser ECM around a neuron (yellow) represents a PNN.

Figure 3. Marked increased of WFA-labeled elements in subjects with schizophrenia
 Photo-composites of sample coronal sections containing amygdala nuclei and ECx from a normal control (A) and a SZ subject (B) show marked WFA-labeling (black reaction product) in SZ. Note increased WFA labeling in subject with SZ. Dashed lines on A indicate the borders of each region (see C). Photomicrographs in D and E show a portion of the superficial layers of the ECx (segment shown in E corresponds to that marked by arrows in B). Photomicrographs in F-I show examples of PVB-IR neurons (F), PNNs (G), WFA-labeled glial cells (H), and GFAP-labeled cells (I). Photomicrographs in G and H are from sections labeled with WFA lectin histochemistry and Nissl-counterstained. PNN (G) net-like labeling is extracellular and surrounds the neurons soma and dendrites. WFA-labeled PNNs are easily distinguishable from WFA-labeled glial cells (H), characterized by intense intracellular labeling showing short “bushy” processes and small cell bodies. Their size and

morphological characteristics are instead very similar to those of GFAP-IR astrocytes (I). Black reaction product in A, B, D-I corresponds to nickel-enhanced diaminobenzidine staining. Abbreviations: AA, anterior amygdaloid nucleus; CE, central nucleus; HP, hippocampus; PRCx, perirhinal cortex. *Modified from* (Pantazopoulos et al., 2010).