

# The role of the extracellular matrix in chronic pain following injury

Maral Tajerian<sup>a,b,c,\*</sup>, J. David Clark<sup>a,b,c</sup>

## 1. Introduction

Tissue injury, including that which results in chronic pain, is associated with changes in the nervous system. Although plasticity after injury is a direct consequence of the insult and could play a regenerative/compensatory role particularly in the early time points after injury, long-term changes in nociceptive networks can contribute to the development of the (maladaptive) consequence: chronic pain. The study of such changes has mainly focused on synaptic plasticity in the peripheral and central nervous system neurons in addition to changes in the numbers and activity of glial cells. In recent years, however, increased emphasis has been placed on the environment in which these cells interact, mainly the extracellular matrix (ECM).

The ECM is a secreted extracellular network composed of structural and nonstructural (matricellular) proteins such as fibrillar proteins (collagens), glycoproteins (laminins, fibronectin, tenascins), and several classes of proteoglycans (heparan sulfate [HS]-, chondroitin sulfate-, dermatan sulfate-, and keratan sulfate proteoglycans) embedded in a hydrogel matrix.<sup>39</sup> Transmembrane receptors, including integrins, act as a hub between intracellular signals and the extracellular space, where they play a unique role of communication and signal transduction between the cell and its external environment. The ECM can be remodeled by an array of enzymes including serine proteases, threonine proteases, and matrix metalloproteinases (MMPs) that are released by various cell types including dermal fibroblasts, macrophages, and keratinocytes.<sup>54</sup>

Here, we review evidence for the role of the ECM in pain-related plasticity in the peripheral and central nervous systems, plasticity that may facilitate the transition of pain from an acute to a chronic form. It is important to note that, while there is a clear ECM contribution in the etiology of painful degenerative conditions such as back pain<sup>44</sup> and osteoarthritis,<sup>28</sup> this article explores the relationship between ECM proteins and nociception in conditions where the immediate source of the painful syndrome is not caused by ECM destruction.

## 2. Extracellular matrix and general nociception

To better understand the ECM contribution to chronic pain, it is important to first explore its function in nociception. Although the field of ECM/pain is relatively young, we do observe a clear role for a tissue-specific ECM in general sensation, including nociception. For instance, in the absence of collagen VI, functional deficits are observed in peripheral nerves and are paralleled by impaired nociception in mice because of disorganized c-fibers in the peripheral nervous system<sup>6</sup> (Fig. 1A, first panel). Similarly, mice lacking the ECM protein Reelin display defects in neuronal migration<sup>49</sup> in addition to deficits in correct neuronal positioning, particularly evident in the spinal cord dorsal horn (SCDH; Fig. 1A, second panel). These positioning errors are accompanied by behavioral changes showing decreased chemical and mechanical properties and increased thermal sensitivity.<sup>50,51</sup> Furthermore, heterozygous “reeler” mice present altered pain thresholds.<sup>27</sup>

In another example, increased heparanase in transgenic mice (resulting in a decrease in the ECM heparin) was shown to be associated with decreased nociceptive response to inflammatory pain, potentially because of the role of HS proteoglycan as a cytokine reservoir.<sup>30</sup> Indeed, HS has been shown to be involved in various inflammatory models, including inflammatory bowel disease<sup>29</sup> and diabetic nephropathy.<sup>16</sup> One way in which HS could be directly involved in nociception is through the sensitization of macrophages resulting in increased levels of tumor necrosis factor alpha and interleukin 1 (IL-1), both key inflammatory mediators in nociception (Fig. 1A, third panel).

These examples show that a dysregulated ECM can impact both the generation (release of pronociceptive cytokines) and the transmission (correct neuronal position in the SCDH and the presence of intact c-fibers) of nociceptive signals. Reciprocally, the induction of painful injuries can cause unique ECM changes at the acute and chronic time points after injury.

## 3. Extracellular matrix changes in injury and acute pain

Injury is often accompanied by alteration in the surrounding ECM, where the peripheral terminals of nociceptors are localized. Some of the most convincing evidence for ECM involvement after injury comes from observations about the role of MMPs and the role of integrins, with MMP activity signaling extracellular remodeling events and integrin activity signaling changes in cell function based on those extracellular events. The possibility of manipulating the ECM (through MMPs) and integrins (through antibodies directed against specific integrin isoforms) has provided researchers with various tools to study ECM/injury interactions.

Several animal studies show that MMPs are elevated in response to injury and could play a direct role in the nociceptive response. For

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

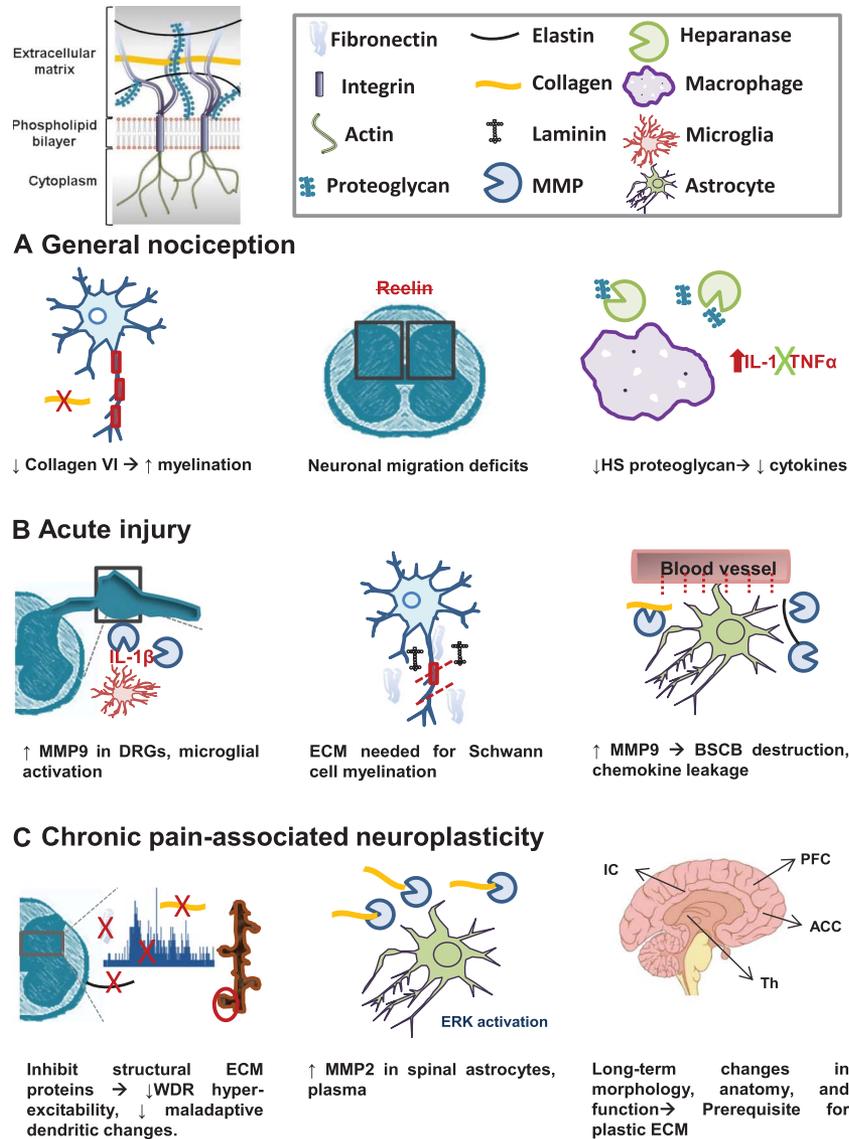
<sup>a</sup> Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA, <sup>b</sup> Department of Anesthesiology, Stanford University School of Medicine, Stanford, CA, USA, <sup>c</sup> Palo Alto Institute of Research and Education, Palo Alto, CA, USA

\*Corresponding author. Address: Anesthesia Service, Veterans Affairs Palo Alto Health Care System, 3801 Miranda Ave, Palo Alto, CA 94304, USA. Tel.: +1 650-493-5000 ext. 68825; fax: +1 650-852-3423. E-mail address: maral@stanford.edu (M. Tajerian).

PAIN 156 (2015) 366–370

© 2015 International Association for the Study of Pain

<http://dx.doi.org/10.1097/01.j.pain.0000460323.80020.9d>



**Figure 1.** Examples of ECM involvement in general nociception (A), acute injury (B), and chronic pain-associated neuroplasticity (C). ACC, anterior cingulate cortex; BSCB, brain–spinal cord barrier; DRG, dorsal root ganglion; ECM, extracellular matrix; ERK, extracellular signal–regulated kinase; HS, heparan sulfate; IC, insular cortex; IL-1, interleukin 1; MMP, matrix metalloproteinase; PFC, prefrontal cortex; Th, thalamus; TNFα, tumor necrosis factor alpha; WDR, wide dynamic range.

instance, at early time points, MMP9 cleaves IL-1β and results in microglial activation; MMP inhibition (transgenic or pharmacologic intervention) results in the amelioration/prevention of the hyperalgesic response<sup>21,25</sup> (Fig. 1B, first panel). Similarly, integrins could modulate hyperalgesic signaling through the modulation of second-order messenger interactions, and peripherally administered monoclonal antibodies against integrin subunits block inflammation-induced hyperalgesia dose dependently.<sup>9</sup> Although these factors are crucial after injury, it is entirely possible that these extracellular changes have little direct involvement in baseline nociceptive responses; for example, in animal models of neuropathy, the transient receptor potential vanilloid 4 is associated with α2β1 integrin in neurons regulating mechanotransduction in hyperalgesic but not normal nociceptive states.<sup>1</sup>

In cases where direct injury to the nerve is evident, both ECM proteins (such as laminin and fibronectin) and proteinases are needed in the degenerative (to remove degenerative debris such as collapsing myelin sheaths and neurofilaments) and

regenerative (to support the elongation of sprouting neurites) stages<sup>15,26,57</sup>; and after Wallerian degeneration, of specific interest is the role of the ECM in the myelination of Schwann cells<sup>5,19</sup> (Fig. 1B, second panel). In diabetic neuropathy, the glycation of laminin results in deficits in regenerative ability of peripheral nerves,<sup>43</sup> potentially contributing to the chronification of the neuropathy and to the subsequent pain. Equally important is the cross talk between the immune and nervous system within the ECM: Both during the degenerative and regenerative phases after peripheral nerve injury, the initial inflammatory response through macrophages is crucial.<sup>14</sup> On one hand, they release inflammatory neurotoxins and cytokines (degenerative), whereas on the other, they stimulate trophic factors and remodel the ECM (regenerative).<sup>4,22</sup> It is conceivable, therefore, that any dysregulation of the “regenerative” macrophages could result in long-term changes in ECM integrity and composition.

Finally, there seems to be a dual role for ECM proteins in nervous/vascular barrier function. In the periphery, there is

evidence that, after the initial injury and axonal degeneration, the compromised blood–nerve barrier permits the entry of several blood-derived molecules (eg, fibrinogen) into the nerve and the formation of a “provisional” ECM that is more conductive of a regenerative environment for the nerve.<sup>37</sup> However, fibrinogen is also implicated in microglial activation leading to the induction of inflammation in the nervous system at sites of vascular damage.<sup>41</sup> Peripheral injury is often accompanied by blood–spinal cord barrier compromise, leading to plasma extravasation and infiltration of immune cells into an otherwise “immune-privileged” SC. This is followed by the influx of inflammatory mediators into the spinal parenchyma, resulting in the development of pain.<sup>10</sup> Matrix metalloproteinases are thought to participate in this process by the degradation of ECM proteins in the neurovascular unit, and at least in models of spinal cord injury, proteolytic activity of MMPs has been shown to lead to blood–spinal cord barrier disruption<sup>33</sup> (Fig. 1B, third panel). Similar mechanisms could be at play during the disruption or compromise of the blood–brain barrier, which can “trap” chemokines by glycosaminoglycan-mediated immobilization,<sup>17</sup> leading to patches of highly concentrated chemokines, which would then activate and traffic immune cells across the blood–brain barrier.<sup>38</sup> These findings indicate the complexity of the process and the fine balance that must exist between regenerative and degenerative cues at the neural/vascular site.

#### 4. Extracellular matrix and the chronification of pain

Although most painful injuries resolve without long-term complications, some persist and transition to chronic pain long after the resolution of the initial insult. The mechanisms behind the chronification of pain are not clear with hypotheses ranging from dysregulated descending inhibitory pathways<sup>35</sup> to primary nociceptor plasticity<sup>18</sup> and altered central pain processing.<sup>55</sup>

After injury, the ECM–neuron cross talk is particularly relevant because pain is associated with spinal plasticity,<sup>20</sup> including changes in dendritic architecture (dendritic length and branching and dendritic spine density and morphology)<sup>46</sup> that often rely on structural proteins.<sup>48</sup> These plastic changes could be maladaptive, resulting in central sensitization of second-order spinal neurons and, ultimately, the chronification of pain.<sup>53</sup> It is well established that the ECM is a key player in CNS neuroplasticity and connectivity<sup>32,34</sup>: in the juvenile brain, heightened plasticity is paralleled by the activity-dependent maturation of the ECM,<sup>31</sup> and in the mature brain, proteins such as chondroitin sulfate proteoglycans have been shown to inhibit dendritic spine motility and thus act to “stabilize” the brain.<sup>8</sup> This direct link can be elucidated by enzymatic degradation of chondroitin sulfate proteoglycans, which promotes axonal regeneration.<sup>36</sup>

Based on the assumption that the ECM is important in plasticity, it stands to reason that manipulating it would interfere with synaptic plasticity. Indeed, studies of dendritic structure in the wide dynamic range neurons of the SCDH have shown that dendritic spine remodeling is a key contributor to pain after injury and that disrupting dendritic plasticity by inhibiting structural ECM proteins (through rac-1 signaling) attenuates the pain and hyperexcitability in these neurons<sup>47</sup> (Fig. 1C, first panel). It is, therefore, possible to manipulate the ECM to prevent injury-induced plasticity and ensuing chronic pain, particularly because ECM involvement is unique at the acute vs chronic time points. For instance, MMP9 was found to be upregulated acutely in dorsal root ganglion neurons, whereas MMP2 is upregulated at a more chronic time point in dorsal root ganglion satellite cells and spinal astrocytes<sup>21</sup> (Fig. 1C, second panel).

In addition to this ECM/neuronal mechanism of plasticity, it is also important to consider ECM/astrocyte-mediated central sensitization that parallels peripheral nerve injury.<sup>12,13</sup> Extracellular matrix and astrocytes influence one another bidirectionally: on one hand, astrocytes express various proteoglycans<sup>52</sup> and release proteases (including MMPs) that are in turn involved in the release of signaling molecules from astrocytes<sup>26</sup>; on the other, ECM proteins, such as fibronectin, stimulate astrocytic proliferation<sup>56</sup> and integrins (such as  $\beta 1$  integrin) could activate them.<sup>40</sup>

Alterations in the ECM may modulate pain chronification by changing pain-processing centers in the brain. After chronic pain, brain neuroplasticity (functional, morphologic, and anatomical) is observed both in various preclinical models<sup>2,23,45,46</sup> and in human subjects,<sup>3,42</sup> suggesting the requisite for a more plastic ECM (Fig. 1C, third panel). Although, to date, we have little information regarding dendritic/synaptic changes in human brains after chronic pain, data from animal studies have shown that pain associated with peripheral neuropathy is linked to increased formation of new persistent spines and increases elimination of previously persistent spines in the somatosensory cortex,<sup>24</sup> strongly suggesting the involvement of the ECM.

Furthermore, there are several studies linking the ECM to phenotypes (such as anxiety and memory impairment) that are often comorbid with chronic pain. For instance, modifying the ECM in the periaqueductal gray has anxiogenic effects in rats,<sup>7</sup> potentially through the regulation of cell proliferation and axonal growth. Finally, there are numerous studies showing the involvement of ECM glycoproteins, such as Tenascin C, in learning and memory through the modulation of fibronectin domains.<sup>11</sup>

#### 5. Conclusions

Although our current doctrine emphasizing neuronal and glial functioning has helped pain researchers understand the basic mechanisms of nociceptive signal transmission and the experience of pain, perhaps a more integrative model that takes into account the environment, in which various cell types interact, is needed. This approach may reveal ECM proteins to be valuable biomarkers and/or therapeutic targets in chronic pain and could help explain the comorbidities (anxiety, mood changes, memory deficits, etc.) associated with chronic injury. It is, therefore, important to consider the ECM as more than mere scaffolding for cellular support but rather as a crucial component of the chronic pain equation.

#### Conflict of interest statement

The authors have no conflicts of interest to declare.

#### Acknowledgements

The authors thank Dr. Sebastian G. Alvarado for the critical review of the article.

#### Article history:

Received 19 June 2014

Received in revised form 8 October 2014

Accepted 4 December 2014

#### References

- Alessandri-Haber N, Dina OA, Joseph EK, Reichling DB, Levine JD. Interaction of transient receptor potential vanilloid 4, integrin, and SRC tyrosine kinase in mechanical hyperalgesia. *J Neurosci* 2008;28:1046–57.
- Alvarado S, Tajerian M, Millecamps M, Suderman M, Stone LS, Szyf M. Peripheral nerve injury is accompanied by chronic transcriptome-wide changes in the mouse prefrontal cortex. *Mol Pain* 2013;9:21.

- [3] Apkarian AV, Hashmi JA, Baliki MN. Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. *PAIN* 2011;152(3 suppl): S49–64.
- [4] Badylak SF, Valentin JE, Ravindra AK, McCabe GP, Stewart-Akers AM. Macrophage phenotype as a determinant of biologic scaffold remodeling. *Tissue Eng Part A* 2008;14:1835–42.
- [5] Bunge RP. Expanding roles for the Schwann cell: ensheathment, myelination, trophism and regeneration. *Curr Opin Neurobiol* 1993;3: 805–9.
- [6] Chen P, Cescon M, Megighian A, Bonaldo P. Collagen VI regulates peripheral nerve myelination and function. *FASEB J* 2014;28: 1145–56.
- [7] De Araujo JE, Hasenohr RU, Huston JP, Brandao ML. Hyperanxiety produced by periaqueductal gray injection of chondroitin sulphate glycosaminoglycan. *Neuroreport* 2001;12:3081–4.
- [8] de Vivo L, Landi S, Panniello M, Baroncelli L, Chierzi S, Mariotti L, Spolidoro M, Pizzorusso T, Maffei L, Ratto GM. Extracellular matrix inhibits structural and functional plasticity of dendritic spines in the adult visual cortex. *Nat Commun* 2013;4:1484.
- [9] Dina OA, Parada CA, Yeh J, Chen X, McCarter GC, Levine JD. Integrin signaling in inflammatory and neuropathic pain in the rat. *Eur J Neurosci* 2004;19:634–42.
- [10] Echeverry S, Shi XQ, Rivest S, Zhang J. Peripheral nerve injury alters blood-spinal cord barrier functional and molecular integrity through a selective inflammatory pathway. *J Neurosci* 2011;31:10819–28.
- [11] Evers MR, Salmen B, Bukalo O, Rollenhagen A, Bosl MR, Morellini F, Bartsch U, Dityatev A, Schachner M. Impairment of L-type Ca<sup>2+</sup> channel-dependent forms of hippocampal synaptic plasticity in mice deficient in the extracellular matrix glycoprotein tenascin-C. *J Neurosci* 2002;22:7177–94.
- [12] Gao YJ, Ji RR. Targeting astrocyte signaling for chronic pain. *Neurotherapeutics* 2010;7:482–93.
- [13] Garrison CJ, Dougherty PM, Kajander KC, Carlton SM. Staining of glial fibrillary acidic protein (GFAP) in lumbar spinal cord increases following a sciatic nerve constriction injury. *Brain Res* 1991;565:1–7.
- [14] Gaudet AD, Popovich PG, Ramer MS. Wallerian degeneration: gaining perspective on inflammatory events after peripheral nerve injury. *J Neuroinflammation* 2011;8:110.
- [15] Gearing AJ, Beckett P, Christodoulou M, Churchill M, Clements J, Davidson AH, Drummond AH, Galloway WA, Gilbert R, Gordon JL, Leber TM, Mangan M, Miller K, Nayee P, Owen K, Patel S, Thomas W, Wells G, Wood LM, Woolley K. Processing of tumour necrosis factor- $\alpha$  precursor by metalloproteinases. *Nature* 1994;370:555–7.
- [16] Goldberg R, Rubinstein AM, Gil N, Hermano E, Li JP, van der Vlag J, Atzmon R, Meirovitz A, Elkin M. Role of heparanase-driven inflammatory cascade in pathogenesis of diabetic nephropathy. *Diabetes* 2014; 63:4302–13.
- [17] Handel TM, Johnson Z, Crown SE, Lau EK, Proudfoot AE. Regulation of protein function by glycosaminoglycans—as exemplified by chemokines. *Annu Rev Biochem* 2005;74:385–410.
- [18] Hucho T, Levine JD. Signaling pathways in sensitization: toward a nociceptor cell biology. *Neuron* 2007;55:365–76.
- [19] Ide C. Peripheral nerve regeneration. *Neurosci Res* 1996;25:101–21.
- [20] Ji RR, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? *Trends Neurosci* 2003;26: 696–705.
- [21] Kawasaki Y, Xu ZZ, Wang X, Park JY, Zhuang ZY, Tan PH, Gao YJ, Roy K, Corfas G, Lo EH, Ji RR. Distinct roles of matrix metalloproteases in the early- and late-phase development of neuropathic pain. *Nat Med* 2008; 14:331–6.
- [22] Kigerl KA, Gensel JC, Ankeny DP, Alexander JK, Donnelly DJ, Popovich PG. Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord. *J Neurosci* 2009;29:13435–44.
- [23] Kim SK, Eto K, Nabekura J. Synaptic structure and function in the mouse somatosensory cortex during chronic pain: In vivo two-photon imaging. *Neural Plast* 2012;2012:640259.
- [24] Kim SK, Nabekura J. Rapid synaptic remodeling in the adult somatosensory cortex following peripheral nerve injury and its association with neuropathic pain. *J Neurosci* 2011;31:5477–82.
- [25] Komori K, Nonaka T, Okada A, Kinoh H, Hayashita-Kinoh H, Yoshida N, Yana I, Seiki M. Absence of mechanical allodynia and Abeta-fiber sprouting after sciatic nerve injury in mice lacking membrane-type 5 matrix metalloproteinase. *FEBS Lett* 2004;557:125–8.
- [26] Kozai T, Yamanaka H, Dai Y, Obata K, Kobayashi K, Mashimo T, Noguchi K. Tissue type plasminogen activator induced in rat dorsal horn astrocytes contributes to mechanical hypersensitivity following dorsal root injury. *Glia* 2007;55:595–603.
- [27] Laviola G, Ognibene E, Romano E, Adriani W, Keller F. Gene-environment interaction during early development in the heterozygous reeler mouse: clues for modelling of major neurobehavioral syndromes. *Neurosci Biobehav Rev* 2009;33:560–72.
- [28] Lee AS, Ellman MB, Yan D, Kroin JS, Cole BJ, van Wijnen AJ, Im HJ. A current review of molecular mechanisms regarding osteoarthritis and pain. *Gene* 2013;527:440–7.
- [29] Lerner I, Hermano E, Zcharia E, Rodkin D, Bulvik R, Doviner V, Rubinstein AM, Ishai-Michaeli R, Atzmon R, Sherman Y, Meirovitz A, Peretz T, Vlodavsky I, Elkin M. Heparanase powers a chronic inflammatory circuit that promotes colitis-associated tumorigenesis in mice. *J Clin Invest* 2011;121:1709–21.
- [30] Li L, Wang B, Gao T, Zhang X, Hao JX, Vlodavsky I, Wiesenfeld-Hallin Z, Xu XJ, Li JP. Heparanase overexpression reduces carrageenan-induced mechanical and cold hypersensitivity in mice. *Neurosci Lett* 2012;511:4–7.
- [31] Miyata S, Komatsu Y, Yoshimura Y, Taya C, Kitagawa H. Persistent cortical plasticity by upregulation of chondroitin 6-sulfation. *Nat Neurosci* 2012;15:414–22; S411–412.
- [32] Muller CM, Griesinger CB. Tissue plasminogen activator mediates reverse occlusion plasticity in visual cortex. *Nat Neurosci* 1998;1:47–53.
- [33] Noble LJ, Donovan F, Igarashi T, Goussev S, Werb Z. Matrix metalloproteinases limit functional recovery after spinal cord injury by modulation of early vascular events. *J Neurosci* 2002;22:7526–35.
- [34] Oray S, Majewska A, Sur M. Dendritic spine dynamics are regulated by monocular deprivation and extracellular matrix degradation. *Neuron* 2004;44:1021–30.
- [35] Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. *Curr Opin Support Palliat Care* 2014;8:143–51.
- [36] Pizzorusso T, Medini P, Berardi N, Chierzi S, Fawcett JW, Maffei L. Reactivation of ocular dominance plasticity in the adult visual cortex. *Science* 2002;298:1248–51.
- [37] Previtali SC, Malaguti MC, Riva N, Scarlato M, Dacci P, Dina G, Triolo D, Porrello E, Lorenzetti I, Fazio R, Comi G, Bolino A, Quattrini A. The extracellular matrix affects axonal regeneration in peripheral neuropathies. *Neurology* 2008;71:322–31.
- [38] Proudfoot AE. The biological relevance of chemokine-proteoglycan interactions. *Biochem Soc Trans* 2006;34:422–6.
- [39] Rauch U, Clement A, Retzler C, Frohlich L, Fassler R, Gohring W, Faissner A. Mapping of a defined neurocan binding site to distinct domains of tenascin-C. *J Biol Chem* 1997;272:26905–12.
- [40] Robel S, Mori T, Zoubaa S, Schlegel J, Sirko S, Faissner A, Goebbels S, Dimou L, Gotz M. Conditional deletion of beta1-integrin in astroglia causes partial reactive gliosis. *Glia* 2009;57:1630–47.
- [41] Ryu JK, Davalos D, Akassoglou K. Fibrinogen signal transduction in the nervous system. *J Thromb Haemost* 2009;7(suppl 1):151–4.
- [42] Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, Jarzem P, Bushnell MC, Shir Y, Ouellet JA, Stone LS. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *J Neurosci* 2011;31:7540–50.
- [43] Sugimoto K, Yasujima M, Yagihashi S. Role of advanced glycation end products in diabetic neuropathy. *Curr Pharm Des* 2008;14:953–61.
- [44] Tajerian M, Alvarado S, Millicamps M, Dashwood T, Anderson KM, Haglund L, Ouellet J, Szyf M, Stone LS. DNA methylation of SPARC and chronic low back pain. *Mol Pain* 2011;7:65.
- [45] Tajerian M, Alvarado S, Millicamps M, Vachon P, Crosby C, Bushnell MC, Szyf M, Stone LS. Peripheral nerve injury is associated with chronic, reversible changes in global DNA methylation in the mouse prefrontal cortex. *PLoS one* 2013;8:e55259.
- [46] Tajerian M, Leu D, Zou Y, Sahbaie P, Li W, Khan H, Hsu V, Kingery W, Huang TT, Becerra L, Clark JD. Brain neuroplastic changes accompany anxiety and memory deficits in a model of complex regional pain syndrome. *Anesthesiology* 2014;121:852–65.
- [47] Tan AM, Chang YW, Zhao P, Hains BC, Waxman SG. Rac1-regulated dendritic spine remodeling contributes to neuropathic pain after peripheral nerve injury. *Exp Neurol* 2011;232:222–33.
- [48] Tan AM, Stamboulian S, Chang YW, Zhao P, Hains AB, Waxman SG, Hains BC. Neuropathic pain memory is maintained by Rac1-regulated dendritic spine remodeling after spinal cord injury. *J Neurosci* 2008;28: 13173–83.
- [49] Trommsdorff M, Gotthardt M, Hiesberger T, Shelton J, Stockinger W, Nimpf J, Hammer RE, Richardson JA, Herz J. Reeler/Disabled-like disruption of neuronal migration in knockout mice lacking the VLDL receptor and ApoE receptor 2. *Cell* 1999;97:689–701.
- [50] Villeda SA, Akopians AL, Babayan AH, Basbaum AI, Phelps PE. Absence of Reelin results in altered nociception and aberrant neuronal positioning in the dorsal spinal cord. *Neuroscience* 2006;139:1385–96.
- [51] Wang X, Babayan AH, Basbaum AI, Phelps PE. Loss of the Reelin-signaling pathway differentially disrupts heat, mechanical and chemical nociceptive processing. *Neuroscience* 2012;226:441–50.

- [52] Wiese S, Karus M, Faissner A. Astrocytes as a source for extracellular matrix molecules and cytokines. *Front Pharmacol* 2012; 3:120.
- [53] Wiesenfeld-Hallin Z, Xu XJ. Plasticity of messenger function in primary afferents following nerve injury—implications for neuropathic pain. *Prog Brain Res* 1996;110:113–24.
- [54] Woessner JF Jr. Matrix metalloproteinases and their inhibitors in connective tissue remodeling. *FASEB J* 1991;5:2145–54.
- [55] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *PAIN* 2011;152(3 suppl):S2–15.
- [56] Xia M, Zhu Y. Fibronectin enhances spinal cord astrocyte proliferation by elevating P2Y1 receptor expression. *J Neurosci Res* 2014;92:1078–90.
- [57] Yamanaka H, Obata K, Fukuoka T, Dai Y, Kobayashi K, Tokunaga A, Noguchi K. Tissue plasminogen activator in primary afferents induces dorsal horn excitability and pain response after peripheral nerve injury. *Eur J Neurosci* 2004;19:93–102.