REVIEW

The Role of Neuro-Immune Interactions in Chronic Pain: Implications for Clinical Practice

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Abstract: Chronic pain remains a public health problem and contributes to the ongoing opioid epidemic. Current pain management therapies still leave many patients with poorly controlled pain, thus new or improved treatments are desperately needed. One major challenge in pain research is the translation of preclinical findings into effective clinical practice. The local neuroimmune interface plays an important role in the initiation and maintenance of chronic pain and is therefore a promising target for novel therapeutic development. Neurons interface with immune and immunocompetent cells in many distinct microenvironments along the nociceptive circuitry. The local neuroimmune interface can modulate the activity and property of the neurons to affect peripheral and central sensitization. In this review, we highlight a specific subset of many neuroimmune interfaces. In the central nervous system, we examine the interface between neurons and microglia, astrocytes, and T lymphocytes. In the periphery, we profile the interface between neurons in the dorsal root ganglion with T lymphocytes, satellite glial cells, and macrophages. To bridge the gap between preclinical research and clinical practice, we review the preclinical studies of each neuroimmune interface, discuss current clinical treatments in pain medicine that may exert its action at the neuroimmune interface, and highlight opportunities for future clinical research efforts.

Keywords: neuroimmune, chronic pain, glial cells, macrophage, T-cells

Introduction

Chronic pain remains a major public health problem. The most recent Center for Disease Control and Prevention (CDC) survey between 2016 and 2019 reveals an estimated 50 million (20.4%) of US adults affected by chronic pain; and up to 60% of emergency department visits are for pain-related complaints.[1–3] This staggering number has many implications: chronic pain results in about $61 billion dollars per year in lost productivity, the treatment of chronic pain costs between $560 to $635 billion dollars annually (more than cancer and heart disease combined), and chronic pain perpetuates health disparities by preferentially impacting females, elderly patients, and those from lower socioeconomic backgrounds.[1,2,4,5] Despite these ramifications, the current status quo of chronic pain treatment still leaves many patients with poorly managed pain – and poorly controlled pain contributes to the current opioid epidemic.[6,7]

The bidirectional interface between neurons and immune or immunocompetent cells is an area of interest in the pathogenesis of chronic pain. Immunogenic inflammation, the response of the immune system to injuries or harmful stimuli, evokes nociception by activating and sensitizing nociceptors. Reciprocally, neurogenic inflammation, which is caused by the release of mediators from activation or injury of nociceptors, can activate innate and adaptive immune systems.[8] While acutely, the neuroimmune interface may play a protective role in avoiding harmful stimuli and encouraging tissue healing, current research points to the role of sustained, localized neuroinflammation in the patho-physiology of chronic pain conditions.[9,10] For example, in chronic migraine, the level of calcitonin gene-related peptide (CGRP) is elevated in the cranial but not peripheral circulation.[11] Translation of preclinical research into successful clinical treatments for patients has historically been challenging due to a multitude of possible factors discussed

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elsewhere.[12] Nevertheless, in this review, we highlight some of the preclinical work on central and peripheral neuroimmune interfaces and emphasize current clinical therapies that target each interface. Where applicable, we highlight clinical trials specific to the treatment of chronic pain conditions. While many neuroimmune interfaces exist along the nociceptive circuitry, the scope of this review is limited to profiling a subset of these interfaces.[9,13] Within the central nervous system (CNS), we will examine the interactions between neurons with microglia, astrocytes, and T lymphocytes (Figure 1); and within the peripheral nervous system (PNS), we will highlight the interactions between sensory neurons within the dorsal root ganglion (DRG) with satellite glial cells (SGC), peripheral T lymphocytes and macrophages (Figure 2).
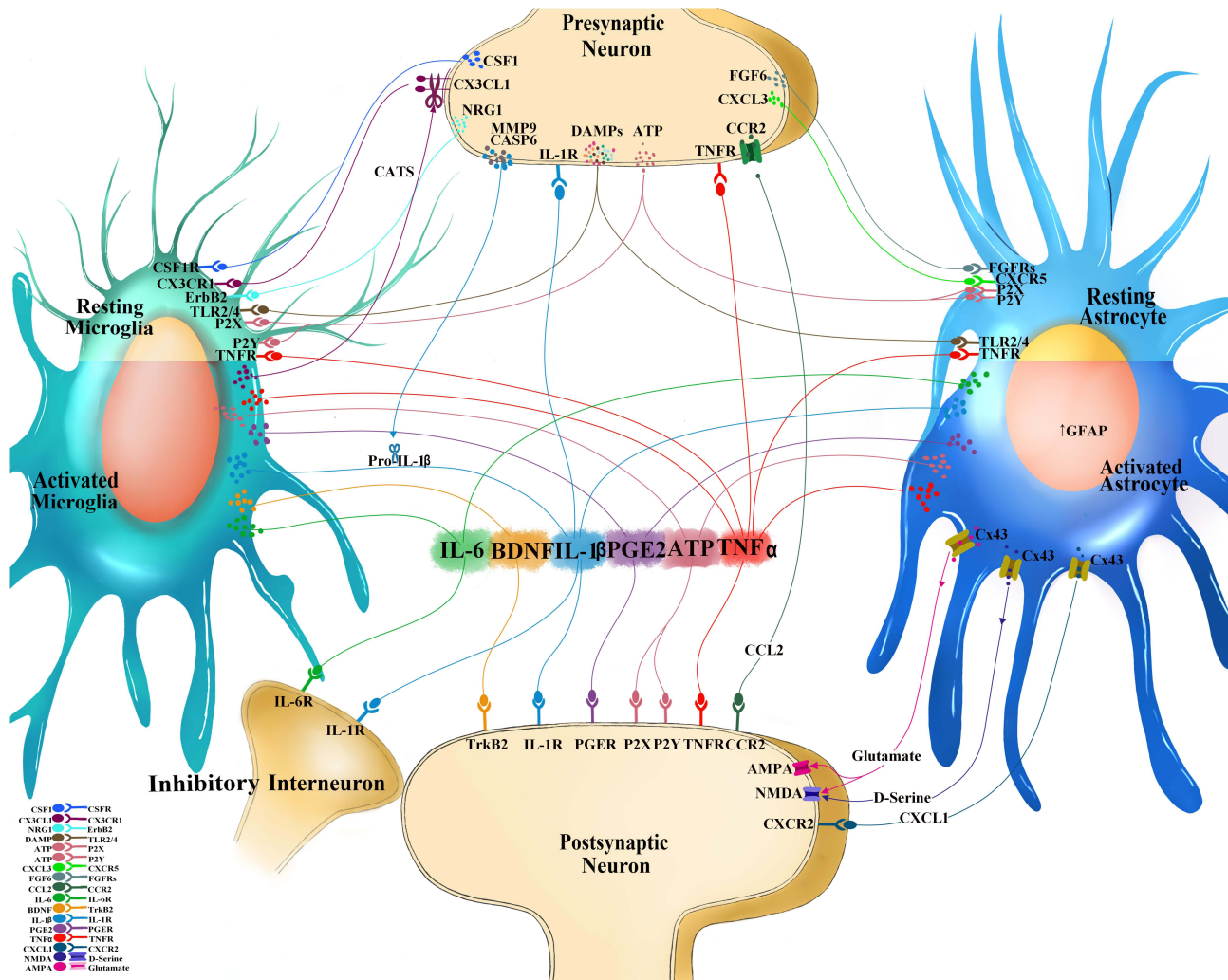

Figure 1 Interactions at the central neuroimmune interface. Sensory neurons after injury or high-stimulation activation releases mediators from the presynaptic central terminal in the dorsal horn of the spinal cord to engage cognate receptors on immunocompetent cells in the central nervous system (CNS) such as microglia and astrocytes. Colony-stimulating factor 1 (CSF1) binds to CSF1 receptor (CSF1R), neuregulin 1 (NRG1) binds to tyrosine-protein kinase (ErbB2), CX₃-C-chemokine ligand 1(CX3CL1) binds to CX3C receptor 1 (CX3CR1), matrix metalloprotease 9 (MMP9) and caspase 6 (CASP6) both facilitate the cleavage of Pro-interleukin-1 beta (IL-1b) into the mature IL-1b, fibroblast growth factor 6 (FGF6) binds to FGF receptors (FGFRs), CXC chemokine ligand 3 (CXCL3) binds to CXC receptor 5 (CXCR5), and damage associated molecular patterns (DAMPs), which include adenosine triphosphate (ATP; which can bind to purinoceptors (P2X, P2Y)), heat shock proteins (HSP) 70, HSP90, fibronectin, high mobility group box 1 (HMGB1) that all bind to toll-like receptors (TLR) 2 and 4. Unique and shared soluble mediators from neurons, immune, and immunocompetent cells of the spinal cord form feedback and feedforward signaling mechanisms which affect the nociceptive excitability and contribute to pain behavior: IL-1b binds to IL-1 receptor (IL-1R), IL-6 binds to IL-6 receptor (IL-6R), prostaglandin E2 (PGE2) binds to PGE receptor (PGER), tumor necrosis factor alpha (TNFa) binds to TNF receptor (TNFR). Activated microglia release cathepsin S (CatS) which further cleaves CX3CL1. Activate astrocytes are identified by the increased expression of glial fibrillary acidic protein (GFAP). Activated astrocytes increase Connexin 43 (Cx43) hemichannels which allows for extracellular release of CXCL1 (binding to CXCR2 on postsynaptic dorsal horn neuron), C-C chemokine ligand 2 (CCL2; binding to CCR2 on neurons), and glutamate (binding to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartic acid (NMDA) glutamatergic receptors). D-serine, a potent co-agonist of the NMDA receptor is also released from activated astrocytes.

A Common Repertoire of Proinflammatory Mediators

Immune cells secrete proinflammatory mediators to exert an immune response.[14] Except for microglia, which are myeloid cells of the CNS, other glial cells (astrocytes, satellite glial cells) are developmentally different from immune cells but are considered immunocompetent since they too can secrete immune mediators upon activation. In addition to cell-type-specific mediators, activated immune and glial cells release a shared repertoire of proinflammatory mediators that contribute to neuronal plasticity and overall nociceptive hyperexcitability, highlighted among them are tumor necrosis factor alpha (TNFa), interleukin-1-beta (IL-1b), interleukin-6 (IL-6), and prostaglandin E2 (PGE2).

TNFa promotes the excitability of neurons through TNF receptor subtypes 1 and 2 (TNFR1, TNFR2) located on presynaptic and postsynaptic neurons in the spinal cord. Presynaptically, TNFa facilitates glutamate release from presynaptic terminals of primary sensory neurons through a transient receptor potential cation channel subfamily V member 1 (TRPV1)-dependent mechanism and increases the frequency of excitatory postsynaptic current (EPSC). Postsynaptically, TNFa potentiates the function of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartic acid (NMDA) glutamatergic receptors and increases the amplitude of EPSC in spinal dorsal cord (SDH) neurons.[17–19] IL-1b overlaps with TNFa to mediate central sensitization of spinal cord neurons through both enhanced excitation and decreased inhibition. IL-1b binds to IL-1 receptor (IL-1R) to cause postsynaptic NMDA facilitation with increased amplitude of EPSC of SDH neurons; and IL-1b also suppresses inhibitory neurotransmission from interneurons.[18–22] IL-6 binds to membrane-bound and soluble IL-6 receptors (IL-6R) to mediate its signaling. In the spinal cord, IL-6 can affect spinal cord interneurons to suppress the release of γ-aminobutyric acid (GABA) and glycine. The decrease in frequency and amplitude of inhibitory postsynaptic currents (IPSC) in interneurons results in the overall excitability of the SDH neurons.[19] PGE2, generated by the cyclooxygenase-2 (COX-2) enzyme, can act directly on spinal cord neurons by activating non-selective cation channels and via prostanoid receptors to mediate presynaptic neurotransmitter release from presynaptic terminals of primary sensory neurons and depolarize postsynaptic spinal cord neurons.[23–25] Nonsteroid anti-inflammatory drugs (NSAIDs) may exert their effects within the neuroimmune interface at the COX-2 control of PGE2 production.[26] Each proinflammatory cytokine alone is sufficient to sensitize ascending SDH neurons and each mediator reflects a potential target for therapeutic intervention that will be reviewed in the subsequent clinical section.

Neuroimmune Interfaces Within the Central Nervous System

The Microglia-Neuron Interface

Microglia are canonical immune cells of the CNS.[27] In a conserved fashion across species, microglia originate from yolk sac progenitor cells and migrate into the developing brain where they expand to colonize the entire CNS.[28–30] The microglia-neuron interface is implicated in the pathogenesis of many brain diseases including chronic pain and is one of the most studied CNS neuroimmune interfaces.[16,31–35]

Clinical correlation of the microglia-neuronal interface is largely absent despite much work in preclinical models of chronic pain. The inability to identify the microglia-neuron interface clinically is a major limitation, let alone to follow how this interface changes over the course of chronic pain. Postmortem spinal cord section of a patient with complex regional pain syndrome (CRPS) on chronic opioid therapy revealed increased microglia throughout the entire spine.[36] Positron emission tomography (PET) scanning using a tracer binding to the translocator protein 18 kDa (TSPO) allows for the visualization of glial activation – however, this is not specific to microglia and includes astrocytes and myeloid cells.[37] Nevertheless, positive TSPO accumulation in the nervous system of patients with CRPS, fibromyalgia, and chronic lower back pain point to a link between overall glial activation and chronic pain conditions.[38–41] While there are no microglia-specific radioligands, there are radioligands that are more specific for astrocytes (radioligand [11C]-L-deprenyl-D2 targets the astrocyte-specific monoamine oxidase B).[42] An interesting PET study examining fibromyalgia patients observed elevated TSPO but not [11C]-L-deprenyl-D2 signals in the frontal and parietal lobes, supporting that microglia, but not astrocytes, contribute to neuroinflammation in these patients.[43] The development of more specific PET tracers for microglia (such as targeting other receptors like P2X purinoreceptor 7; P2XR7) and tracers capable of

differentiating between microglia phenotypes will help advance our clinical understanding of the dynamics of microglial activation in pain and in other neurologic diseases.[37]

Neuron to Microglia Interactions

Microglia constantly survey the local microenvironment of the CNS.[27] Neurons, particularly the central terminals of DRG neurons, release mediators through injury- and/or stimulation-dependent mechanisms to activate microglia; examples of secreted proinflammatory mediators include damage associated molecular patterns (DAMPs), colony stimulating factor 1 (CSF1), neuregulin 1 (NRG-1), CX_3C-chemokine ligand 1 (CX3CL1), matrix metalloprotease 9 (MMP9), caspase 6 (CASP6). Different DAMPs such as adenosine triphosphate (ATP), heat shock proteins (HSP60, HSP90), fibronectin, and high mobility group box 1 (HMGB1) can bind to toll-like receptors 2 and 4 (TLR2, TLR4) expressed on microglia.[44–48] Transgenic mice with neuronal knockout of HMGB1, or global knockout of TLR2 or TLR4 receptors all exhibit reduced pain behaviors in inflammatory and neuropathic models of pain. Notably, TLRs are found in immune cells, astrocytes and neurons; thus, the specific contribution of microglial TLRs to global knockout genetic models remains unclear.[48–51]

ATP binds to numerous purinergic receptors expressed on microglia and the various binding interactions have contributing roles in neuropathic pain.[52] In particular, P2X purinoceptor 4 (P2XR4) is exclusively upregulated on spinal cord microglia in response to C-C motif chemokine ligand 21 (CCL21) secreted from injured DRG neurons.[53] Blockade or knockout of P2X4R is sufficient to suppress mechanical hypersensitivity in preclinical models of inflammatory and neuropathic pain.[33,54]

CSF1 receptor (CSF1R) is expressed on microglia. Tonic signaling via CSF1R is critical for the development and maintenance of microglia in the adult nervous system.[28,55] Additional release of CSF1 induced by injured DRG sensory neurons leads to local spinal cord microglia activation and proliferation via microglia CSF1R.[56–58] Transgenic mice lacking CSF1 in DRG neurons fail to develop pain behavior after nerve injury, while administration of intrathecal CSF1 alone is sufficient to induce pain behavior in uninjured mice.[56] CSF1R is also present in peripheral myeloid cells and regulates the differentiation of macrophages. Dysregulation of the CSF1-CSF1R pathway is implicated in certain myeloid cancers.[59] Currently, there are small molecules and monoclonal antibodies targeting CSF1R or CSF1 - some already with the United States Food and Drug Administration (FDA) approval (such as pexidartinib, a CSF1R inhibitor) for cancer therapy. Research into whether these medications can provide analgesic benefit in the context of chronic pain will be of great interest.[60]

CX3CL1 is a neuronal transmembrane protein that can be cleaved to release the soluble chemokine. Cleaved CX3CL1 is a ligand for the CX3CL1 receptor 1 (CX3CR1) found exclusively on microglia in CNS.[61] Intrathecal injection of soluble CX3CL1 induces nociceptive behavior in uninjured animals, while global CX3CR1 knockout mice display less severe neuropathic pain behavior in a model-specific manner.[62–64] CX3CL1 cleavage from neuronal membrane requires the cysteine protease, cathepsin S (CatS), which is expressed by activated microglia – this highlights the bidirectionality of the neuron-microglia interface.[62] KAND567, a small-molecule inhibitor of CX3CR1, is a potential clinical anti-inflammatory agent. Current clinical trials are primarily studying this molecule in the context of myocardial infarction and SARS-CoV-2 (COVID-19) infections, but the manufacturer has advertised future plans to explore this medication for pain treatment.[65]

MMP9 and CASP6 are neuronal proteases induced under various animal pain models. MMP9 exemplifies an indirect interaction between neurons and microglia. MMP9 is transiently induced in DRG neurons after nerve injury.[66] Released MMP9 mediates the cleavage of extracellular pro-interleukin-1b (pro-IL-1b) to the active IL-1b whereby it can act directly on neurons, microglia, astrocytes, and other IL-1R expressing cells.[67] The central terminals of injured or activated DRG nociceptors release CASP6 into the spinal cord.[68] In vitro culture of microglia with CASP6 elicits a dose-dependent release of microglial TNFa and the pretreatment of rodents with microglial inhibitor minocycline reduces CASP6-evoked pain behavior, but the exact interaction of CASP6 with microglia remains a mystery.[68,69]

NRG-1 is released from primary afferent terminals after injury. NRG-1 activates microglia through receptor tyrosine-protein kinase ErbB2 to drive the release of IL-1b, microglia proliferation, and pain behavior after injury.[70]

Microglia to Neuron Interactions

The activation of microglia ultimately results in the secretion of the aforementioned repertoire of proinflammatory cytokines in the spinal cord to mediate central sensitization and pain behavior.[15,19,21,71–73] Neurons express tropomyosin receptor kinase B (TrkB), a receptor for brain-derived neurotrophic factor (BDNF), and the binding of BDNF to TrkB on second-order SDH neurons leads to a depolarizing reversal in anion gradient such that SDH neurons become excited upon stimulation by conventionally inhibitory GABA or glycine.[74–76] BDNF also disinhibits NMDA receptor (NMDAR) potentiation and facilitates action potential firing in SDH neurons.[77] While BDNF signaling via TrkB in SDH neurons is characterized, the source of BDNF is not clear. One potential source of BDNF is from de novo synthesis and release of microglia through activation via ATP-P2X4R signaling, but the detection of BDNF in spinal microglia is inconsistent and thus continues to spark debate.[57,78,79] Regardless of the source of BDNF, blocking of TrkB signaling might hold potential therapeutic promise. Two FDA-approved, selective Trk inhibitors are available for the treatment of solid tumors with Trk gene mutations, larotrectinib and entrectinib; however, they have yet to be studied for the treatment of pain.[80,81]

Microglia can also biosynthesize specialized pro-resolving mediators (SPM) that bind to specific SPM receptors expressed on DRG nociceptors and SDH neurons.[82] Direct stimulation of human vagal nerve is sufficient to enhance endogenous SPM production.[83] In fact, activation of SPM receptors on nociceptors can block capsaicin-induced EPSC and is a mechanism by which microglia can mediate analgesia at the central microglia-neuron interface.[84] Supplementation with marine lipids, which can be metabolized into pro-resolving mediators, may improve clinical quality of life and pain in adults with chronic pain.[85,86]

The Astrocyte–Neuron Interface

Astrocytes are the most abundant cell type in the CNS and comprise about 40–50% of all glial cells or 20–40% of the total number of CNS cells. Astrocytes tile the entire CNS in a non-overlapping, organized fashion. Each individual astrocyte has innumerous processes that contact multiple neurons and envelop over 100,000 synapses.[87] Astrocytes not only maintain the extracellular environment of CNS but also participate in synaptic activity; in fact, the interactions between neurons, microglia, astrocytes, and other glial cells are commonly viewed to form a quad- or even penta-partite synapse.[88–90] Networks of astrocytes form a functional syncytium through gap junctions that allows cytoplasmic continuity for exchange of small molecules and electrical coupling.[91] Connexin 43 (Cx43) is a specific gap junction protein, which forms the building blocks of these gap junctions. Each adjacent astrocyte contributes a hemichannel to form a full cell–cell channel. Each hemichannel, however, can also be unopposed and open directly to the extracellular space, which has implications for the astrocyte–neuron interface.

Given the abundance of astrocytes in the CNS, it is not surprising that astrocytes play important roles in preclinical models of pain.[9,10,92] Activated astrocytes exhibit increased expression of their prototypical glial fibrillary acidic protein (GFAP); and the extent of astrocyte activation correlates with observed pain behavior.[93–98] Inhibition of astrocytes using toxins attenuates pain hypersensitivity after injury, while intrathecal injection of TNFa-activated astrocytes or glial-restricted precursor-derived astrocytes in uninjured animals promotes mechanical hypersensitivity.[99–102] Elegantly, optogenetic stimulation of spinal astrocytes is sufficient to produce pain behavior in naïve, uninjured rats.[103]

Like microglia, clinical correlates of the astrocyte–neuron interface in chronic pain are not well established. In a postmortem analysis of matched human patients (1. Without HIV, 2. With HIV, but without chronic pain and 3. With HIV and with chronic pain), HIV-positive patients with chronic pain exhibited greater astrocyte activation in the SDH compared to HIV-positive patients without chronic pain. The expression levels of microglia markers were comparable between the three groups.[104] Advances in molecular imaging technology have heralded potential visualization strategies for astrocytes but have been studied primarily in other neurologic diseases and not necessarily for chronic pain.[105] The PET tracer targeting TSPO, as discussed previously, cannot distinguish between microglia and astrocytic activity, but the tracer ligand [11C]-L-deprenyl-D2 is generally accepted for the detection of astrocytes due to the selective expression of its monoamine oxidase B target.[42,106–108]

Neuron to Astrocyte Interactions

Different cell types likely interact with astrocytes and influence the transition to reactive astrogliosis, so it is difficult to distinguish the direct or indirect actions between the various CNS cell types and astrocytes. For example, TNFa signaling through TNFR is a major axis for astrocyte activation, and intrathecal injection of TNFa-activated astrocytes into the spinal cord is sufficient to induce pain behavior in the absence of any injury.[109] However, the source of TNFa in vivo is indistinguishable from astrocytes or microglia, though less likely from neurons.[68,100,109]

Neural activity is sufficient and required to induce astrocyte activation. Electrical stimulation of nerve fibers leads to increased intracellular calcium and GFAP levels in astrocytes, while pretreatment with local anesthetics prevented GFAP increase after inflammatory pain model.[110–112] Neural activation also releases neurotransmitters and other mediators that may interface with astrocytes. For example, glutamate is the predominant excitatory amino acid released by nociceptors, and glutamate-evoked membrane currents in astrocytes result in astrocyte activation through p38 mitogen-activated protein kinase (p38 MAPK) signaling.[113,114] ATP from synaptic terminals or as a result of nerve injury can also interface with astrocytes through many surface-expressed ionotropic and metabotropic purinergic receptor subtypes.[115] Intrathecal injection of ATP is sufficient to produce astrocyte activation and pain behavior even when microglia activation is inhibited by minocycline.[116] Similar to microglia, astrocytes also express DAMP-sensing TLR4 receptors and may contribute to inflammatory and neuropathic pain.[50,117]

An inducible C-X-C motif chemokine ligand 13 (CXCL13), otherwise not expressed in the healthy CNS, is upregulated in the ipsilateral SDH neurons after spinal nerve ligation model of neuropathic pain.[118] Interestingly, the expression of C-X-C chemokine receptor 5 (CXCR5), the sole receptor for CXCL13, is also significantly increased in spinal cord astrocytes after nerve injury. Inhibition or genetic deletion of CXCR5 results in less astrocyte GFAP signal after nerve injury and less mechanical hypersensitivity, while intrathecal injection of CXCL13 is sufficient to induce pain hypersensitivity and activation of astrocytes.[118] The CXCL13-CXCR5 axis also contributes to certain autoimmune diseases and cancers, and neutralizing antibodies to human CXCL13 are currently under development.[119]

It has long been recognized that the basic fibroblast growth factor (bFGF) induces mitosis, growth, differentiation and activation of astrocytes by binding to its cognate FGF receptors (FGFR1-4).[120,121] bFGF is expressed by astrocytes and DRG sensory neurons; and the level of expression further increases after nerve injury. Neutralizing bFGF reduces astrocyte activation and pain behaviors after nerve injury.[122–124] Drugs capable of trapping bFGF are being actively explored for treating endometrial carcinoma.[125]

Astrocyte to Neuron Interactions

Activation of astrocytes occurs through downstream activation of kinase and protease pathways including c-Jun N-terminal Kinase (JNK) and Extracellular-signal-Regulated Kinase (ERK).[126] Astrocyte activation leads to the expression of receptors and mediators to allow astrocytes to interface with neurons and other cells of the nervous system. In immuno-competent cells, activated astrocytes synthesize and release a shared repertoire of proinflammatory mediators (TNFa, IL1b, and IL6, PGE2) and alter the neuronal activity in widespread models of pain as previously described.[98,127–129] Astrocytes also upregulate matrix metalloprotease 2 (MMP2) to cleave pro-IL-1b into the active form, although this induction is delayed and contributes more to the maintenance of IL-1b levels.[67] Astrocytes also release unique mediators capable of altering neuronal activity. For example, D-serine is synthesized by activated astrocytes and is a potent co-agonist at NMDAR to facilitate long-term potentiation; intrathecal injection of D-serine is sufficient to induce pain behavior in uninjured animals.[130,131] In this section, we will further highlight some astrocyte-mediated neuronal interactions.

Extracellular facing Cx43 hemichannels are present on astrocytes and the opening of these hemichannels allows for the astrocytic release of ATP and glutamate, as well as the chemokines CXCL1 and CCL2.[132,133] The level and activity of Cx43 hemichannels on astrocytes increase following nerve injury or activation by TNFa.[132] Intracellular CXCL1 and CCL2 expressions also increase following astrocyte activation and provide a larger pool of chemokines primed for release.[132,134] CXCL1 binds its cognate receptor CXCR2 expressed on SDH neurons, and CXCL1-CXCR2 signaling induces increased spontaneous EPSC frequencies. CXCR2 antagonists suppress spontaneous EPSC and pain behavior after nerve injury in animal models.[132] Danirixin, a selective CXCR2 inhibitor, has already been studied clinically for chronic obstructive pulmonary disease (COPD) and could be of interest for investigation in chronic pain.[135] Similarly, drugs and gene therapies

against Cx43 also exist – in particular, one company has been testing a combination of FDA-approved amitriptyline and mefloquine, a potential Cx43 channel blocker, for neuropathic pain.[136,137] The Cx43 channel blocker, tonabersat, is utilized to target cortical spreading of depression observed in acute migraines.[137,138] On the other hand, CCL2 signals through the C-C motif chemokine receptor 2 (CCR2) expressed on DRG and spinal cord neurons whose levels increase after nerve injury.[139,140] Binding of CCL2 to CCR2 results in overall neuronal hyperexcitability via increased presynaptic glutamate release, enhancement of AMPA- and NMDA-associated glutamatergic synaptic transmission, and suppression of inhibitory synaptic transmission.[134,139,141] CCL2 neutralizing antibodies and antagonists or genetic knockout of CCR2 result in reduced pain behaviors after nerve injury and in HIV-associated neuropathy.[134,142–145] Of note, the CCL2-CCR2 signaling also exists between peripheral nerves, DRG neurons, and macrophages.[145]

Astrocytes contribute to extracellular glutamate homeostasis in the synaptic microenvironment by regulating the clearance of glutamate via glutamate transporter 1 (GLT1).[146] Nerve injury induces an initial increase then persistent decrease levels of GLT1. The decrease in GLT1 results in increased spinal extracellular glutamate and elicits mechanical and thermal hypersensitivity.[147–149] Inhibition of GLT1 is sufficient to induce spontaneous pain behavior without injury, while gene therapy introduction of GLT1 into the spinal cord attenuates inflammatory and neuropathic pain behaviors.[150,151] Riluzole, an FDA-approved medication for the treatment of amyotrophic lateral sclerosis, has positive regulatory activities against GLT1 and is capable of attenuating neuropathic pain in preclinical models of nerve injury.[147,152] Unfortunately, riluzole was unsuccessful in two separate randomized, cross-over, placebo-controlled trials of patients with peripheral neuropathy in pain or neuropathy outcomes.[153]

The T Lymphocyte–Neuron Interface

The adaptive immune system consists of B and T lymphocytes. A unique feature of the adaptive immune system is the expression of highly variable antigen recognition receptors generated from random genetic rearrangement during the lymphocyte maturation process. The highly variable repertoire of antigen receptors allows for recognition of specific antigen epitopes presented by antigen presenting cells. T cells can further be distinguished into subsets based on their functions. CD8+ T cells function as cytotoxic T cells, which can kill virus-infected and tumor cells, while CD4+ T cells, which help optimize the immune response, can be further subdivided into additional niches: T-helper cells (Th1 and Th17) produce proinflammatory cytokines, Th2 and regulatory T cells (Treg) produce anti-inflammatory cytokines and suppresses the activity of other immune cells. The dynamic functionality within the family of T cells may explain the conflicting observations regarding the role of T cells across different models of pain. In neuropathic pain models, T cells are mostly detrimental, and depletion or neutralization of T cells reduces pain behavior.[154–158] However, in models of chemotherapy-induced peripheral neuropathy (CIPN) and inflammatory pain, depletion of T cells either has no effect or actually worsened pain behavior, suggesting a potential protective or analgesic role.[159–163] In clinical studies, while the absolute number of circulating T cells between patients with and without neuropathic pain remains comparable, some studies report an imbalance between the subsets of CD4+ T cells in chronic pain patients.[164–166] Unfortunately, the relevance and meaning of this finding in peripheral circulating T cells to the maintenance or development of chronic pain remains unclear.

At baseline, T cells are seldomly found in the peripheral nerve, DRG, or spinal cord. The role of the T cell–neuron interface at the spinal cord level in the pathogenesis of chronic pain is unclear. Lymphocyte attractants are induced in the spinal cord after nerve injury, but there are conflicting reports as to whether T cells infiltrate into the spinal cord after peripheral nerve injury.[167] Some studies reported detectable CD4+ T cells, although the number remains low, while other studies did not find evidence to support T cell infiltration after nerve injury.[168,169] Additional confounders include localization of T cells in meningeal structures, including leptomeninges and perivascular spaces; while these are technically extra-parenchymal to the spinal cord, these T cells may still functionally participate in the neuroimmune interface as these areas are bathed by the cerebral spinal fluid.[170] The development of pain hypersensitivity does not correlate with T cell infiltration into the spinal cord since maximal pain behavior is observed before any detectable infiltration of T cells.[154,167,171,172] However, CD4+ T cells infiltrate the peripheral nerve and DRG late (7 days after injury) and persist (lasting beyond 40 days) after nerve injury and may contribute to maintenance or transition from acute to chronic pain.[155,157,169]

T cells contribute to sexual dimorphism observed in certain preclinical models of chronic pain. First published by Sorge et al, pharmacologic inhibition and depletion of microglia abolished pain behavior in only male rodents but had no effects in

females, which still exhibited pain hypersensitivity after nerve injury; this effect was dependent on testosterone. However, depletion of T cells renders female mice sensitive to glial inhibitors comparable to their male counterparts and this observation is reversed with adoptive transfer of T cells into T cell-deficient females.[158] Meningeal Tregs in females are capable of interacting with spinal cord microglia to suppress the microglia-dependent pathway for pain hypersensitivity.[173] Sexual dimorphism in pain is a fascinating area of research, and current preclinical studies span beyond T cell and microglia function and implicate other neuroimmune players, such as myeloid cells and even neurons themselves.[51,174]

Neuron and T Lymphocyte Interactions

T cells respond to neuronal outputs as they express receptors including ionotropic and metabotropic glutamate receptors, CGRP receptors, and neurokinin-1 (NK1) receptors.[175–177] Depending on the specific subtype of T cells (Th1, Th17), they can release IL-1b, interference gamma (IFNg), TNFa, and IL-17 that can increase neuronal excitability and promote neuroinflammation.[178,179] Infiltrating T cells in the DRG release leukocyte elastase (LE), a serine protease, which activates MMP9 to facilitate the cleavage of pro-IL-1b into the active IL-1b.[180] IFNg can directly bind AMPA receptors to increase postsynaptic calcium influx.[181–183] T cells can also serve as a source of BDNF – although studies of T cell-derived BDNF have been in the setting of neurodevelopment, whether this source of BDNF can mediate anion reverse potential in the setting of neuropathic pain in adults still needs to be addressed.[184] Conversely, other subsets of T cells such as Treg and Th2 cells reduce or resolve pain likely through secretion of anti-inflammatory cytokines (IL-4, IL-10, transforming growth factor beta (TGFb)), which most likely interact with glial and immune components. T cells can also produce endogenous opioids (enkephalins and b-endorphins) that act directly on neuronal opioid receptors to provide analgesia.[159,185] T-cell-derived opioids also exert anti-inflammatory effects by reducing proinflammatory CD4+ subtypes (Th1, Th17) and increasing anti-inflammatory CD4+ subtypes (Th2).[186,187] Modulating specific subsets of T cells not only have the potential to interrupt but also possibly reverse neuroinflammation.

Neuroimmune Interfaces Within the Peripheral Nervous System
The Satellite Glial Cell–Neuron Interface

Satellite glial cells (SGC) are derivatives of pluripotent neural crest cells and comprise the glial cells of the peripheral nervous system (along with Schwann cells).[188] Multiple SGC, connected by adhesive and gap junctions, wrap around the surface of typically one sensory neuron cell body and its proximal axon to form a functionally distinct neuron-glial unit. Each functional neuron-SGC unit is separated by connective tissues, but in 4–9% of DRG neurons, SGC share glial envelopments and connections with one or two other neurons. Distinct neuron-glial functional units are important to mention because nerve injury induces the formation of new intra- and inter-ganglion gap junctions that contribute to pain behavior.[189–191] SGCs are often compared to astrocytes of the CNS as they share molecular and functional similarities – expression of GFAP, maintenance of microenvironmental glutamate and potassium via glutamate aspartate transporter and inward rectifying potassium channels (Kir4.1), respectively, and electrical coupling between SGCs through adjoining gap junctions.[190] Although several different preclinical models of pain implicate SGC in the initiation and maintenance of pain, the specific role of SGC in humans is not well characterized.[192–196]

Neuron to SGC Interactions

The soma of sensory neurons in DRG releases excitatory mediators like glutamate, substance P, CGRP, CCL2, and ATP upon depolarization or injury.[197–201] Extracellular glutamate is carefully regulated by glutamate transporters expressed by SGC;[202] glutamate can also activate SGC by binding NMDAR expressed by SGC.[203] Substance P binds to NK1 on SGC and leads to downstream release of IL-1b.[204,205] CGRP released from the soma of sensory neurons binds to its cognate receptor on SGC, receptor activity modifying protein 1 (RAMP1), and mediates nitric oxide release to, in turn, sensitize neurons.[198] CGRP receptor-blocking antibodies (ie, erenumab) represent the successful stories in targeted drug developments for the treatment of chronic migraines.[206] CCL2 induced in DRG neurons upon stimulation or injury can activate SGC through CCR2 receptors.[140,200]

ATP plays a critical bidirectional role in neuron-SGC signaling because purinergic receptors are expressed on both neurons and SGC. Injury or stimulation elicits robust release of neuron-derived ATP, and the activation of P2Y
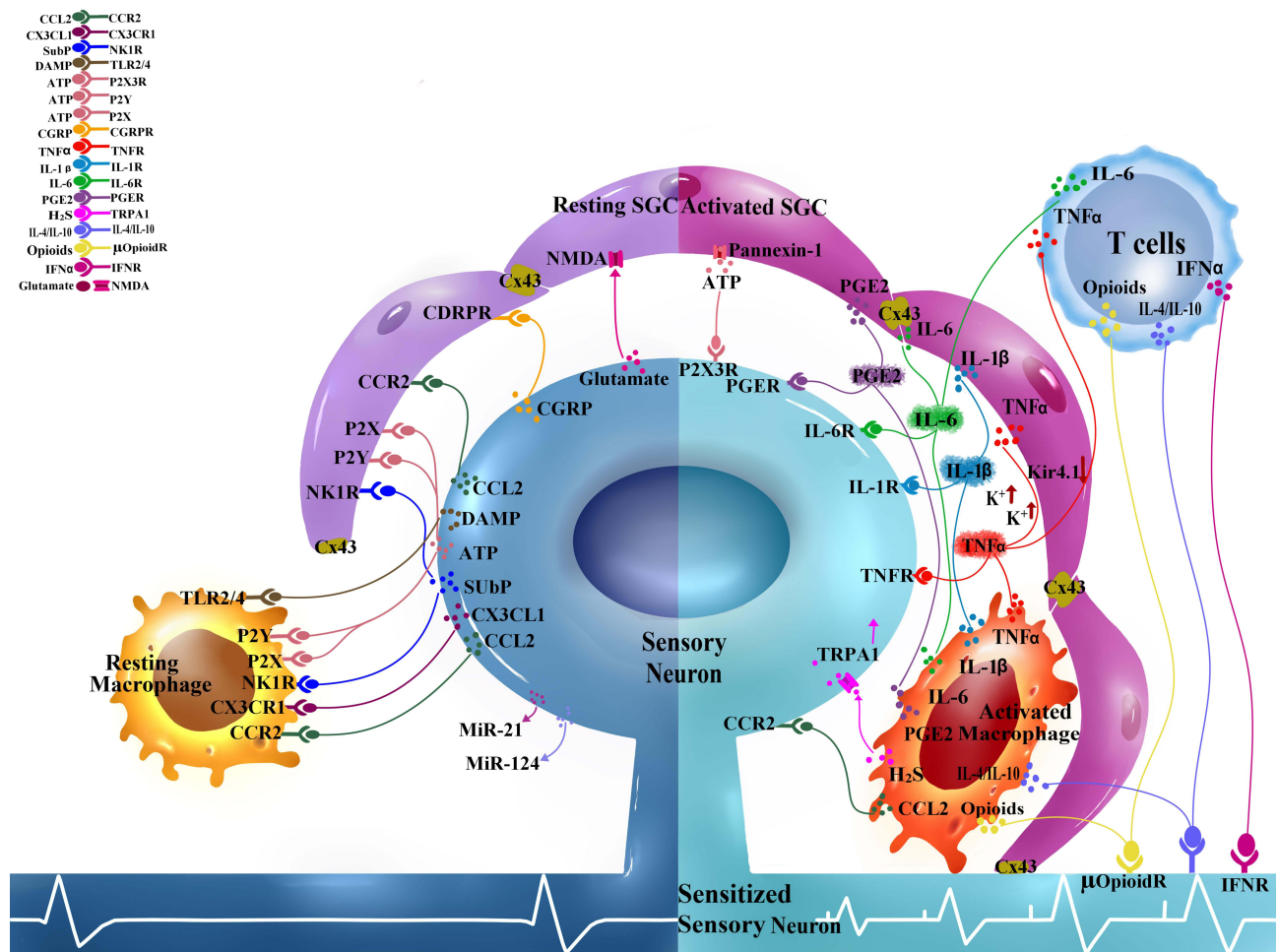
Figure 2 Interactions at the peripheral neuroimmune interface. Sensory neurons cell bodies and satellite glial cells (SGC) form tight neuron-glial units in the dorsal root ganglion (DRG). Soluble mediators are released from the sensory neuron soma and readily bind to receptors on SGC and also serve as chemoattractant for macrophages and T cells: Glutamate activate N-methyl-D-aspartic acid (NMDA) glutamatergic receptors, substance P (SP) binds to neurokinin 1 receptor (NK1R), C-C motif chemokine ligand 2 (CCL2) binds to C-C motif chemokine receptor 2 (CCR2), calcitonin gene-related peptide (CGRP) binds to CGRP receptors (CGRPR), adenosine triphosphate (ATP) binds to various purinoceptors (P2X, P2Y), damage associated molecular patterns (DAMPs) bind to toll-like receptors (TLR2, TLR4). Injured sensory neurons also release microRNAs (MiR-21 and miR-124 which can have pro-inflammatory and anti-inflammatory effects). Activated SGC, T cells, and macrophages in the DRG respond with shared and unique mediators that in turn bind to receptors on the DRG sensory neurons to affect neuronal excitability. Interleukin-1-beta (IL-1b) binds to IL-1 receptor (IL-1R), IL-6 binds to IL-6 receptor (IL-6R), prostaglandin E2 (PGE2) binds to PGE receptor (PGER), tumor necrosis factor alpha (TNFa) binds to TNF receptor (TNFR). Activated SGC increase Connexin-43 (Cx43) gap junctions between adjacent cells to allow for increased electrical coupling. Activated SGC also increase extracellular channels such as Pannexin-1, which allows for ATP release. Inward rectifying potassium channels (Kir4.1) are downregulated in activated SGC which results in increased extracellular potassium gradient and making neurons hyperexcitable. Activated macrophage produce hydrogen sulfide (H2S) that can activate neuronal transient receptor potential cation channel A1 (TRPA1). Infiltrating T cells depending on the subtype can contribute to pro-excitatory neuronal and is a source of interferon gamma (IFNg) which can bind to IFN receptor (IFNR). Subtypes of macrophage and T cells can contribute to anti-inflammation by releasing IL-4, IL-10, and opioids.

metabotropic receptors on SGC leads to alteration of the extracellular potassium gradient through potassium channels and ultimately increases downstream neuronal excitability.[201,207] Activation of SGC P2X purinoceptors (in particular, P2X7) can also lead to SGC TNFa release.[201] Additionally, P2X7 can inhibit neuron excitability via tonic inhibition of P2X3R expression on neurons (P2X3R promotes neuron excitability).[201,208,209] Despite the divergent effects of purinergic signaling in preclinical studies, there is a paucity of knowledge on the effects of purinergic signaling of SGCs in humans.

SGC to Neuron Interactions

SGC and neurons interact through secreted mediators, and given their proximity, through rapid ion channels and electrophysiologic signaling. SGCs are immunocompetent cells and release the common repertoire of proinflammatory mediators upon activation.[195,210–212] These mediators act not only on neurons but also on neighboring SGCs facilitating paracrine and autocrine positive feedback.[213–215] SGCs represent a source of ATP through vesicular- or channel-mediated

release. For example, activation of SGC P2X7 channel releases ATP from SGC, which in turn acts on purinergic receptors to exert inhibitory control of P2X3R on neurons.[208] SGCs upregulate ATP-permeable pannexin channels after injury, and mice with glial-specific knockout of pannexin channels do not develop pain after injury.[216–219]

The local extracellular potassium concentration is regulated by Kir4.1 on SGC.[190] After injury, Kir4.1 expression on SGC decreases, which increases the extracellular potassium rendering neurons more excitable. Accordingly, silencing Kir4.1 in rat trigeminal ganglion alone is sufficient to induce spontaneous facial pain behavior.[220] In naïve animals, SGC couples with adjacent SGC to surround a single DRG neuron via gap junctions (prominently via Cx43, similar to astrocytes). After injury, there is enhanced cell–cell coupling through gap junctions expanding beyond SGCs and neurons of a neuron-glia functional unit to include coupling between adjacent units, to allow for vast propagation of calcium waves.[221–227] Blocking gap junctions prevents the cell–cell coupling and reduces the severity of pain behavior in nerve injury, CIPN, and inflammatory pain models.[192,221,225] Blockers of gap junctions such as those specific to Cx43 are clinically evaluated and have been discussed previously.

The Macrophage-Sensory Neuron Interface

Tissue-resident and infiltrating macrophages are two types of macrophages found in healthy or inflamed tissues.[228] Tissue-resident macrophages integrate into various tissue subtypes during development and co-exist in a homeostatic state in adulthood. Infiltrating macrophages derive from monocytes that originate from the hematopoietic stem cells of the bone marrow and migrate into tissues in response to injury or infection. Infiltrating macrophages can be found in peripheral tissue at the site of injury in inflammatory pain or in the peripheral nerves and DRG in case of neuropathic pain (ie, nerve injury, CIPN, diabetic neuropathy). Both subtypes of macrophages contribute to the regulation of pain.[229,230] Macrophages derived from either tissue-resident or infiltrating macrophages can be polarized into pro-inflammatory (M1) or anti-inflammatory (M2) mature macrophages depending on the local milieu.[231]

The best clinical evidence supporting the role of macrophage in chronic pain is in osteoarthritis and rheumatoid arthritis.[232–234] Rheumatoid arthritis patients exhibit increased macrophage numbers in the inflamed synovial membrane, and the radiologic progression of joint destruction correlates with the extent of macrophage infiltration. In fact, macrophage levels serve as a direct biomarker for the responsiveness to disease-modifying antirheumatic drug therapy.[234,235] Similarly, synovial macrophages play a role in the onset and progression of osteoarthritis, with a direct correlation between synovial macrophage infiltration and clinical osteoarthritis pain severity.[236,237] Many of the clinical anti-inflammatory therapies will be discussed in subsequent sections.

The development of CIPN from specific chemotherapeutics also appears to be dependent on the macrophage–neuron interface, particularly paclitaxel. Infiltrating macrophages are found along the nerve as well as in the DRG after treatment with paclitaxel. Paclitaxel directly stimulates macrophages to release HMGB1 to sensitize neurons.[238,239] Clinical support for this pathway comes from a randomized, Phase II clinical trial of recombinant human thrombomodulin. Thrombomodulin degrades HMGB1 and is approved in Japan for the treatment of disseminated intravascular coagulation.[240] Patients with colon cancer undergoing chemotherapy that receive thrombomodulin are less likely to develop severe sensory neuropathy.[241]

Neuron to Macrophage Interactions

Sensory neurons can regulate macrophage states. The release of neuronal ATP attracts infiltrating macrophages (into the DRG for example) and activates P2X and P2Y receptors on macrophages.[219] Activation of macrophage P2X4 receptors induces the release of IL-1b and PGE_2.[242,243] Meanwhile, activation of P2Y7 on macrophage leads to a further wave of IL-1b through inflammasome activation.[244] Substance P released by sensory neurons stimulates macrophages NK-1 receptors and leads to macrophage release of IL-1b, TNFa and CCL2.[245,246] Similarly, the release of CCL2 and CX3CL1 from injured sensory neurons can also activate macrophages through CCR2 and CX3CR1.[247,248]

Non-coding micro-RNAs in exosomes are another interesting form of communication between injured sensory neurons and macrophages: MiR-21 enhances pain by promoting M1 macrophage polarization, while miR-124 reduces pain by promoting M2 macrophage polarization.[249] Even more surprisingly, macrophages can even transfer mitochondria to sensory neurons; this transfer is hypothesized to help with resolution of oxidative stress in sensory neurons during the resolution phase of inflammation.[250]

Macrophage to Sensory Neuron Interactions

Most of the mediators secreted by macrophages, especially by the M1 subtype, are pro-inflammatory. As mentioned above, IL-1b, IL-6, PGE$_2$, TNFa and CCL2 released by macrophages can stimulate specific cognate receptors on nociceptive neurons contributing to the development of neuropathic pain.[213,251–254] Activated macrophages secrete HMGB1, which binds to TLR4 receptors on sensory neurons to play a role in the pathogenesis of neuropathic pain in animal models.[46,239,240] Hydrogen sulfide (H$_2$S) is generated in activated macrophages and contributes to neuronal hyperexcitation by upregulating and activating neuronal calcium channels (transient receptor potential cation channel A1; TRPA1).[255–257] Macrophages also secrete anti-inflammatory mediators. More specifically, M1 macrophages can secrete endogenous opioids by IL-4 signaling to downregulate the excitability of neurons;[258] meanwhile, M2 macrophages can secrete IL-10 to reverse TNFa-induced upregulation of sodium channels in DRG neurons and alleviate pain behavior.[259]

Clinical Pain Therapies Targeting the Neuroimmune Interface

In the subsequent sections, we will explore current clinical therapies in pain management and how they mediate analgesia by potentially targeting the neuroimmune interface.

Anti-Inflammatory Mediators and the Neuroimmune Interface

Certain therapeutics targeting specific pro-inflammatory signaling pathways are clinically successful in the management of inflammatory pain, especially in rheumatoid arthritis (RA) or low back pain due to ankylosing spondylitis.[260,261] Modulators of the IL-1b/IL-1R signaling include anakinra (a monoclonal IL-1 receptor antagonist), riloncept (IL-1 soluble decoy receptor), and canakinumab (anti-IL-1b monoclonal antibody). All three IL-1b inhibitors are well tolerated and effective in patients with RA, gouty arthritis, ankylosing spondylitis, systemic juvenile idiopathic arthritis, and other auto-inflammatory diseases that involve deregulation of IL-1b.[260–266] In a systematic review and meta-analysis of six clinical trials, RA patients treated with anakinra are 42% more likely to have clinical benefits compared to placebo; reduction in clinical markers of inflammation and slowed radiographic evidence of joint damage are also observed in anakinra-treated patients.[267–269] In another clinical application, a small pilot trial of a single intraarticular injection of anakinra for acute anterior cruciate ligament knee injury provided a reduction in knee pain and improvement in function over a 2-week interval.[270] On the horizon is the promising potential of IL-1 antagonists for treating neuropathic pain. CRPS can be modelled by injecting serum immunoglobulin G from patients with CRPS into mice with hind-paw injuries. Treatment with anakinra prevents the transferred CRPS pain behavior and blocks microglia and astrocyte activation in this translational CRPS mouse model.[271]

Like IL-1R antagonist, antagonists of TNFa, including etanercept (soluble TNFa decoy receptor), adalimumab and infliximab (both monoclonal TNFa antibodies), are used clinically to alleviate pain and symptoms of RA, psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel diseases.[272–277] The combination of TNFa antagonists with methotrexate is the most potent therapy against RA.[279–280] TNFa antagonists are also beneficial for the treatment in disc-related pain including radicular and axial back/neck pain. The mechanism is thought to arise partly from the penetration of anti-TNFα into the cerebrospinal fluid and selective delivery to spinal structures, although evidence to support this is weak and the benefits are not seen in all clinical studies; thus, anti-TNFa therapy is not widely adopted in regular pain practice.[281–284]

IL-6 is another dysregulated proinflammatory cytokine described in chronic pain conditions as well as inflammatory diseases.[285–289] Tocilizumab, sarilumab, and satralizumab are currently available monoclonal IL-6 receptor inhibiting antibodies; and siltuximab is an IL-6 sequestering antibody. IL-6 antagonists are effective clinically and offer another FDA-approved biologic therapeutic option for the treatment of RA.[290–292] Current research into additional applications of IL-6 antagonists includes the context of lower back pain. In a few small clinical studies of lower back pain, systemic and local application of tocilizumab was effective in reducing pain and disability; in fact, the results suggest that tocilizumab is more effective than the current practice of steroid injections.[293–295]

The clinical benefit of CGRP antagonists in the preventative treatment of migraine headaches is a model example of drug development born out of preclinical research.[206] CGRP dysregulation in the trigeminal system is implicated in the pathophysiology of migraine. Injection of CGRP into migraine patients precipitates headaches.[296] This ultimately led to the development of erenumab, an inhibitory monoclonal antibody against the CGRP receptor – approved by the FDA for

the preventative treatment of migraines.[297–300] Current clinical studies are underway to study the effect of CGRP antagonists on other pain conditions, such as trigeminal neuralgia and fibromyalgia.[301–303]

Unfortunately, not all drugs targeting neuroimmune signaling translate successfully into clinical practice. A double-blind, randomized, multicenter study of CCR2 antagonist (AZD2423) demonstrated no clinical benefit over placebo in the treatment of posttraumatic neuralgia.[304] A TLR4-blocking antibody, NI-0101, was unsuccessful in improving clinical outcomes in RA despite inhibiting in vivo LPS-induced cytokine release in healthy volunteers.[305] Antagonist of the P2X7 purinergic receptor (AZD9056) was also ineffective for the treatment of RA-associated joint pain.[306] However, the effects of these drugs on other pain conditions have yet to be explored, and many more available drugs targeting the neuroimmune interface in the context of inflammatory, immune, and cancer disorders have yet to be explored in the context of pain too.

Glial Inhibitors/Modulations and the Neuroimmune Interface

Several drugs capable of inhibiting glial action in preclinical studies have not been effective clinically. Minocycline is a semi-synthetic tetracycline, which has been used as an antibiotic for more than 30 years. Minocycline has properties beyond its antibiotic activity, including being anti-inflammatory, anti-apoptotic, anti-angiogenic[307,308] – and most relevantly, able to inhibit microglial activation.[309] Several preclinical studies supported minocycline's benefits in attenuating pain behavior in several neuropathic pain models.[16,310,311] However, the clinical evidence for minocycline is weak and mixed. Several clinical studies across various pain settings suggested minocycline either did not provide clinically meaningful benefits to pain or actually increased the duration of pain in certain patient populations.[312–314] In one small randomized control study with 25 subjects with type 2 diabetes randomized to receive minocycline, the minocycline group recorded improvement in peripheral and autonomic neuropathy outcomes.[315] The discrepancy between preclinical and clinical results may be due in part to the small sample sizes of the clinical studies, the assumption that microglial activation is the predominant driver of pathogenesis in the various clinical pain settings, and minocycline likely has non-microglia targets.[316] Propentofylline suffered a similar fate to minocycline. Propentofylline is a nonspecific microglia and astrocyte glial inhibitor with promising preclinical results in preventing and reversing neuropathic pain, but it was not effective when administered to patients with post-herpetic neuralgia in a randomized clinical trial.[317–319] Ibudilast is a non-selective cyclic nucleotide phosphodiesterase (PDE) inhibitor used as a bronchodilator for asthma but is reported to have glial inhibitory effects via stimulating IL-10 release from activated microglia and suppressing production of TNFa, IL-1β, IL-6.[320] While ibudilast is not effective in clinical studies of chronic migraines, diabetic neuropathy or CRPS, there may be promise in its use for the treatment of substance use (stimulant, alcohol, and opioid) disorders.[321–326]

Steroids and Neuro-Immune Interface

Injection of steroids into or around pain generators is one of the keystones of interventional pain management.[327–329] Epidural glucocorticoid injection, for example, is one of the most commonly performed interventional pain procedures for the treatment of chronic spinal pain, with over 2.2 million lumbar epidural glucocorticoid injections performed each year in the Medicare population alone.[330–332] Epidural steroids are effective in reducing pain severity, decreasing opioid use, improving function, avoiding the need for surgery, and even treating pain in patients who have not responded to surgical intervention.[329,333–337] Steroids may exert anti-inflammatory effects on the neuroimmune interface. Consistently with preclinical models, steroid administration (local, intrathecal, or systemic administration) before or at the time of injury reduces proinflammatory cytokines, neuronal firing rates, glial cell activation in the spinal cord, and correlates with a reduction in pain behavior after nerve injury.[338–340] It is interesting to point out that, although steroids reduce proinflammatory cytokines after injury, anti-inflammatory cytokine such as IL-4 and IL-10, which also decrease after injury, are not affected by steroids – supporting a steroid-independent anti-inflammatory process.[339]

However, there are mixed results regarding the ability of steroids to reverse established pain behavior in animal models.[338–340] Similarly, clinical evidence supporting the use of epidural steroids for spinal pain is also not always positive.[331,341] Steroids used in clinical practice (dexamethasone, triamcinolone, methylprednisolone, betamethasone) can activate pro-inflammatory mineralocorticoid receptors found in DRG sensory neurons.[342–344] Co-administration of mineralocorticoid receptor antagonist with dexamethasone is more effective in reducing SGC activation in the DRG, evoked and spontaneous pain behaviors than dexamethasone alone in rodent models of lower back pain.[342,343,345] It is

interesting to wonder if the propensity to activate different steroid receptors may account for why steroids are sometimes ineffective or wane in efficacy over time in clinical practice. Ultimately, this could be a promising area of future clinical research as mineralocorticoid receptor antagonists (spironolactone, eplerenone) are widely used in the clinical treatment of hypertension and heart failure.

Neuromodulation and the Neuro-Immune Interface

Neuromodulation is a growing field within pain medicine, which treats chronic pain by using electrical stimulus.[346] The types of interventions range from peripheral nerve stimulation, dorsal root ganglion stimulation, spinal cord stimulation (SCS), to brain stimulation. The role of non-neuronal activity including glial cells builds to our understanding of the mechanism of neuromodulation.

The most prevalent therapy in neuromodulation, SCS, may exert benefits in part by modulating the neuroimmune interface, and is an effective treatment for many neuropathic pain conditions, such as post-laminectomy pain syndrome, complex regional pain syndrome, and diabetic neuropathy.[347–353] Rodent models of SCS after various nerve injury models demonstrate reductions in pain behavior with SCS treatment, which correlates with reduced glial activation markers and transcriptomic changes in genes implicated in neuroinflammation and immune response.[318,353–356] One example of bench-to-bedside translation is a novel SCS waveform designed based on preclinical experiments to engage the transcriptomic signatures of neuronal and glial populations, and the stimulation parameters are designed such that the resulting transcriptomic signatures mimic those of the naïve uninjured profiles.[357–359] In a multicenter clinical trial, this novel SCS waveform was able to achieve 80% responder rate in patients with chronic back pain compared to 50% using conventional waveform.[360]

Another promising avenue for neuromodulation is vagal nerve stimulation. Vagal nerve stimulation has historically been used in the treatment of refractory epilepsy and the treatment of resistant depression.[361] The vagal nerve is appreciated as a critical component of an inflammatory reflex in which the vagal nerve signaling suppresses excessive cytokine release and inflammation.[362,363] Indeed, epilepsy patients with vagal nerve stimulators have lowered peripheral levels of TNFa, IL-1b, and IL-6.[364] A more accessible, noninvasive transcutaneous vagal nerve stimulator is available for the management of acute migraine; this non-invasive device is also capable of decreasing peripheral proinflammatory cytokines.[365,366] Since then, vagal nerve stimulation is being adapted to other inflammatory/autoimmune diseases with success, such as rheumatoid arthritis, Crohn's disease, and COVID-19.[364,367–369]

Regenerative Medicine and the Neuro-Immune Interface

Regenerative medicine is also another frontier of pain medicine. The initial concept was to bolster the body's own regenerative capacity to address degenerative pain conditions. This topic was eloquently reviewed recently.[370] Clinical data examining physical function and pain severity support the use of blood- and cell-derived pain therapies (such as platelet-rich plasma, autologous conditioned serum, mesenchymal stromal cells) in osteoarthritis of knees and hips, tendinopathy, and degenerative spine disease. Although there is some evidence to support tissue regeneration, the results are not consistent.[371–374] The current evidence emphasizes a paradigm shift suggesting that the analgesic effects of regenerative medicine may be largely due to immunomodulatory effects (by providing SPM, IL-4, IL-10, TGFb) and less so from tissue regeneration.[375–378]

Conclusions

Neurons interact with immune and nonimmune cells through classic immune mediators – this bidirectional neuroimmune interface spans the entire nociceptive circuitry from the peripheral tissue to the CNS. Ultimately, neurons change their firing property and manifests on an organism level as pain behavior. In this review, we highlighted how interfaces of the CNS (microglia, astrocytes, T lymphocytes) and PNS (SGC, macrophages) influence pain. Yet, many other neuroimmune interfaces exist and affect pain that are beyond the scope of our review (such as oligodendrocytes, Schwann cells, endothelial cells, cancer cells, gut microbiome).[9] A recurring theme is the paucity of clinical evidence to support neuroimmune interaction in humans despite mounting evidence of the involvement of the neuroimmune interface at a micro- and macrocosm level in preclinical models of chronic pain. Criticism of failed therapeutic trials highlights the assumption that neuroimmune dysfunction drives chronic pain in humans. Future efforts must bridge the gap to safely and non-invasively

study pathogenesis of chronic pain in patients. On the positive side, targeted small molecules and antibodies already exist for many ligand–receptor interactions developed mainly in the context of autoimmune diseases and cancers.[379–382] There are significant parallels between the neuroimmune interactions in chronic pain and autoimmune diseases and cancers. The opportunity to pivot preexisting targeted therapeutics to clinical studies of pain remains wide open.

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