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Glia and pain: Is chronic pain a gliopathy?

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Abstract

Activation of glial cells and neuro-glial interactions are emerging as key mechanisms underlying chronic pain. Accumulating evidence has implicated 3 types of glial cells in the development and maintenance of chronic pain: microglia and astrocytes of the central nervous system (CNS), and satellite glial cells of the dorsal root and trigeminal ganglia. Painful syndromes are associated with different glial activation states: (1) glial reaction (ie, upregulation of glial markers such as IBA1 and glial fibrillary acidic protein (GFAP) and/or morphological changes, including hypertrophy, proliferation, and modifications of glial networks); (2) phosphorylation of mitogen-activated protein kinase signaling pathways; (3) upregulation of adenosine triphosphate and chemokine receptors and hemichannels and downregulation of glutamate transporters; and (4) synthesis and release of glial mediators (eg, cytokines, chemokines, growth factors, and proteases) to the extracellular space. Although widely detected in chronic pain resulting from nerve trauma, inflammation, cancer, and chemotherapy in rodents, and more recently, human immunodeficiency virus-associated neuropathy in human beings, glial reaction (activation state 1) is not thought to mediate pain sensitivity directly. Instead, activation states 2 to 4 have been demonstrated to enhance pain sensitivity via a number of synergistic neuro-glial interactions. Glial mediators have been shown to powerfully modulate excitatory and inhibitory synaptic transmission at presynaptic, postsynaptic, and extrasynaptic sites. Glial activation also occurs in acute pain conditions, and acute opioid treatment activates peripheral glia to mask opioid analgesia. Thus, chronic pain could be a result of “gliopathy,” that is, dysregulation of glial functions in the central and peripheral nervous system. In this review, we provide an update on recent advances and discuss remaining questions.

Keywords

Astrocytes; ATP receptors; Chemokines; Cytokines; Human; Microglia; Rodents; Satellite glial cells; Spinal cord

1. Introduction

It is now well established that chronic pain, such as inflammatory pain, neuropathic pain, and cancer pain, is an expression of neural plasticity, both in the peripheral nervous system

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Conflict of interest statement
The authors declare no conflict of interest in regard to this work.

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(PNS) as peripheral sensitization [11,78] and in the central nervous system (CNS) as central sensitization [111,139]. The most widely studied neuronal mechanisms are hyperexcitability and sensitization of primary sensory neurons (peripheral sensitization) and enhancement of excitatory synaptic transmission in spinal cord, brainstem, and cortical neurons (central sensitization), caused by transcriptional, translational, and post-translational regulation. Other neuronal mechanisms include disinhibition (reduced inhibitory synaptic transmission), descending pathway facilitation (eg, from the brainstem to the spinal cord), and long-term potentiation (LTP) in the cortex and spinal cord. These neuronal mechanisms have been strongly implicated in the development and maintenance of persistent pain in rodents [11,142,195,205,317]. Central sensitization and LTP are also involved in human pain conditions[134,285]. In parallel to the progress in these neuronal mechanisms is the increased recognition of the importance of non-neuronal cells, especially glial cells, in the initiation and maintenance of chronic pain. Of note, over the last 10 years, the field of pain research has witnessed a dramatic increase in the number of publications studying glia and pain. Numerous reviews have been published in high-impact journals to address this topic[24,52,68,80,160,164,200,209,247,273]. Here we provide a comprehensive and updated review of glia and pain by integrating recent advances in both the pain and glial research fields.

Glial cells in the CNS consist of 3 major groups: astrocytes, microglia, and oligodendrocytes [69]. Glial cells in the PNS consist of satellite glial cells (SGCs) in the dorsal root ganglia (DRGs) and trigeminal ganglia (TGs) and Schwann cells in the peripheral nerves. This review will cover 3 types of glia—microglia,astrocytes, and SGCs—as their roles in pain regulation are well documented.

1.1. Microglia

Microglia are macrophage-like cells in the CNS that originate from bone marrow-derived monocytes that migrate during perinatal development. They are heterogeneously distributed throughout the CNS. Under normal conditions, microglia are not as quiescent as many investigators originally thought, as it has been shown that microglia actively sense their environment with their ramified processes [93,175,199]. Notably, microglia dynamically interact with synapses to modulate their structures and functions in healthy brain [246]. During development, microglial processes can engulf synapses, and synaptic pruning by microglia, which involves the activation of the complement system, is necessary for normal brain development. [186,221].

Microglia are further activated after various insults such as nerve injury, by displaying morphological changes, such as a change from ramified to amoeboid shape [57] and upregulation of microglial markers (CCR3/CD11b, major histocompatibility complex II [MHC II], and ionized calcium-binding adaptor molecule-1 [IBA1]) [93,227] (Table 1). After peripheral nerve injury, microglia in the spinal cord undergo rapid proliferation [14,23,55,151], and this proliferation is already very prominent 2 days after spared nerve injury [227].

Numerous studies have demonstrated a critical role of microglia in the development of neuropathic pain [43,113,197,252], as well as acute inflammatory pain [229,311]. Minocycline, a nonselective inhibitor of microglia, has been shown to reduce neuropathic pain, inflammatory pain, and postoperative pain [13,86,100,197], but its role in reducing the established late-phase neuropathic pain is limited [197]. Importantly, recent progress has identified a large number of molecules that are induced in microglia after painful injuries, especially nerve trauma (Tables 1-4).

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1.2. Astrocytes

Astrocytes are the most abundant cells in the CNS and were historically regarded as support cells. Work over the past decade indicates that astrocytes play multiple active roles in acute and chronic neuronal diseases such as seizure, stroke, and ischemia [133]. Unlike microglia and oligodendrocytes, astrocytes form physically coupled networks mediated by gap junctions, which, among other functions, facilitate intercellular transmission of Ca^{2+} signaling and exchange of cytosolic contents, and display oscillations in ion permeability through astrocytic networks. Gap junction communication is mediated by homo- and heteromeric associations of hemichannels, such as connexin-43 (Cx43), the predominant connexin expressed in astrocytes [27]. Although astrocytes are typically immune labeled by glial fibrillary acidic protein (GFAP), GFAP immunoreactivity labels only major branches and processes of astrocytes. The actual territory occupied by an astrocyte is much larger than that revealed by GFAP immunostaining. Of note, each astrocyte forms a non-overlapping territory or domain [106,133], which collectively resemble a lattice framework, appearing crystalline in nature. Although the implications of this organization are not fully understood, it becomes lost when astrocytes transition to reactive states [181]. In addition, astrocytes have extensive contacts with both synapses and cerebral blood vessels, and control the increase in blood flow evoked by synaptic activity. The astrocyte-mediated blood flow increase is fundamental to the bloodoxygen-level-dependent (BOLD) signal detected by functional magnetic resonance imaging (fMRI) [106].

It is estimated that a single astrocyte can enwrap 140,000 synapses and 4 to 6 neuronal somata, and can contact 300 to 600 neuronal dendrites in rodents. [22,69,180]. A close contact with neurons and synapses makes it possible for astrocytes not only to support and nourish neurons but also to regulate the external chemical environment during synaptic transmission.

The growing appreciation for active roles of astrocytes has led to the proposal of a “tripartite synapse” theory, based on the facts that (1) glia respond to neuronal activity with an elevation of their internal Ca^{2+} concentration and trigger the release of chemical transmitters from glia themselves, and (2) glial transmitters cause feedback regulation of neuronal activity and synaptic strength. According to this theory, astrocytic processes are active components of synapses, in addition to pre- and post-synaptic components [7]. Although active contribution to synaptic activity remains a possibility, several recent studies have challenged the theory of the tripartite synapse, by demonstrating that alterations in astrocytic Ca^{2+}do not modulate synaptic transmission[4,172,193]. In reviewing these conclusions, however, it is important to note that most of the classical studies of the tripartite synapse are based on electrophysiological analysis of acute slices prepared from rodent pups. Since the expression of membrane proteins as well as neural circuits undergo significant changes during development [16,61], it is possible that the concept of receptor-mediated Ca^{2+}signaling as a key feature defining astrocytic participation in higher neural function will be expanded to include other intracellular signaling pathways. Of note, glutamate-dependent neuroglial Ca^{2+}signaling differs between the young and adult rodent brain [223]. Thus, alternative pathways for astrocytic modulation of synaptic transmission exist: 1 of the essential housekeeping duties of astrocytes is to maintain potassium hemostasis. Recently, it has been shown that receptor-mediated increases in astrocytic Ca^{2+}can modulate neural network activity by active uptake of extracellular K^+ [263]. Because the extracellular concentration of $K^+$is an important determinant of the resting membrane potential and thereby of neuronal activity, active uptake of K^+represents a simple yet powerful tool for rapid modulation of neural networks.

Studies using astroglial toxins (eg, flurocitrate and a-aminoadipate), astroglial aconitase inhibitor (sodium fluoroacetate), or inhibitors of the astroglial enzyme glutamine synthetase

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(eg, methionine sulfoximine) in adult animals suggest that astrocytes are important both for the induction and maintenance of inflammatory and for neuropathic pain [30,31,69,83,110,161,184,200,272]. Proliferation of spinal cord astrocytes has been demonstrated in models of neuropathic pain, such as rhizotomy [151] and spinal nerve ligation [248]. Conversely, inhibiting astrocyte proliferation in the spinal cord was shown to reduce neuropathic pain [248].

1.3. Satellite glial cells

Satellite glial cells (SGCs) are prominent glial cells in the PNS. They are found not only in sensory glia (DRGs and TGs) but also in sympathetic and parasympathetic ganglia. Like Schwann cells, SGCs are derived from neural crest cells. SGCs are characterized by thin cellular sheaths that surround the individual neurons. They exhibit many similarities to astrocytes: (1) both express the glial markers GFAP, S100, and glutamine synthetase; and (2) both form gap junctions [89]. The number of SGCs in DRGs and TGs is muchlower than that of astroctyes in the spinal cord. Unlike astrocytes, each SGC contacts only 1 neuron. Strikingly, the gap of extracellular space between the SGC sheath and the associated neuronal plasma membrane measures only 20 nm, allowing for close interactions and effective signaling between neurons and SGCs [89]. Emerging evidence suggests that SGCs are activated after painful injuries and play an active role in the development of persistent pain [29,54,91,107,150]. SGCs also exhibit enhanced coupling in persistent inflammatory and neuropathic pain [54,295].

2. Different activation states of glia after painful stimuli and injuries

After painful stimuli and injuries, glia exhibit variable alterations in functions and morphologies, including the following: (1) ionic changes (eg, intracellular Ca^{2+}rises in astrocytes); (2) posttranslational regulation (eg, phosphorylation of mitogen-activated protein kinases [MAPK]); (3) translational and transcriptional modulation (eg, modulation of surface molecules, glial markers, pro- and anti-inflammatory mediators); (4) morphological changes (eg, hypertrophy); and (5) proliferation. These changes are associated with different activation states of glia (Fig. 1). Below we discuss activation states that are frequently measured in the pain research field.

2.1. Glial reaction: Changes in glial markers and/or morphology

Most studies define glial activation as upregulation of the glial markers such as CCR3/CD11b, IBA1, and GFAP, which are often, but not always, associated with morphological changes (eg, hypertrophy or process retraction/extension). Thus, we refer to this glial activation state as glial reaction.

Observations that nerve injury induces microglial responses date back to the 1970s [3]. Microglial reaction (microgliosis) in the spinal cord has been intensively investigated after peripheral nerve injury. Nerve trauma induces very robust microglial reaction, such as hypertrophy and upregulation of the microglial markers CD11b, IBA1, and CD68 in the spinal cord and brainstem[118,252,300] (Fig. 2). IBA1 is probably the most widely used marker for microglial reaction in the pain field, partly because the IBA1 antibody from Wako Chemicals works better than other antibodies of microglial markers. As expected, microglial reaction is also very robust after spinal cord injury [86,102]. Furthermore, chronic opioid exposure, streptozotocin-induced diabetic neuropathy, and surgical incision result in microglial reaction [49,192,275,310]. However, microglial reaction is less evident after bone cancer [98] and chemotherapy-induced neuropathy [297,307], depending on the doses of chemotherapy drugs and severity of nerve damage after tumor growth (as shown by ATF-3 expression in DRG neurons) [23,303]. Intra-articular but not intraplantar injection of

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complete Freund's adjuvant (CFA) induces microglial reaction[222], because of deep tissue (joint) injury and possible axonal injury (Table 1). Interestingly, in young rats (P10), nerveinjury-evoked spinal microglial reaction is not so evident, in parallel with the absence of nerve injury-induced neuropathic pain in these young animals [170,256]. Furthermore, prior neonatal injury can "prime" the spinal microglial response to adult injury, resulting in enhanced microglial reactivity [13]. Microglia can also be primed by previous insult in adults, leading to enhanced pain intensity and duration of the second insult [87].

Compared to microglial reaction, astrocyte reaction in the spinal cord is more general and evident after painful injuries [69]. Robust astrocyte reaction is induced not only by nerve trauma and spinal cord injury [75,76,173,316], but also by chronic opioid exposure [214], intraplantar or intra-articular CFA injection[70,83,198,222], bone [98] and skin cancer [67], chemotherapy, and human immunodeficiency virus (HIV)-induced neuropathy[297]. In addition, it appears that astrocytic reaction is more persistent than microglial reaction. It has been shown that GFAP and CD11b upregulation peaks at 150 and 14 days after nerve injury, respectively, although CD11b upregulation remains after 150 days[298]. GFAP upregulation is also prominent 9 months after spinal cord injury [85,173]. Although most studies have focused on glial reaction in the spinal cord and brainstem, astrocyte reaction has also been found in the forebrain, such as the anterior cingulate cortex, which contributes to affective pain [28]. One caveat is that immunohistochemistry of some GFAP antibodies may detect conformational or solubility changes or post-translational modifications of the protein but not actual changes in protein expression, because of different fixation conditions [15,56]. Thus, it is ideal to validate the results of GFAP immunohistochemistry with different antibodies and different methods such as Western blot and quantitative polymerase chain reaction (PCR).

Less is known about SGC reaction (GFAP upregulation) after painful injuries. SGC reaction is induced not only by nerve injury[150,295] but also by inflammation [235,236] in DRGs and TGs. Nerve injury further results in SGC proliferation [107]. SGCs reaction after nerve injury and DRG compression is very rapid, becoming evident within 4 hours. This reaction peaks at 1 week but declines after 3 weeks. This time course of SGC reaction suggests a possible role of SCGs in the induction and early maintenance of neuropathic pain [150,295]. Administration of glial toxin to DRGs has been shown to reduce neuropathic pain [150]. Also, there is increased coupling between SGCs after nerve injury [185,295] and inflammation [54]. Interestingly, even acute opioid treatment after a subcutaneous injection results in marked SGC reaction in DRGs at 2 hours when morphine analgesia declines [18] (Table 1).

2.2. Phosphorylation of MAPKs and Src in glia

The MAPK family includes 3 major members: extracellular signal-regulated kinase 1 and 2 (ERK1 and ERK2, respectively), p38, and c-Jun N-terminal kinases (JNK)). ERK5 is a new family member and was shown to be activated in spinal microglia after nerve injury [177]. MAPK pathways play an important role in intracellular signaling in neurons and glia, and both are required for the genesis of persistent pain [109,178]. Interestingly, different MAPKs exhibit distinct activation (phosphorylation) patterns in glial cells after painful injuries [109] (Table 2).

Numerous studies have shown increased phosphorylation (activation) of p38 (P-p38) in spinal cord microglia after nerve injury[118,136,251] (Fig. 2), spinal cord injury [46,86], formalin-induced acute inflammatory pain [229], surgery-evoked postoperative pain[192,275], and chronic opioid exposure [47]. Nerve injury also activates microglial p38 in the trigeminal nucleus [194]. It has been shown that the b isoform of p38 (p38b) is expressed in microglia[228]. In addition, P-p38 is induced in neurons and SGCs of DRGs

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following nerve injury [118,179] and also in SGCs of TGs after inflammation in the temporomandibular joint [65].

P-JNK is induced in spinal astrocytes after nerve injury [316], CFA-induced persistent inflammatory pain [70], bone cancer[267], and melanoma-induced skin cancer [67]. Consistently, nerve injury also activates the upstream activator of JNK, the transforming growth factor-activated kinase-1 (TAK1), and the downstream effector of JNK, c-Jun in spinal astrocytes [125,316]. Among several JNK isoforms (JNK 1,2,3), JNK1 was shown to be expressed in spinal astrocytes [70].

P-ERK induction in glia after injury is highly dynamic: induction in spinal microglia corresponds to the early-phase (first week), and gradually transitions to astrocytes in the late phase after nerve injury and bone cancer [268,314]. CFA also induces P-ERK in spinal astrocytes in the late phase [279]. Furthermore, nerve injury evokes P-ERK in SGCs of DRGs [314], and temporomandibular joint inflammation elicits P-ERK in SGCs of TGs [65].

MAPKs are activated by proinflammatory mediators [109] and inactivated by phosphatases, such as MAPK phosphatase (MKP1,2,3). For example, P-p38 expression in spinal microglia after nerve injury can be suppressed by MKP3 [171]. Activation of CB2 in microglia was shown to upregulate MKP1 and MKP3, leading to a reduction of P-ERK in microglia [202]. Inflammation induces rapid upregulation of MKP1, MKP2, and MKP3 in SGCs of TGs [65], which may regulate the resolution of inflammatory pain.

Mounting evidence indicates that activation of MAPKs in spinal cord glial cells is essential for the development of persistent pain[109]. Thus, intrathecal injection(s) of selective inhibitors of MEK (ERK kinase), p38, and JNK, as well as antisense knockdown of ERK5, attenuated inflammatory, neuropathic, and cancer pain in rats and mice [109]. Systemic injection of p38 inhibitor also reduced spinal nerve ligation-induced mechanical allodynia in mice[113]. Upregulation of spinal MKP-3 via gene therapy attenuates neuropathic pain by suppressing P-p38 [171].

The importance of MAPK pathways for neuropathic pain has also been demonstrated in human beings. In HIV patients with neuropathic pain, P-ERK, P-p38, and P-JNK levels in the dorsal horns are significantly increased, compared to those in HIV patients without neuropathic pain [211]. In a double-blind, placebo-controlled clinical trial, oral delivery of a selective p38 inhibitor, dilmapimod (SB-681323) attenuated neuropathic pain in patients with nerve trauma, radiculopathy, or carpal tunnel syndrome [6].

Nerve injury also induces phosphorylation of Src family kinases (Src, Lyn, Fyn) in spinal microglia [126,250]. Intrathecal infusion of a Src inhibitor (PP2) reduced nerve ligation-elicited neuropathic pain. Of interest, PP2 suppressed the activation of ERK but not p38 in spinal microglia [126].

2.3. Regulation of receptors, channels, and transporters in glia

As shown in Table 3, multiple receptors, channels, and transporters are expressed in glial cells and are regulated in different pain conditions. Although these molecules are not secreted, they play active roles in glial intracellular signaling by activating the MAPK pathways and inducing the synthesis, release, and uptake of the secreted molecules (Table 4).

ATP modulates glial activation via activating P2X (ion channels) and P2Y receptors (GPCR-coupled), and these ATP receptors gate microglial signaling for neuropathic pain

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[244,253]. Peripheral nerve injury upregulates P2X4, P2X7, P2Y6, and P2Y12 in spinal microglia; and, furthermore, neuropathic pain is reduced after pharmacological inhibition, antisense knockdown, or genetic deletion of P2X4, P2X7, P2Y6, or P2Y12 [135-137,215,243,244,252,253]. Mice lacking the P2x4 gene display diminished inflammatory pain and blunted neuropathic pain [249]. P2Y12 is also induced in SGCs of TG after nerve injury, and injection of a P2Y12R antagonist into TG reduces trigeminal neuropathic pain [124]. Moreover, chronicopioid treatment upregulates P2X4 and P2X7 in spinal microglia, and opioid tolerance is prevented after spinal knockdown of P2X4 or P2X7 [99,108,310]. However, a recent study demonstrated that opioid-induced hyperalgesia but not tolerance is mediated by opioid receptor-dependent expression of P2X4 in microglia [60].

Toll-like receptors (TLRs) are known to regulate innate immunity and have been strongly implicated in glial activation[152,174]. Lipopolysaccride (LPS), an agonist of TLR4, is highly potent in activating microglia. It also activates TLR4 in astrocytes[152]. Of note, spinal microglial reaction and neuropathic pain after nerve injury are reduced in *Tlr2* knockout mice [130] and *Tlr4* mutant mice [238]. Arthritic pain in the late phase is also reduced in *Tlr4* knockout mice [33]. Strikingly, male but not female mice with *Tlr4* mutation exhibit reduced neuropathic pain [168], suggesting sex differences in TLR4 and microglial signaling. Chronic morphine was shown to induce glial responses via activation of TLR4 [271]. Of note, opioid-inactive isomers were shown to induce spinal proinflammatory responses via activation of TLR4[104]. Pharmacological blockade of TLR4 signaling in vivo attenuated development of analgesic tolerance, hyperalgesia, and opioid withdrawal behaviors in rats [105]. In contrast, Ferrini et al. showed that chronic morphine-induced hyperalgesia is intact in *Tlr4* mutant mice [60].

Microarray analysis reveals that the complement components (eg, C1q, C3, C4, C5) are among the most regulated transcripts in the spinal cord following nerve injury. In particular, these compliment components are upregulated in spinal microglia. Induction of C5aR in spinal microglia has been implicated in neuropathic pain sensitization [82].

Increasing evidence suggests that chemokine receptors contribute to the pathogenesis of chronic pain via modulating glial activation and neural plasticity [1,35,68,280]. CX3CL1 (fractalkine) and CCL2 (MCP-1) are 2 of the most well-studied chemokines for pain modulation. Although a chemokine normally activates multiple receptors, CX3CR1 appears to be the only known receptor for CX3CL1 and is exclusively expressed in microglia. Thus, *Cx3cr*-1GFP mice have been used for studying the localization and activation of microglia [175]. Nerve injury and joint inflammation induce a robust upregulation of CX3CR1 in spinal microglia, and spinal blockade of CX3CR1 with a neutralizing antibody inhibited inflammatory and neuropathic pain [165,222,257,315]. Consistently, mice lacking *Cx3cr1* exhibited reduced inflammatory and neuropathic pain [219]. Compared to selective microglial expression of CX3CR1, CCR2, a major receptor for CCL2, is expressed in both neurons and microglia [2,72,81,84,121,305]. Nerve injury-induced spinal microglial reaction is abolished in *Ccr2* knockout mice[300], whereas intrathecal CCL2 causes microgliosis in the spinal cord [239,300]. Neuropathic pain is impaired in *Ccr2* knockout mice or after spinal injection of CCR2 antagonist [2,300,305]. Activation of CCR2 by CCL2 also rapidly modulates DRG neuronal sensitivity and spinal cord synaptic plasticity [72,81,315].

Like LPS, interferon-γ (IFN-γ) is a strong activator of microglia, by means of inducing microglial reaction, P2X4 upregulation, and Lyn phosphorylation [250]. Nerve injury upregulates INF-γ receptors in spinal microglia, and nerve injury-induced microglial reaction and mechanical allodynia are abrogated in *Ifn*γ receptor knockout mice [250].

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Astrocytes and SGCs are characterized by forming gap junction-coupled networks, leading to the transmission of Ca^{2+}signaling through networks [7,54]. Connexins are the major structural components of gap junctions, and Cx30 and Cx43 are known to be expressed by astrocytes [27]. Cx43 is upregulated in astrocytes after nerve lesion, spinal cord injury, and inflammation[27,62,77,83,145]. Inhibition of gap junction function by carbenoxolone (CBX), a nonselective gap junction inhibitor, reduces inflammatory and neuropathic pain [140,218]. In addition to modulating gap junction communication, recent studies also proposed a paracrine signaling of Cx43 to release key astrocytic mediators such as ATP and glutamate [123,148,240,262]. Unopposed Cx43 hemichannels are ideal for modulating ATP release pathways, as the biophysical properties of these hemichannels enable them to conduct high levels of ATP efflux [17,42,190]. Of note, SCI-induced ATP release in the spinal cord is diminished after Cx43 blockade [45]. In double knockout mice lacking *Cx30*/*Cx43*, the development of neuropathic pain (heat hyperalgesia and mechanical allodynia) is prevented, and spinal astroglial reaction is reduced [27]. Nerve injury was shown to upregulate Cx43 in SGCs of TGs. Of interest, reducing Cx43 expression in SGCs via RNAi reduced neuropathic pain in nerve-injured rats but induced pain-like behaviors in normal rats, suggesting different roles of SGCs-Cx43 in pain modulation in non-injured vs injured animals [183]. Notably, the gap junction blocker CBX also inhibits pannexin-1 (PNX1), which is expressed in astrocytes and modulates ATP release [74]. The role of PNX1 in pain control needs further investigation.

The following ion channels have also been implicated for glial signaling in pain. The K^+channel subunit Kir 4.1 is expressed in SGCs, and silencing this K^+subunit with RANi leads to pain hypersensitivity [261]. The water channel aquaporin-4 (AQP4) is induced in spinal cord astrocytes after spinal cord injury [173], and mice lacking *Aqp4* display decreased pain sensitivity (hypoalgesia) [9]. TRPM2 is expressed in microglia and contributes to spinal cord microglial activation. Inflammatory and neuropathic pain are impaired in *Trpm2* knockout mice [95].

The glutamate transporters such as GLT-1 and GLAST are expressed in astrocytes (Table 3) and regulate the clearance of glutamate from synaptic clefts and extracellular space, leading to altered glutamatergic transmission and neuronal plasticity[203,204]. Nerve injury and chronic morphine elicit a sustained down-regulation, after an initial upregulation, of glutamate transporter-1 (GLT1) and glutamate and aspartic acid transporter (GLAST) in the spinal cord [158,224,288]. Inhibition of glutamate transporters results in an elevation in spinal extracellular glutamate and spontaneous pain [147,278]. Consistently, GLT-1 gene delivery to the spinal cord attenuates inflammatory and neuropathic pain [157], supporting a role of astroglial glutamate transporters in the resolution of chronic pain.

Several enzymes are also actively involved in glial signaling in pain. Cyclooxygenase-1 and -2 (COX-1 and COX-2, respectively) are induced in microglia after surgical incision and nerve injury to facilitate postoperative and neuropathic pain [306,312,313]. NADPH oxidase 2 (Nox2) expression is induced in dorsal horn microglia after L5 spinal nerve transection, and *Nox2*-deficient mice showed decreases in oxidative stress, microglial reaction, and proinflammatory cytokine expression in the spinal cord, as well as neuropathic pain[131]. Of interest, G-protein-coupled receptor kinase (GRK2) in microglia was implicated in the transition from acute to chronic inflammatory pain. Spinal microglia/macrophage GRK2 expression is reduced after inflammation, leading to the activation of microglia and persistent pain via p38 and interleukin-1β (IL-1β) signaling [283].

Furthermore, nerve injury upregulates the transcriptional factors in spinal cord glia, including c-Jun in astrocytes [316], signal transducers and activators of transcription 3

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(STAT3) in microglia [53] and astrocytes [248], and nuclear factor-κB (NF-κB) in microglia [227] and astrocytes [167], to enhance and maintain neuropathic pain.

Finally, painful injuries also induce upregulation of anti-inflammatory receptors in glia for the resolution of acute pain. Inflammation increases lipoxin receptor ALX expression in spinal cord astrocytes, and lipoxin A4 reduces inflammatory pain via inhibiting JNK phosphorylation in astrocytes [231]. Lipoxin A4 also attenuates morphine tolerance via modulating glial activation and cytokine expression [117]. Nerve injury increased cannabinnoidreceptor CB2 expression in spinal microglia [299], and CB2 agonists suppressed microglial reaction and neuropathic pain [282]. Of interest *Cb2* knockout mice displayed increased microglial and astrocytic reactivity in the spinal cord and enhanced neuropathic pain, whereas transgenic mice overexpressing *Cb2* showed attenuated glial reactivity and neuropathic pain [196].

2.4. Regulation of cytokines, chemokines, growth factors, and proteases in glia

A key issue regarding glial control of pain is to understand how glial mediators are produced and released. As shown in Table 4, glia produce both large molecules (cytokines, chemokines, growth factors, and proteases) and small molecules (glutamate, ATP, D-serine, and prostaglandin E_2(PGE_2). These glial mediators can modulate neuronal and synaptic activity and pain sensitivity.

Proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-1β, and IL-6 are among the most well-studied glial mediators. They are upregulated in spinal cord glia after nerve in-jury, inflammation, bone cancer, and chronic opioid exposure, and they contribute to the development of and maintenance of inflammatory, neuropathic, and caner pain and morphine tolerance[52,213,230,273]. TNF-α is primarily produced by microglia and plays an essential role in the generation of central sensitization and persistent pain [92,289,301,308], in addition to its well-documented role in modulating peripheral sensitization [119,207,216]. IL-1β is induced in astrocytes after bone cancer, inflammation, and nerve injury [83,274,279,303]. IL-1β can also be produced by microglia and neurons in the spinal cord [36,51,92]. Inhibition of spinal and brain IL-1β signaling reduces inflammatory, neuropathic, and cancer pain [83,163,232,274,303] and enhances morphine analgesia [120,270]. IL-18 is highly related to IL-1β, and both require caspase-1 and inflammasomes for active cleavage[146]. Nerve injury induces IL-18 expression in spinal microglia[34,167]. Furthermore, painful injuries induce cytokine expression in peripheral glia. For example, nerve injury and CFA inflammation increase IL-1β expression in SGCs of DRGs and TGs [127,234]. Of note, acute morphine upregulates IL-1β only in peripheral glia (SGCs) in DRGs but not in central glia (microglia and astrocytes) in the spinal cord [18].

Chemokines are expressed in glial cells, particularly in astrocytes in the CNS [68], as well as in neurons [84]. In primary cultures of astrocytes, TNF-α induced rapid expression of CCL2, CXCL10, and CXCL1 [72]. Spinal injection of TNF-α-activated astrocytes results in persistent mechanical allodynia via releasing CCL2 [71]. Spinal nerve ligation also induces CCL2 in spinal astrocytes, and intrathecal administration of an MCP-1 neutralizing antibody reduces neuropathic pain [72]. CCL2 expression is further increased in astrocytes of the medullary dorsal horn and contributes to trigeminal neuropathic pain [305]. Consistently, mice with CCL2 overexpression in astrocytes display pain hypersensitivity [162].

Growth factors are known to be induced in spinal glia by nerve injury. In particular, nerve ligation upregulates brain-derived neurotrophic factor (BDNF) in spinal microglia, via activation of P2X4 and p38 [244,254]. Spinal injection of ATP-activated microglia is sufficient to induce mechanical allodynia via releasing BDNF, and, conversely, neuropathic pain is suppressed by spinal blockade of the BDNF receptor TrkB [43]. Furthermore,

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treatment of microglial cultures with morphine increases BDNF release, which does not require μ-opioid receptor and TLR [60]. BDNF is also induced in DRG neurons after nerve injury and can be released from primary afferents in the spinal cord [66,143]. Unlike BDNF, basic fibroblast growth factor (bFGF or FGF-2) is induced in reactive astrocytes of the spinal cord in the late phase (3 weeks) of nerve injury [110]. Intrathecal infusion of bFGF produces persistent activation of spinal astrocytes (upregulation of P-JNK and GFAP) and sustained mechanical allodynia [110]. By contrast, intrathecal administration of a bFGF-neutralizing antibody attenuates established neuropathic pain [156]. Therefore, bFGF maintains chronic pain via activation of astrocytes.

Proteases are also upregulated in spinal glia after nerve injury. Notably, spinal nerve ligation induces matrix metalloprotease-2 (MMP-2) in spinal cord astrocytes and DRG SGCs in the late phase of neuropathic pain to maintain neuropathic pain, via activation of IL-1β and ERK [127]. Nerve injury further induces cathepsin S in spinal microglia [37] and tissue type plasminogen activator (tPA) in spinal astrocytes [138] to enhance neuropathic pain.

A recent study showed that nerve injury increases the expression of thrombospondin-4 (TSP4), an extracellular matrix glycoprotein, in spinal cord astrocytes. This increase is not only correlated but also required for the development neuropathic pain [132]. TSP4 release from astrocytes can promote synaptogenesis. Of great interest, the α2δ-1 calcium channel subunit, a possible target of gabapentin, was shown to be a neuronal receptor of TSP4. Thus, gabapentin may inhibit neuropathic pain via modulating synaptogenesis [58]. Astrocytes also produce small molecule mediators such as D-serine, ATP, and glutamate to enhance pain states [69]. Interestingly, inhibition of glycinergic transmission, which is known to occur in chronic pain, results in D-serine release from astrocytes to generate tactile allodynia [166]. D-serine is known as an agonist of glycine site of *N*-methyl-D-aspartate (NMDA) receptors [176].

In addition to the pro-inflammatory and pronociceptive mediators, glial cells may also produce anti-inflammatory and antinociceptive mediators, such as IL-4, IL-10, and TGF-β [92] for the recovery and resolution of pain [41,92,94,114,164]. Enhancement of endogenous production of interleukin-10 via gene therapy has been shown to produce long-term relief in neuropathic pain[212]. Of interest, a possible off-target effect of high doses of siR-NAs is to induce IFN-α in spinal astrocytes for eliciting antinociceptive effects [237].

3. Neuronal–glial and glial–glial interactions in persistent pain

Because pain is conveyed only by neurotransmission in the neural circuits, glia must interact with neurons to modulate pain sensitivity. Here we focus on neuronal–glial (neuronal–glial) (Section 3.1) and glial–glial (Section 3.2) interactions in the CNS under persistent pain conditions (Fig. 3). We also discuss neuroglial interactions in the PNS after painful injuries and acute morphine treatment (Section 3.3) (Fig. 4).

3.1. Neuronal–glial interactions: Signals from neurons to glia

It is generally believed that injury-induced spontaneous discharge from primary afferents drives neuropathic pain[149,155,286]. Several lines of evidence suggest that nerve injury-released signaling molecules from primary afferent central terminals trigger microglial activation (Fig. 3). A brief, lowfrequency electrical stimulation of the peripheral C-fibers was shown to induce spinal microglial reaction without causing noticeable nerve injury [97]. Sustained nerve blockade via bupivacaine microspheres prevented nerve injury-induced microglial responses (CD11b expression and P-p38 induction) [276,287]. However, inhibition of C-fiber activity alone in the sciatic nerve with resininferatoxin may not be sufficient to prevent spared nerve injury-induced microglial activation [226], suggesting

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possible contribution of large A-fibers. Consistently, deletion of vesicular glutamate transporter-2 (vGluT2) in Nav1.8-expressing nociceptors did not prevent nerve injury-induced spinal microglial reaction, suggesting that glutamate release from nociceptors may not be sufficient to drive microglial reaction [208]. Although spontaneous activity is important for the initiation of microglial activation, it is not so critical for the maintenance of microglial activation [276].

Chemokines, such as CCL2, CCL21, and CX3CL1, are ideal for mediating neuronal–microglial interactions, given the distinct expression of their ligands and receptors. Nerve injury induces CCL2 and CCL21 expression in DRG neurons [19,281,298]. Stimulation of the dorsal root results in activity-dependent CCL2 release in the spinal cord [239,255]. Chemokines may activate microglia via P2X4 signaling: CCL2 induces the surface trafficking of P2X4[242], and CCL21 increases the expression of P2X4 [19]. Activation of P2X4 resulted in BDNF expression and release from microglia via p38 activation [245].

Proteases have also been implicated in microglial activation. Nerve injury induces rapid and transient upregulation of MMP-9 in DRG neurons, which is essential for the early-phase development of neuropathic pain [115]. Activity-dependent release of MMP-9 from primary sensory neurons was implicated in microglial activation, in part through IL-1b cleavage [127]. Cathepsin S is also involved in microglial–neuronal–microglial signaling. Nerve injury-evoked release of cathepsin S from microglia results in further activation of microglia, through the cleavage and release of CX3CL1 from primary sensory neurons [35,37].

The growth factor neuregulin-1 (NRG1) plays an active role in microglial activation. Although NRG1 is expressed in DRG neurons, its receptor, erbB2, is expressed in microglia. NRG1 was shown tostimulate microglial proliferation, chemotaxis, and IL-1b release via erbB2 [26]. Blockade of the erbB2 receptor or sequestration of endogenous NRG1 reduces nerve injury-induced microglial proliferation, p38 activation, and neuropathic pain [26]. NRG1 also induces microglial proliferation via phosphorylation of ERK and AKT [23]. In addition, release of the neuropeptide CGRP from primary sensory neurons is not only involved in neurotransmission but also contributes to microglial activation after chronic morphine exposure [269].

p38 MAPK serves as a key signaling molecule in microglia by integrating various input to microglia [112]. Microglia p38 is activated by ATP [79], TNF-α [230], and IL-1b [225]. After nerve injury, p38 is phosphorylated following the activation of multiple receptors, such as ATP receptors (P2X4 and P2Y12) [136,245] and chemokine receptors (CCR2 and CX3CR1) [2,315]. Microglial p38 is also activated by CGRP in chronic morphine-induced tolerance [269]. Notably, minocycline inhibits microglial activation by inhibiting spinal microglial p38 activation after inflammation and chronic morphine treatment [48,100]. Upon activation, p38 induces the synthesis and release of microglial mediators TNF-α, IL-1β, and BDNF [277]. Although p38 is critical for the synthesis and release of inflammatory mediators, it has a limited role in morphological changes (microgliosis) and proliferation of microglia, which could be mediated by another MAPK family member, ERK [25].

Neuronal signals are also important for the activation of astroytes. For example, neuronal activity appears to drive astrocyte activation after nerve injury [287] and inflammation [264]. Basic fibroblast growth factor (bFGF or FGF-2) is induced in primary sensory neurons after nerve injury and has an active role in neuronastrocyte signaling. As a well-known activator of astrocytes, bFGF elicits mitosis, growth, differentiation, and gliosis of

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astrocytes[110]. Nerve injury not only induces bFGF in DRG neurons [116] but also produces a delayed bFGF upregulation in astrocytes for maintaining neuropathic pain [110].

3.2. Glial–glial interactions

Astrocytic reaction is often preceded by microglial reaction, and microglial activation is known to drive astrocyte activation [197]. TNF-α, a key signal molecule produced by microglia, causes rapid JNK activation in astrocytes [72]. Of interest, nerve injury elicits IL-18 and IL-18R expression in spinal microglia and astrocytes, respectively, and IL-18 released from microglia was shown to activate IL-18R in astrocytes to upregulate NF-κB and facilitate neuropathic pain [167].

On the other hand, astrocytes can also release signaling molecules to activate microglia. After spinal cord injury, Cx43 is upregulated and gains a new function of paracrine signaling, leading to the release of ATP and glutamate [123,148,240,262]. Increases inextracellular ATP have been documented in a wide range of peripheral and central nervous system injuries, such as sciatic nerve entrapment [159], traumatic brain injury [50,64], and spinal cord injury [191,265]. ATP is critical for nerve injury-evoked microglial activation via activation of P2X4, P2X7, P2Y6, and P2Y12 receptors[244,253]. Of note, CCL2 is induced not only in primary sensory neurons but also in astrocytes [72,281]. Although DRG-CCL2 induces microglial activation, astrocytic-CCL2 may maintain microglial activation. IFN-γ, a strong microglial activator and neuropathic pain inducer [250], is also produced by astrocytes [196].

Finally, microglia and astrocytes could be self-activated via autocrine or paracrine signals. For example, bFGF is upregulated in spinal astrocytes after nerve injury to maintain astrocyte activation [110]. Nerve injury-induced astrocytic MMP-2 upregulation in the late phase can maintain astrocytic activation and neuropathic pain through IL-1β cleavage (activation) and phosphorylation of ERK in astrocytes [127].

3.3. Neuronal–glial interactions in dorsal root and trigeminal ganglia in the PNS

SGCs in DRGs and TGs are tightly associated with sensory neurons via gap junction; and gap junction communication between SGCs and SGC and neurons is greatly enhanced in persistent pain conditions [54,90,91]. Nerve injury-induced SGC activation requires neuronal activity and local inflammation [144,287]. Purinergic signaling is critically involved in neuronal–glial communication in DRGs [29,304]. For example, activity-dependent ATP release from neuronal soma activates P2X7 in SGCs [304], leading to TNF-α release from SGCs, which can in turn act on surrounding neurons to increase their excitability [119,216] (Fig. 4). ATP can also be released from SGCs to activate P2X3 receptor, which is expressed in primary sensory neurons and plays an important role in peripheral sensitization [40,217].

Of note, MMP-9 mediates neuron-SGC interaction in DRGs after acute morphine treatment, which can mask morphine analgesia[153] (Fig. 5). Systemic morphine administration was shown to elicit rapid MMP-9 upregulation in DRG neurons in the recovery phase of morphine analgesia (2 hours), which requires activation of μ-opioid receptors[153]. Notably, morphine analgesia is enhanced and prolonged in *Mmp9* knockout mice [153]. Acute morphine also upregulates GFAP and IL-1β in SGCs of DRGs, and both require MMP-9 [18]. MMP-9 release from neurons results in IL-1β cleavage and release, which in turn activates IL-1β receptors in sensory neurons to elicit action potentials [20]. IL-1β is known to increase the excitability of sensory neurons via enhancing sodium currents and suppressing potassium currents [20,233,236]. Of interest, IL-1β has also been shown to mask morphine-induced analgesia [103,120]. Thus, targeting peripheral neuronal–glial

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interactions, in addition to previously recognized central neuronal–glial interactions, can also enhance opioid analgesia.

4. Glial mediators modulate excitatory and inhibitory synaptic transmission

A key issue regarding glial control of pain is how glial mediators regulate synaptic transmission. Strikingly, glial mediators can modulate spinal cord synaptic transmission at very low concentrations. Although neurotransmitters (eg, glutamate, GABA, glycine, and substance P) normally regulate neuronal and synaptic activity at micromolar concentrations, glial mediators (cytokines, chemokines, and growth factors) can change synaptic activity at nanomolar concentrations in vitro [43,72,128]. In particular, glial mediators can modulate both excitatory and inhibitory synaptic transmission (Fig. 5). Although most studies used young (3- to 5-week-old) and adult animals (rats and mice) for recording spinal neuronal activities [43,72,128,189,296], some studies used neonatal animals [73,81,259]. It is well known that the gene expression profiles of primary sensory and spinal cord neurons, glial responses, as well as spinal cord pain circuits undergo dramatic changes in the first 2 weeks after birth [16,61,172]. Thus, caution must be taken to interpret the data from neonatal animals.

4.1. Modulation of excitatory synaptic transmission

Glial mediators can modulate excitatory synaptic transmission via pre-, post-, and extrasynaptic mechanisms (Fig. 5). The effects of proinflammatory cytokines and chemokines on excitatory postsynaptic currents (EPSCs) have been examined in lamina II neurons using ex vivo spinal cord slice preparations [293]. Although the EPSC frequency change may result from presynaptic mechanisms (due to glutamate release from presynaptic terminals), the EPSC amplitude increase is caused by enhanced signaling of glutamate receptors (AMPA subtype) in post-synaptic sites.

Incubation of spinal cord slices with TNF-α, IL-1β, and CCL2 very rapidly (within minutes) increased spontaneous EPSC (sEPSC) frequency [72,128,296]. Chronic exposure of cultured dorsal horn neurons to IFN-γ also increased sEPSC frequency [260] (Fig. 5A), supporting a possible presynaptic modulation. TNF-α increases sEPSC frequency via activation of TRPV1 in presynaptic terminals, as this sEPSC increase is abolished in *Trpv1* knockout mice. Single-cell PCR analysis indicates that TNF-α-responding lamina II interneurons are exclusively excitatory ones, because they all express vesicular glutamate transporter-2 (vGluT2). These lamina II neurons also receive input from TRPV1-expressing C-fibers and make synapses to lamina-I projection neurons [241], forming aspinal circuit to mediate TNF-α-induced pain. A recent study also demonstrated that TSP4, produced by astrocytes, increased sEPSC frequency [132].

Glial mediators such as IL-1β and CCL2 also increase the amplitudes of sEPSCs, via AMPA-mediated postsynaptic mechanisms (Fig. 5A). TNF-α is known to induce the trafficking and surface expression of AMPA receptors in hippocampal neurons [12,220]. After spinal cord injury, TNF-α induces rapid trafficking of GluR2-lacking AMPARs to the plasma membrane in spinal cord motor neurons [59]. Of note, inflammation induces a TNF-α-dependent surface trafficking of GluR1-AMPARs in the dorsal horn [32]. Although TNFR1 is the predominant receptor mediating the effects of TNF-α, both TNFR1 and TNFR2 are required for the induction of central sensitization [301,309].

Pro-inflammatory cytokines and chemokines further induce central sensitization via extrasynaptic mechanisms (Fig. 5A). NMDA currents in lamina II neurons, induced by bath application of NMDA to spinal cord slices, are enhanced by IL-1β, TNF-α, or CCL2 [72,128]. TNF-α increases NMDA receptor (NMDAR) activity through phosphorylation of

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ERK in dorsal horn neurons [292]. IL-1β induces phosphorylation of the NR1 subunit in spinal cord neurons [302]. Astrocytic D-serine enhances NMDA currents via binding the glycine site of NMDA receptors [201]. Interestingly, astrocytic glutamate release can be detected as slow inward currents, via patch-clamp recordings in nearby neurons. Slow inward currents are mediated by extrasynaptic NR2B receptors and induced in spinal dorsal horn neurons after inflammation [10].

4.2. Modulation of inhibitory synaptic transmission

Reduction or loss of inhibitory synaptic transmission (disinhibition) in the spinal cord pain circuit has been strongly implicated in the genesis of central sensitization and chronic pain[8,44,169,294]. Disinhibition after peripheral nerve injury involves a trans-synaptic reduction in the expression of the potassium-chloride co-transporter KCC2 and subsequent disruption of anion homeostasis (chloride homeostasis) in spinal lamina I neurons. In some cases, the shift in the transmembrane anion gradient can convert normally inhibitory anionic synaptic currents to be excitatory [44].

Glial mediators such as BDNF, cytokines, chemokines, and PGE_2 can also modulate inhibitory synaptic transmission via pre-, post-, and extrasynaptic mechanisms (Fig. 5B). Presynaptically, IL-1β and IL-6 were shown to inhibit the frequency of spontaneous postsynaptic currents (sIPSCs) in spinal lamina II neurons [128]. Postsynaptically, IL-1β reduces the sIPSC amplitude [128]. PGE_2 inhibits glycinergic neurotransmission in the dorsal horn via post-synaptic GlyR3 and the cAMP/PKA pathway [5,96].

At extrasynaptic sites, GABA and glycine currents, induced by bath application of GABA and glycine, can be suppressed by IL-1α and IL-6 [128]. BDNF acts on spinal lamina I neurons to reverse GABA inhibition by altering chloride reverse potential [43]. Furthermore, ATP or morphine-stimulated microglia result in a depolarizing shift in the anion reversal potential by releasing BDNF[43,60]. Like nerve injury, administration of ATP-stimulated microglia or pharmacological disruption of chloride transport in vivo alter the phenotype of spinal lamina I output neurons, leading to neuropathic pain phenotypes [129]. TNF-α was also shown to suppress action potentials in GAD67+ inhibitory neurons in spinal cord slices [296]. Moreover, CCL2 and IFN-γ inhibit GABA-induced responses in spinal cord neurons [81,259].

It remains to be investigated how anti-inflammatory cytokines (eg, IL-4, IL-10, TGF-β) regulate synaptic plasticity. It appears that IL-10 can suppress TNF-α-induced synaptic plasticity (unpublished observations). In particular, the anti-inflammatory lipid mediators such as resolvin E1 (RvE1) and neuroprotectin (NPD1) blocked TNF-α-induced synaptic plasticity (sEPSC frequency increase)[292]. NPD1 and RvD2 further reversed inflammation-induced synaptic plasticity and tetanic stimulation-induced spinal long-term potentiation (LTP) [189].

Finally, the proinflammatory cytokines TNF-α, IL-1β, and IL-6 also elicit long-term neuronal plasticity in the pain circuit by inducing the phosphorylation of the transcription factor cAMP response element-binding protein (CREB), leading to the transcription of CREB-mediated pronociceptive genes (eg, cyclooxygenase-2 [COX-2], neurokinin-1 [NK-1]) in spinal cord neurons[111,128,206]. Of note, TNF-α is sufficient to induce spinal LTP after nerve injury [154], and tetanic stimulation-induced spinal LTP is abolished in TNFR1 or TNFR2 knockout mice [188].

4.3. Concluding remarks

In the past decade great progress has been made to demonstrate critical roles of glial cells, such as microglia, astrocytes, and SGCs in the genesis of persistent pain. As evidence

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emerges, the list of glial-derived signaling molecules and mediators continues to grow (Tables 1-4). Glia can communicate with neurons by “listening” and “talking” to neurons. It is increasingly appreciated that chronic pain can manifest not only by neural plasticity but also by dysfunction of glial cells. Under the normal physiological conditions, astrocytes and SGCs provide trophic support to neurons and maintain the homeostasis of K^+, glutamate, and H_2O in CNS and PNS [258]. Astrocytes and SGCs could also “insulate” the neural circuit of pain by forming a structural barrier and keep the circuit silent by releasing inhibitory mediators [172]. Nerve injury-induced chronic pain is associated not only with neuropathy but also with “gliopathy.” Astrocytes lose their ability to maintain the homeostasis of $K^+$and glutamate, leading to neuronal heperexcitability, as a result of higher extracellular levels of glutamate and K^+. Dysfunction of astrocytic water channel (AQP4) will also result in edema in the CNS and PNS [258]. As a result of gliopathy, glia can no longer insulate the pain circuit; instead they serve as an amplifier of pain, by producing proinflammatory and pronociceptive mediators.

Painful injuries evoke rapid reaction of SGCs in the PNS, followed by microglial and astrocytic reaction in the CNS. Most studies on glia and pain focus on microglia and astrocytes in the spinal cord. Upon activation, presumably initiated by neuronal signals, glia synthesize and release proinflammatory and pronociceptive mediators (eg, proinflammatory cytokines and chemokines and growth factors) to enhance pain states, via activation of key signaling pathways, such as the MAP kinase pathways. Activation of hemichannels (eg, Cx43 and PNX1) and P2X7 results in the release of ATP and glutamate from astrocytes. Importantly, glial mediators (eg, TNF-α, IL-1β, IL-6, CCL2, BDNF) can powerfully modulate excitatory and inhibitory synaptic transmission at comparably lower concentrations. Glial mediators (ATP, CCL2, IFN-γ , bFGF, MMP-2) also result in further activation of glial cells via paracrine or autocrine regulation. Last but not the least, glia may also produce antiinflammatory and antinociceptive mediators for the resolution of acute pain. Further inquiry is needed to determine whether failure in the production of these resolution mediators leads to the transition from acute pain to chronic pain.

5. Remaining questions and future directions

5.1. Is glial activation associated with pain?

Despite the growing importance of glial cells in pain regulation, “glial activation” is not well defined. Most studies in the field use glial reaction (upregulation of the glial markers IBA1, CD11b, andGFAP to define the activation of microglia (IBA1/CD11b), astrocytes (GFAP), and SGCs (GFAP) (Table 1). Although the upregulation of these markers is associated with pain behaviors, especially in the induction phase, there are several caveats related to these markers. First, dissociation between microglial marker expression and pain behaviors has been reported by different groups [21,38,307]. Compared to microglial markers (IBA1 and CD11b), the astrocytic marker GFAP is better correlated with pain behaviors, especially after inflammation, bone cancer, chemotherapy, and HIV neuropathy[98,211,297,307]. Second, we should not exclude microglial activation if there is no change in IBA1 expression. Glial activation can also manifest as quick responses, such as Ca^{2+}changes and phosphorylation of signaling molecules (eg, MAPKs) that could occur within minutes after a stimulation or insult. Indeed, sensory whisker stimulation was shown to evoke rapid increases, within several seconds, in astrocytic cytosolic Ca^{2+}in the barrel cortex of adult mice [266]. Third, even under the activation states with upregulation of glial markers and hypertrophy, microglia could still have different functional states by exhibiting either pro-inflammatory (neurotoxic, M1) and anti-inflammatory (neuroprotective, M2) phenotypes [93,284]. Finally, and importantly, glial reactivity and morphological changes do not directly modulate pain. Neuronal activity and pain sensitivity are controlled by the glial mediators (cytokines, chemokines, ATP, BDNF, glutamate). Thus, the regulation of glial

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signaling molecules and glial mediators after painful injuries (Tables 2–4) could be better associated with pain states than glial reactivity.

5.2. Can we target glia for pain therapy?

How can we design drugs to target glial activity for pain control? Do we really need glia-selective drugs? Indeed, it is extremely difficult to design drugs that target only glial cells without affecting neurons. Furthermore, elimination of glial cells with glia-selective toxins may cause detrimental effects, given the supportive and protective roles of glia. Instead, there are alternative strategies: (1) to target the MAPK signaling pathways (ERK, p38, JNK), hemichannels (eg, Cx43 and PNX1), or P2X7 to suppress the release of glial mediators; (2) to target the upstream activators of glia, such as P2X4, P2Y6/12, MMP-9/2, and cathepsin S; and (3) to target the downstream mediators released by glia, such as TNF-α, IL-1β, IL-6, or BDNF.

We should learn lessons from recent failures in 2 clinical trials: 1 trial with a glial modulator, propentofylline, which showed no efficacy in reducing neuropathic pain in patients with post-herpetic neuralgia [141]; another trial with a CCR2 antagonist AZD2423, which showed no significant effects, compared to placebo, in post-traumatic neuralgia patients [122]. The failures may result from multiple reasons, including lack of translation from rodents to human beings, different ways of pain measurement in rodents and human beings (evoked pain vs spontaneous pain), and different pain conditions tested in rodents and human beings (nerve trauma-induced pain hypersensitivity in several weeks vs post-herpetic/traumatic neuralgia after many years). Of note, propentofylline is a well-known inhibitor of phosphodiesterase, and therefore could alter cAMP levels in glial and non-glial cells [63]. Propentofylline is also an adenosine uptake inhibitor [63]. Compared to the complete lack of effect of propentofylline, AZD2423 (150 mg) showed some trends toward reduction in paroxysmal pain and paresthesia/dysesthesia, indicating that a CCR2 antagonist may have some possible effects for some sensory components of pain [122]. Notably, the variability between and within individuals was very high, in part because of the nature of a multicenter trial. It is also a concern that inhibition of glial responses in the CNS cannot be validated in this trial, because of the lack of effective imaging technique for detecting glial responses (see Section 6.3).

Theoretically, it should be more effective for a drug to target both neurons and glia for pain relief. For example, p38 is activated both in spinal cord microglia and DRG neurons, and systemic p38 inhibitor has been shown to alleviate neuropathic pain in a clinical trial [6]. Recent studies have demonstrated that the anti-inflammatory and pro-resolution lipid mediators such as resolvins (RvD1, RvD2, RvE1), protectins/neuroprotectins (PD1/NPD1), and lipoxins (LXA4) could potently reduce inflammatory and postoperative pain, at very low doses [101,114,231]. Peri-surgical application of PD1/NPD1 effectively protects nerve trauma-induced neuropathic pain and spinal cord glial activation in mice [291]. RvE1 and PD1 further inhibit glial activation in cultures [290,291]. The receptors of these mediators, such as ChemR23 (RvE1) and ALX (RvD1 and LXA4) are widely expressed in neurons, glia, and immune cells[39,114,210,231]. Thus, these lipid mediators not only inhibit glial activation and inflammation but also inhibit TRP channels (eg, TRPA1/V1) and reverse synaptic plasticity in neurons[114,188,189]. Given the potency and safety, these endogenous lipid mediators, or their analogs, or small-molecule agonists of theirreceptors, could be developed for preventing and treating chronic pain, via targeting both neuronal and non-neuronal (immune and glial) mechanisms.

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5.3. How much do we know about human glia?

Little is known about the role of human glia in pain control. Indeed, astrocytes from mice, monkeys, and human beings are quite different in their sizes [180,182] (Fig. 6). The human brain appears to contain subtypes of GFAP-positive astrocytes that are not represented in rodents. In human cortex, astrocytes are more than 2-fold larger in diameter and extend 10-fold more GFAP-positive primary processes than their rodent counterparts (Fig. 6). The domain of a single human astrocyte has been estimated to contact up to 2 million synapses [133,180]. Remarkably, human glial progenitor cells (GPCs), after being implanted into neonatal immunodeficient mice, are gap junction-coupled to host astroglia, propagate Ca^{2+}signals 3-fold faster than their hosts, and exhibit enhanced LTP and learning capability [88]. Hence, human astrocytes could play a more sophisticated role in chronic pain than rodent astrocytes. Importantly, astrocyte reaction, but not microglial reaction, is associated with chronic pain in HIV-infected patients [211]. Activation of the MAPK pathways is also correlated with neuropathic pain in these patients [211]. Future research should focus on the following: studying the responses of human glia in cultures and human glia transplantation in mice; investigating the changes in human glia in painful disease conditions in post mortem tissues; and imaging real-time glial activation in patients with chronic pain.

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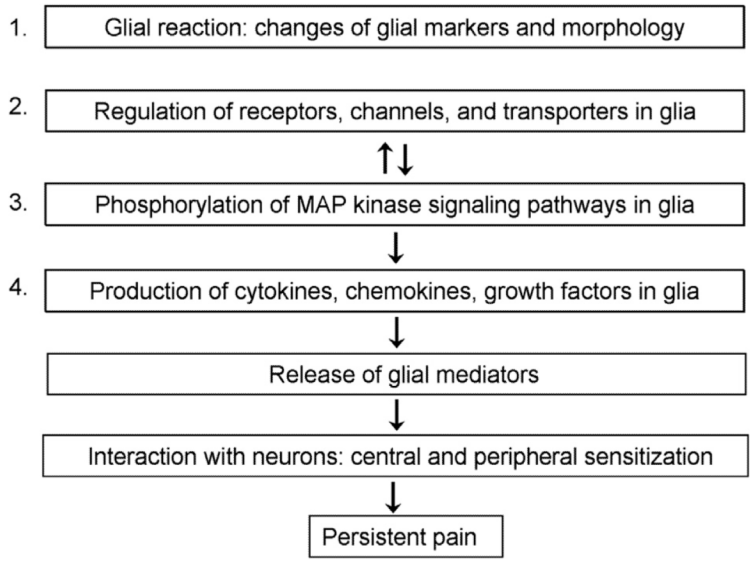

Fig. 1.

Different activation states of glia. Glia exhibit different activation states after painful injuries. (1) Glial reaction refers to upregulation of glial markers and morphological changes of glia (gliosis); (2) upregulation of glial receptors such as adenosine triphosphate (ATP) receptors, chemokine receptors, and Toll-like receptors, which will lead to the third activation state: (3) activation of intracellular signaling pathways, such as mitogen-activated protein kinase (MAPK) pathways. Phosphorylation of MAPKs will lead to the next activation state: (4) upregulation of glial mediators, such as cytokines, chemokines, and growth factors. Upon release, these glial mediators can interact with neurons to elicit pain via central and peripheral sensitization. Unlike glial reaction (state 1), the other activation states (states 2-4) have been shown to induce pain.

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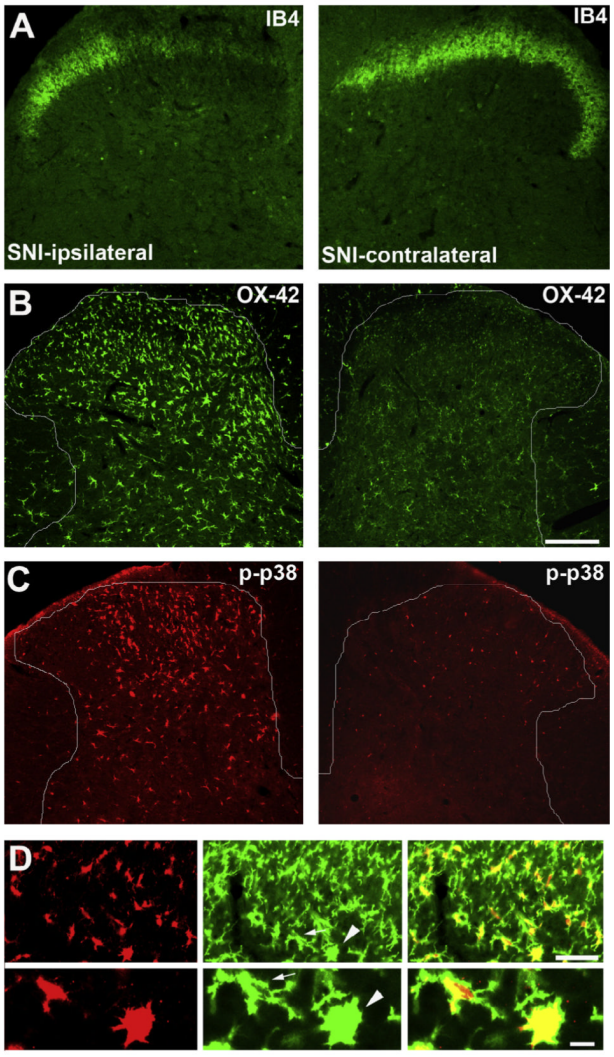

Fig. 2.

Activation of microglia in the spinal cord dorsal horn 3 days after spared nerve injury (SNI) in rats. (A) IB4 staining in the spinal cord dorsal horn ipsilateral and contralateral to the injury side. Note a loss of IB4 staining in the dorsal horn region innervated by the injured nerve branches. (B and C) CD11b (OX-42) and phosphorylated p38 (p-p38) immunostaining in the dorsal horn ipsilateral and contralateral to the injury side. Note overlapping expression patterns of OX-42 and p-p38 in the injury side. (D) Double staining of p-p38 (red) and OX-42 (green) in the ipsilateral dorsal horn. Lower panel presents high-magnification images of 2 microglial cells (indicated by arrow and arrowhead) from the upper panel. Note that p-p38 is completely co-localized with OX-42. Scale, 100 lm. Images are modified from Wen et al. [276], with permission.

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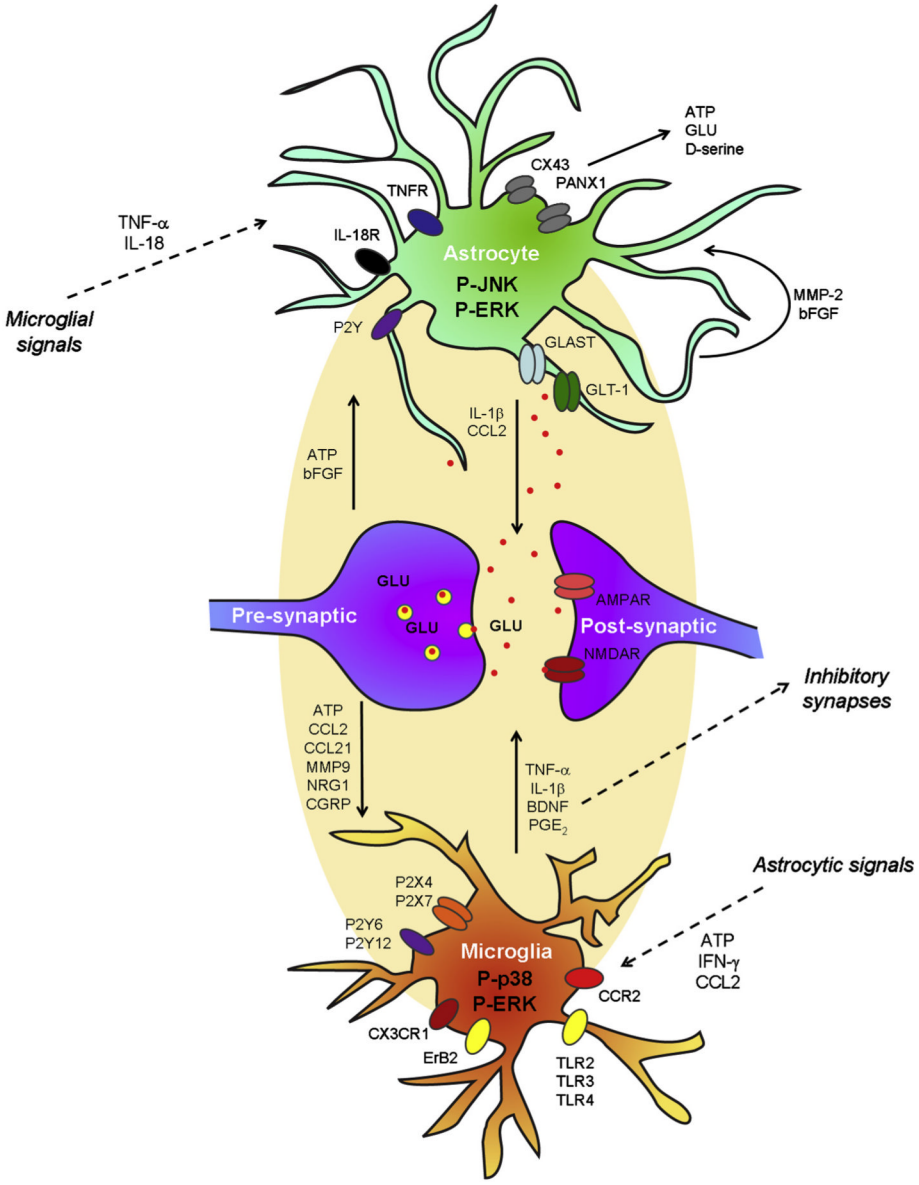

Fig. 3.

Schematic of neuronal–glial and glial–glial interactions in the spinal cord in persistent pain. Spontaneous discharge after a painful injury (eg, nerve injury) results in the release of ATP, chemokines (CCL2, CCL21, CX3CL1), MMP-9, NRG1, and CRGP from primary afferent central terminals, leading to activation of microglia in the dorsal horn. Spinal microglia express the receptors for ATP (P2X4, P2X7, P2Y6, P2Y12), and chemokines (CX3CR1, CCR2), and NRG1 (ErB2). Activation of these receptors induces phosphorylation of p38 and ERK (early phase) in microglia, leading to the production and release of the proinflammatory cytokines (TNF-α, IL-1β, IL-18) and the growth factor BDNF, and the consequent sensitization of dorsal horn neurons. Astrocytes can be activated by microglial mediators (TNF-α and IL-18), as well as astrocytic mediators (matrix metalloprotein-2 (MMP-2) and bFGF). Subsequent phosphorylation of JNK and P-ERK in astrocytes results in the production and release of chemokines (eg, CCL2) and cytokines (eg, interleukin-1β [IL-1β]). Astrocytes also produce adenosine triphosphate (ATP) and glutamate after the

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activation of the hemichannels (Cx43 and PNX1). After nerve injury, downregulation of astrocytic GLT1 results in decrease in astrocytic uptake of glutamate. Release of astrocytic mediators (CCL2, interleukin-1β [IL-1β], glutamate) can elicit NMDAR-mediated central sensitization. Release of adenosine triphosphate (ATP) and CCL2 from astrocytes can further maintain microglial activation.

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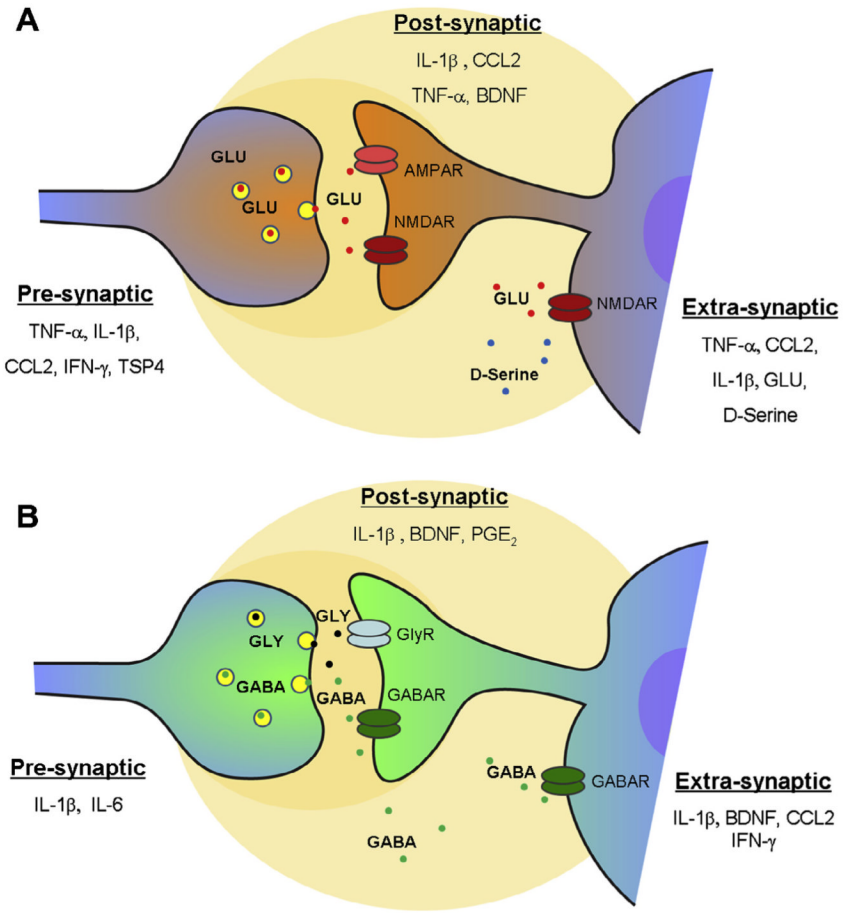

Fig. 4.

Glial mediators modulate excitatory and inhibitory synaptic transmission in the spinal cord. (A) Modulation of excitatory synaptic transmission at presynaptic, postsynaptic, and extrasynaptic sites by glial mediators. Presynaptically, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), CCL2, interferon-γ (IFN-γ), and TSP4 increase glutamate release to enhance EPSC frequency. Postsynaptically, IL-1β TNF-α, and CCL2 increase AMPAR activity. Extrasynaptically, TNF-α, IL-1β, CCL2, and D-serine increase NMDAR-NR2B activity and enhance NMDA-induced currents. Astrocyte-released glutamate can further induce NR2B-mediated inward currents in surrounding neurons. (B) Modulation of inhibitory synaptic transmission at presynaptic, postsynaptic, and extrasynaptic sites. Presynaptically, IL-1β and IL-6 decrease GABA and glycine release to decrease IPSC frequency. Postsynaptically, IL-1β decreases GABA/GlyR activity and IPSC amplitude. Prostaglandin E_2(PGE_2) inhibits evoked glycine current. Extrasynaptically, IL-1β, CCL2, and IFN-γ suppress GABA-and/or glycine-induced currents. TNF-α inhibits action potentials in inhibitory neurons. In lamina I neurons, BDNF produces disinhibition by altering chloride reverse potential.

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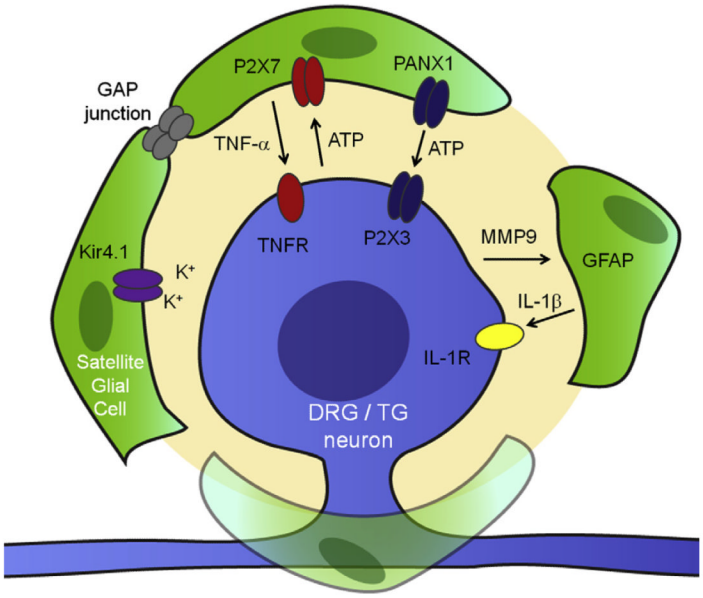

Fig. 5.

Schematic representation of neuronal-glial interactions in dorsal root and trigeminal ganglia of the peripheral nervous system (PNS). Spontaneous neuronal discharge after painful injury results in adenosine triphosphate (ATP) release in neuronal somata, leading to the activation of P2X7 and subsequent release of tumor necrosis factor-α (TNF-α) in satellite glial cells (SGCs). Persistent nociceptive activity or activation of opioid receptors by morphine also results in matrix metalloproteinase-9 (MMP-9) release from primary sensory neurons, causing the cleavage (activation) and release of interleukin-1β (IL-1β) in SGCs. TNF-α and IL-1β bind respective TNFR and IL-1R on sensory neurons to elicit hyperexcitability. SGCs can also release ATP via hemichannels (Cx43 and PNX1) or gap junction communication to activate P2X3 in neurons for triggering peripheral sensitization. In addition, SGCs express Kir 4.1 to maintain homeostasis of extracellular K^+levels of sensory neurons, and injury-induced downregulation of Kir4.1 in SGCs will disrupt this K^+homeostasis and generate neuronal hyperexcitability.

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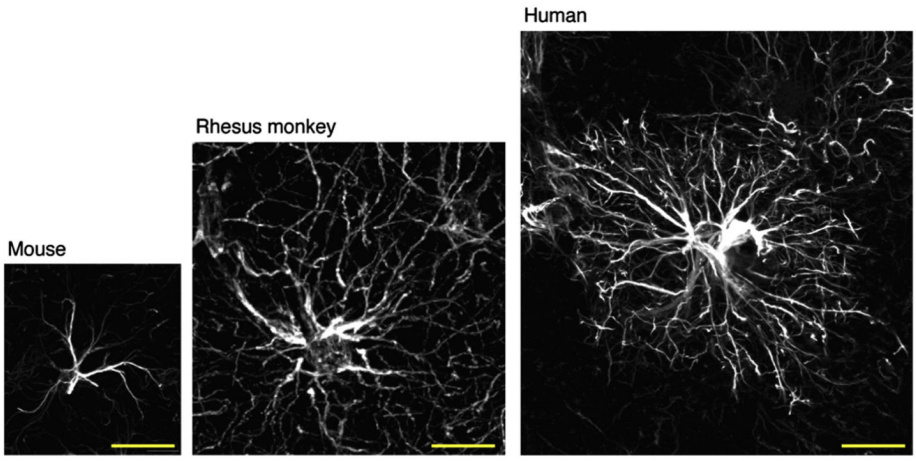

Fig. 6.

Glial fibrillary acidic protein (GFAP) immunostaining of mouse, rhesus monkey, and human astrocytes in cortex. Note striking differences in the sizes of mouse, monkey, and human astrocytes. Also note differences in the number and lengths of branches of astrocytes from mouse, monkey, and human being. Sizes of astrocytes increase with increasing complexity of brain function. Scale, 50 μm. Images are reproduced from Kimelberg and Nedergaard [133], with permission.

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Table 1

Distinct reaction of microglia, astrocytes, and satellite glial cells (SGCs) in different pain conditions, as examined by upregulation of the glial markers IBA1, CD11b, and glial fibrillary acidic protein (GFAP).

Pain conditions	Microglia	Astrocytes	SGCs
Nerve injury	↗	↗	↗
Spinal cord injury	↗	↗	
Paw incision	↗	↗	
Inflammation	↔/↗	↗	↗
Joint arthritis	↗	↗	↗
Bone cancer	↔/↗	↗	↗
Skin cancer	↔	↗	
Chemotherapy	↔/↗	↗	↗
Diabetes	↗	↗	
HIV neuropathy	↔	↗	
Chronic opioid	↗	↗	
Acute opioid	↔	↔	↗

Detailed, with related references, in Section 2.1.

Symbols: Right-upward diagonal arrow (↗) denotes upregulation; right&left horizontal arrow (↔) denotes no regulation; right-downward diagonal arrow (↘) denotes downregulation.

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Table 2

Phosphorylation of mitogen-activated protein kinases (MAPKs; ERK, p38, JNK, ERK5) in microglia, astrocytes, and satellite glial cells (SGCs) in different pain conditions.

Pain conditions	Microglia	Astrocytes	SGCs
Nerve injury			
P-ERK	↗	↗	↗
P-p38	↗		↗
P-JNK		↗	
P-ERK5	↗		
SCI			
P-ERK	↗		
P-p38	↗		
Paw incision			
P-p38	↗		
Inflammation			
P-ERK		↗	↗
P-p38	↗		
P-JNK		↗	
Bone cancer			
PERK	↗	↗	
P-p38	↗		
P-JNK		↗	
Skin cancer			
P-JNK		↗	
Diabetes			
P-ERK	↗		
P-p38	↗		
Chronic opioid			
P-ERK		↗	
P-p38	↗		

Detailed, with related references, in Section 2.2.

SCI = spinal cord injury.

Symbols: Right-upward diagonal arrow (↗) denotes upregulation; right&left horizontal arrow (↔) denotes no regulation; right-downward diagonal arrow (↘) denotes downregulation.

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Table 3

Regulation of receptors, channels, transporters, enzymes, and transcriptional factors in microglia, astrocytes, and satellite glial cells (SGCs) in different pain conditions.

Pain conditions	Microglia	Astrocytes	SGCs
Nerve injury			
P2X4	↗	↔	
P2X7	↗		
P2Y6	↗		
P2Y12	↗		↗
TLR2	↔		
TLR3	↔		
TLR4	↗		
C1q, 3, 4, 5	↗	↔	
CX3CR1	↗	↔	
CCR2	↗		
IFN-γ R	↗		
Cx43		↗	↗
Kir4.1	↗		↘
TRPM2	↔	↔	
GLT-1		↘	
GLAST		↘	
COX-1	↗		
COX-2	↗		
NF-kB	↗	↗	
NOX-2	↗		
STAT3	↗	↗	
c-Jun		↗	
CB2	↗		
SCI			
Cx43		↗	
Inflammation			
TLR3	↔		
TLR4		↗	
Cx43		↗	
TRPM2	↗		
GRK2	↘		
ALX		↘	
Joint arthritis			
CX3CR1	↗		
Bone cancer			
CX3CR1	↗		
HIV			

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Pain conditions	Microglia	Astrocytes	SGCs
TLR2		↗	
TLR9		↘	
Chronic opioid			
P2X4	↗		
P2X7	↗		
TLR2	↗		
TLR4		↔	

Detailed, with related references, in Section 2.3.

Symbols: Right-upward diagonal arrow (↗) denotes upregulation; right&left horizontal arrow (↔) denotes no regulation; right-downward diagonal arrow (↘) denotes downregulation.

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Table 4

Regulation of the glial mediators cytokines, chemokines, growth factors, and proteases in microglia, astrocytes, and satellite glial cells (SGCs).

Pain conditions	Microglia	Astrocytes	SGCs
Nerve injury			
TNF-α	↗		
IL-1β	↗	↗	↗
IL-6	↗		
IL-18	↗		
CCL2		↗	
BDNF	↗		
bFGF		↗	↗
MMP-2		↗	↗
tPA		↗	↗
CatS	↗		
TSP4		↗	
SCI			
IL-1 β		↗	
Inflammation			
TNF-α	↗		
IL-1 β		↗	↗
IL-6	↗		
Bone cancer			
TNF-α	↗		
IL-1 β		↗	
IL-6	↗		
Chronic opioid			
TNF-α		↗	
IL-1 β		↗	
IL-6	↗		
Acute morphine			
IL-1 β			↗

Detailed, with related references, in Section 2.4.

Symbols: Right-upward diagonal arrow (↗) denotes upregulation; right&left horizontal arrow (↔) denotes no regulation; right-downward diagonal arrow (↘) denotes downregulation.