

Review Article

How Do Satellite Glial Cells Control Chronic Pain?

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ABSTRACT

Aim of review: Pain afflicts more than 1.5 billion people worldwide, with hundreds of millions suffering from unrelieved chronic pain. Accumulating evidence suggests that satellite glial cells (SGCs) play active roles in the pathogenesis of pain. We review how SGCs interact with nociceptive neurons by secreting neuroactive signaling molecules that modulate pain, which may offer new therapeutic strategies for the prevention and treatment of chronic pain.

Methods: According to the available literature, we first described the morphology and physiology of SGCs in sensory ganglia and then provided an overview of the signaling molecules by which SGCs contribute to the modulation of the neuronal activity in various animal models of acute and chronic pain. Finally, we addressed some outstanding questions about SGCs that remain to be answered in future research and clinical applications.

Recent findings: Accumulating evidence has implicated structural and biochemical changes in SGCs in chronic pain: gliosis (i.e. proliferation), increase in expression of glial fibrillary acidic protein (a marker for their activation), modulation of glutamate transporters and ion channels, increases in purinergic and cytokine signaling, as well as aberrant connectivity between neighboring SGCs and sensory neurons. These changes alter the activity of sensory neurons and contribute to the development and maintenance of chronic pain. Remarkably, SGCs also participate in acute pain, and acute opioid treatment activates SGCs to mask opioid analgesia.

Summary: SGCs are now recognized players in the pathogenesis of chronic pain through the secretion of neuroactive signaling molecules and controls of nociceptive neurons. Given the inadequate treatment of chronic pain by the current “neurocentric” drugs, these recently recognized roles of SGCs and their neuroactive signaling molecules are exciting as they predict novel approaches for effective control of chronic pain. (Funded by the National Institutes of Health/National Institute of Neurological Disorders and Stroke (NIH/NINDS), and the University of Cincinnati.)

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Pain is an important, evolutionarily conserved physiological phenomenon that is necessary for survival. At the same time, pain is one of the most frequent symptoms of a variety of pathological disorders and its chronification represents a major clinical challenge. Chronic pain is a rising health concern worldwide, affecting up to 30% of adults (1). Chronic pain typically includes inflammatory pain after tissue injury, cancer pain, and neuropathic pain after nerve injury as a result of diabetic neuropathy, viral infection, or major surgeries. Furthermore, therapeutic treatments such as chemotherapy and opioids can also cause chronic pain.

Chronic pain is a pathology by itself, resulting from the maladaptive plasticity of both neurons and glial cells in the peripheral nervous system (PNS) and central nervous system (CNS) (2-4). While both neurons and glial cells contribute to chronic pain, current treatments mostly aim to alleviate neuronal activities, and are often palliative and associated with CNS-related undesirable side effects (5). For instance, opioids produce a brief pain relief via blockade of neurotransmission, but also tolerance and deadly addiction that have limited their clinical use in chronic pain (6).

In the past decades, great progress has been made to demonstrate and understand the critical roles of glial cells in the pathogenesis of chronic pain (4, 7, 8). Different types of glial cells influence chronic pain including astrocytes, microglia, Schwann cells and satellite glial cells (SGCs). In this review we focus on SGCs that surround the somata of neurons in the sensory ganglia and are directly coupled to each other via gap junctions (9-13), participating in the peripheral sensitization of nociceptive neurons (i.e. nociceptors) by reduction in the threshold and an increase in the magnitude of a response to noxious stimulation. Given that peripheral sensitization in nociceptors is essential for the transition from acute to chronic pain (14,15) and many SGC neuroactive signaling molecules are potentially “druggable”, targeting SGCs and their signaling molecules holds great promise for the development of new therapeutics to control chronic pain.

Satellite Glial Cells and Pain

The German pathologist Virchow designated the

term glial cells in the 1850s, because he considered these cells to serve in the nervous system as a kind of glue (glia means glue in Greek). However, glial cells are much more than just a glue between neurons and several types of glial cells have now been identified and characterized by different morphologies and functions. There are five main types of glial cells: oligodendrocytes, microglia, and astrocytes in the CNS, and Schwann cells and SGCs in the PNS (Figure 1). Oligodendrocytes in the CNS and Schwann cells in the PNS produce myelin to ensheath neuronal axons. Microglia are the resident macrophage-like cells of the CNS. Astrocytes contact neurons and synapses in the CNS to support and nourish neurons, and regulate synaptic transmission. Extensive studies have shown the active contribution of microglia and astrocytes to chronic pain in the CNS (4, 8, 16). However, glial cells are directly involved in chronic pain not only in the CNS, but also in the periphery. In particular, SGCs enwrap the somata of neurons located in the sensory ganglia constituting distinct morphological and functional units (13). In the past few years, SGCs have emerged as crucial players in the development and maintenance of chronic pain through the release of neuroactive signaling molecules and participating in the peripheral sensitization of nociceptors (9-13).

SGCs are glial cells in the PNS that surround and support the neurons not only in sensory, but also in sympathetic and parasympathetic ganglia (13). SGCs have mostly been studied in sensory ganglia, within which multiple SGCs completely envelop the cell bodies of the primary sensory neurons, including nociceptors that are responsible for the decoding and transmission of pain (17). SGCs have often been compared to astrocytes because they share similar features. Similar to astrocytes, SGCs tightly control the physiological functions and communication among neurons (18-21). They react to and clear neurotransmitters, and express common molecular and cellular markers such as glutamine synthetase (GS) and glial fibrillary acidic protein (GFAP) (4). However, SGCs and astrocytes greatly diverge in their morphology and interactions with neurons. Astrocytes have stellate forms with complex branches that contact multiple neuronal somata, axons and dendrites (22). In contrast, ultrastruc-

ture studies have shown that SGCs consist in flat envelopes surrounding one neuronal soma creating an extracellular space between glial and neuronal surfaces of only 15-20 nm (23), suggesting an extensive and active exchange of chemicals between the two cell types.

SGCs are important for the maintenance of neuronal homeostasis through their control of the ionic and molecular environment around the sensory neurons. For instance, SGCs control the extracellular potassium levels around these neurons by their unique expression of the inwardly rectifying potassium channel Kir4.1. Consistently, knockdown of this channel in SGCs by RNA interference (RNAi) has resulted in pain-like in naïve animals (24, 25). Kir4.1 expression levels and mediated-currents are significantly decreased in SGCs following tissue and nerve injury (24, 26).

Indeed, tissue and nerve injury can lead to the activation of SGCs. Although glial activation is a very popular and powerful concept for understanding the pathological mechanisms of chronic pain, the term “activation” is still poorly defined and should be used carefully (4). Activation of SGCs is commonly characterized by their proliferation and a significant increase in expression levels of GFAP (4, 9, 10). In contrast to astrocytes, SGCs express low levels of GFAP that are below the detectability of immunocytochemistry in normal conditions, but are drastically increased in pathological pain conditions. Increased GFAP expression levels in SGCs have been found in various chronic pain conditions or as a consequence of a therapeutic treatment, such as after peripheral nerve injury, inflammation, chemotherapy and opioid treatment (18, 27-30) (Table 1). The functional role of this increase is still unclear. Although intrathecal injection of small interfering RNA targeting GFAP expression in astrocytes and SGCs has been shown to alleviate pain behaviors after peripheral nerve injury (31), the molecular contribution of GFAP to chronic pain is unclear. Because GFAP acts to anchor the glutamate transporter GLAST (encoded by the SLC1A3 gene) at the plasma membrane of astrocytes (32), the regulation of GFAP may be involved in the control of the extracellular concentration of glutamate and neuronal activity in chronic pain conditions.

Table 1: Activation of SGCs, as Examined by Up-regulation of GFAP.

Pain conditions	References
Nerve injury	(54,60,68,94–109)
Spinal cord injury	(110)
Paw incision	(111)
Inflammation	(57,75,112–116)
Joint inflammation	(9,117)
Cancer pain	(118,119)
Chemotherapy	(27,56,120–126)
Diabetes	(127–129)
Viral infection	(25,130)
Acute opioid	(30)

SGC, satellite glial cell; GFAP, glial fibrillary acidic protein.

The activation of SGCs is not only associated with the regulation of neurotransmitters, but also cytokines, ion buffering, purinergic signaling, and gap junctions. Far from being exhaustive, here is a selected account of the main and current knowledge of these neuroactive signaling molecules, and their fundamental contributions to the development and maintenance of chronic pain in various animal models.

Satellite Glial Cells and Neuroactive Signaling Molecules

Peripheral sensitization in nociceptors is essential for the transition from acute to chronic pain (14, 15). Peripheral sensory neurons are pseudo-bipolar with terminals located in the PNS and in the superficial dorsal horn of the spinal cord for somatic neurons and in the spinal nucleus of the trigeminal for those innervating the face. This structure allows them to interact with multiple neurons, glial and immune cells to direct pain and immune responses (16). We choose here to focus on nociceptors because reducing their sensitivity or blocking their input to the CNS can attenuate or relieve the complex sensory and emotional consequences not only of acute pain, but also for many types of chronic pain (14). It is now established that peripheral sensitization of nociceptors is controlled by SGCs and the regulation of neuroactive signaling molecules, such as neurotransmitters, purinergic receptors, gap junctions, potassium

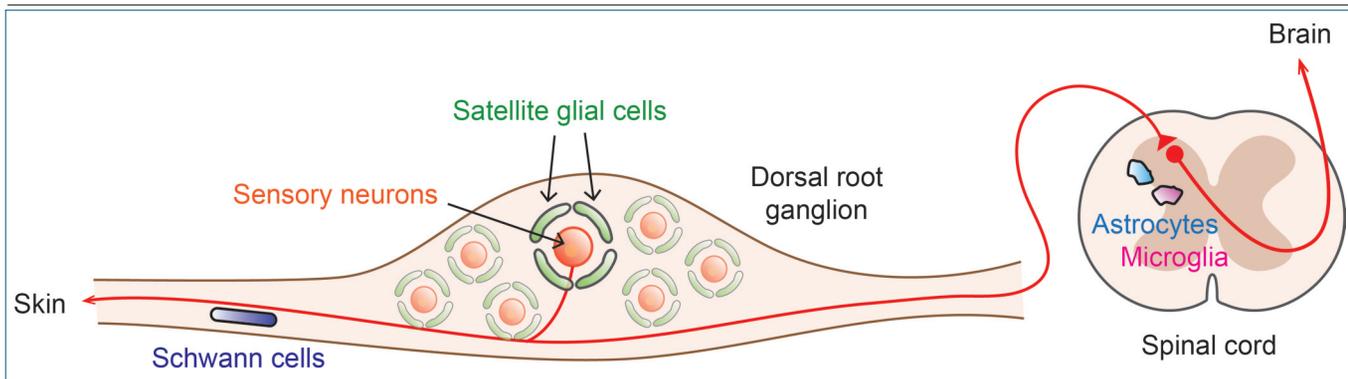


Figure 1. A Schematic Diagram Showing the Relationship Between Sensory Neurons and Glial Cells.

Noxious, mechanical, thermal and chemical stimuli are detected by sensory neurons and transmitted into the spinal cord and ultimately to the brain where the different stimuli are ultimately decoded. However, neurons are not alone in the nervous system and are surrounded by glial cells such as Schwann cells and Satellite glial cells in the peripheral nervous system and microglia and astrocytes in the central nervous system that play an important role in various chronic pain conditions.

channels, and cytokines (Figure 2).

Regulation of Neurotransmitters

Several neuromediators such as substance P, calcitonin gene-related peptide (CGRP), endothelin-1, gamma-aminobutyric acid (GABA) and glutamate have been shown to be released by the cell body of sensory neurons (33-38). These mediators can activate SGCs, and can be produced by SGCs. In astrocytes, the glutamate transporters GLAST and the glial glutamate transporter GLT-1 are responsible for the uptake of the glutamate released by neurons into the synaptic cleft (4). Glutamate is then converted into glutamine by GS and released by astrocytes to be reused by CNS neurons. Vesicular release of glutamate occurs in the neuronal somata of DRGs (36) and intraganglionic injection of glutamate evokes neuronal discharge and facial pain (39). Similarly to astrocytes, SGCs express GLAST, GLT-1, and GS to regulate the concentration and recycling of glutamate in sensory ganglia, as well as pain (40-42). Knockdown of GLAST and GLT-1 by RNAi was found to produce nociceptive behaviors to inflammatory and tactile stimuli (42, 43). Are these receptors in SGCs decreased in chronic pain conditions? SGCs also express the GABA-A receptor (44). Although it is not entirely clear, activation of GABA-A receptor tends to

depolarize astrocytes and can activate voltage-gated Ca^{2+} channels (45, 46). Given the recent findings of a major role of local GABAergic signaling within sensory ganglia that controls the peripheral nociceptive transmission (33), it is of interest to determine the role of GABA-A receptor and signaling in SGCs and their contribution to chronic pain.

Regulation of Purinergic Signaling

In addition to glutamate and GABA, there is compelling evidence for major releases of adenosine-5'-triphosphate (ATP) in sympathetic and sensory ganglia in chronic pain conditions (47). ATP activates both ionotropic purinergic P2X receptor channels and G-protein coupled metabotropic P2Y receptors. P2X2, 4, 5, and 7 receptors, as well as P2Y1, 2, 4, 5, 12, 13, and 14, have been found in SGCs (10, 48).

The P2X7 receptor is uniquely expressed in SGCs in DRGs and accordingly P2X7 agonist, BzATP, induced a large calcium response in SGCs and no or rather small calcium response in neurons (49). Following activation of P2X7 receptor, SGCs release a significant amount of the ATP in the DRGs. The functional role of the activation of P2X7 receptor and ATP release by SGCs is still unclear. It has been suggested that this ATP release can stimulate neuronal P2Y1 re-

ceptor and inhibit the activity of P2X3 receptor mediating the nociceptive signaling in sensory neurons (34). However, it was also demonstrated that activation of P2X7 receptors by ATP can result in the release of tumor necrosis factor- α (TNF α) from SGCs (49). TNF α in turn potentiates the P2X3 receptor-mediated responses and increases the excitability of sensory neurons and leads to chronic pain (49, 50). These dual anti- and pro-nociceptive actions of P2X7 receptors warrant more studies, but the observation that tissue and nerve injury fail to produce enhanced pain behaviors in P2X7 knockout mice suggests an important role of this receptor in the development of chronic pain (51). Consistent with this suggestion, the same study demonstrated that the expression levels of P2X7 receptor are significantly elevated in human SGCs after nerve injury.

More recently, P2Y receptors have been involved in the regulation of chronic pain by SGCs. CGRP release by the somata of sensory neurons activates P2Y receptors in SGCs resulting in an increase in the release of cytokines (35). Activation of P2Y4 receptor elicits calcium responses in SGCs and release of ATP, which is believed to change the extracellular concentration of potassium (K^+) in sensory ganglia and the excitability of the sensory neurons (52). Interestingly, P2Y12 expression levels are increased in SGCs following an animal model of trigeminal nerve crush, and a selective antagonist of P2Y12 receptors has demonstrated a significant reduction of SGC activation and pain behaviors in this animal model of neuropathic pain (53). For more details about purinergic signaling in SGCs, please read the more extensive reviews of Huang et al. and Magni et al. (10, 11).

Regulation of Gap Junctions

In physiological conditions, SGCs wrapping one neuron form a single unit with limited communications among different neighboring units (13). However, communications among SGCs belonging to different units are significantly increased in inflammatory and neuropathic pain conditions (12, 18). After tissue and nerve injury, SGCs contacted neighboring SGCs surrounding other neurons through the formation of new gap junctions (13, 23). This coupling among SGCs

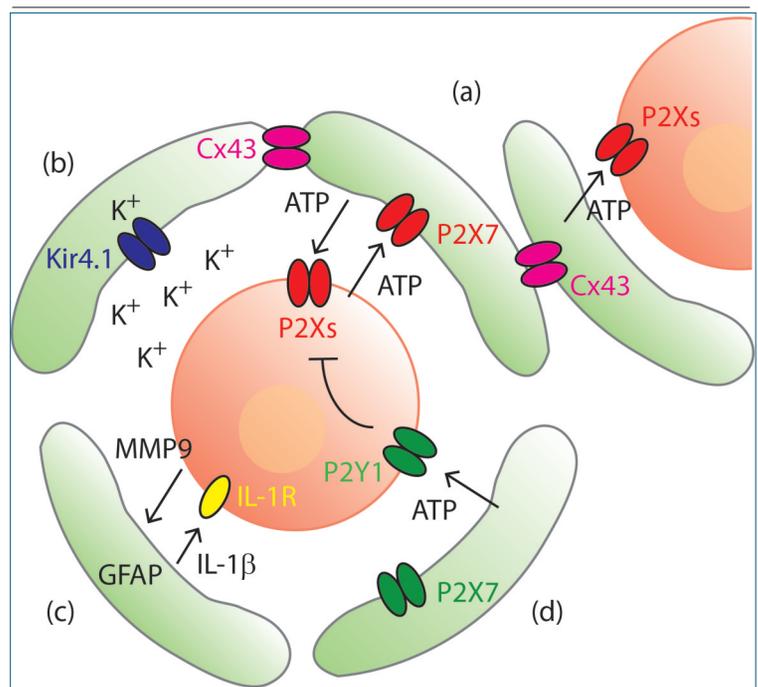


Figure 2. Examples of Modulation of The Activity of Sensory Neurons by SGCs.

(a) Inflammation and nerve injury result in neuronal ATP release leading to the activation of P2X7 and further production and release of ATP. ATP has been shown to increase neuronal excitability in chronic pain conditions via P2X receptors (e.g., P2X4), as well as promote SGCs and neuronal aberrant coupling and activation through Cx43. (b) Nerve injury reduced expression of Kir4.1 increasing the extracellular concentration of K^+ and neuronal excitability. (c) SGCs can diminish current analgesic treatments. Activation of opioid receptors by morphine also results in MMP-9 release from primary sensory neurons, causing activation of SGCs and release of IL-1 β , which binds to IL-1R to increase neuronal excitability. (d) SGCs can also display a protective function. In some cases, P2X7 in SGCs tonically inhibits P2X3 in neurons by activating P2Y1.

seems to follow the development of chronic pain (54), and gap junction blockers have been shown to reduce injury-induced spontaneous neuronal activity and chronic pain behaviors (11, 55-57). ATP release from sensory neurons and SGCs, along with the increase of gap junctions between SGCs can lead to the propagation of calcium waves and aberrant excitability between neighboring sensory neurons (55, 58). Among different intercellular membrane channels forming

gap junctions, connexin 26 and connexin 43 (Cx43) were found to be increased in SGCs after tissue and nerve injury (18, 59, 60). In particular, the increased expression of Cx43 paralleled the increase of coupling among SGCs after inflammation and nerve injury (18). Accordingly, it was found that conditional knockout of Cx43 in SGCs significantly reduced this coupling and chronic pain behaviors in both animal models of inflammatory and neuropathic pain (18). Similarly, knockdown of Cx43 by RNAi was sufficient to decrease orofacial pain behavior after nerve injury (42, 60). On the other hand, knockdown of Cx43 in naïve mice resulted in pain behaviors (60), suggesting a much more complex and distinct biology of gap junctions and SGC coupling in acute and chronic pain conditions. However, it has been suggested that SGC coupling in chronic pain may be important in maintaining the intraganglionic recycling of glutamate, diffusion of inflammatory mediators and buffering of extracellular potassium (K⁺) (57, 60, 61).

Regulation of Ionic Environment

SGCs control extracellular K⁺ homeostasis through gap junctions (61) and the inwardly rectifying potassium channel Kir4.1, which is uniquely expressed in SGCs in sensory ganglia (24, 26, 62). Silencing of the Kir4.1 in SGCs results in spontaneous and stimuli-evoked pain, which disappears when Kir4.1 expression is returned to normal (24, 25), highlighting the importance of this channel for the regular processing of pain. Genetic analysis also identified that potential mutation of the Kir4.1 gene may be responsible for attenuated analgesic responses among inbred strains of mice (63). Kir4.1 is reduced in SGCs after nerve injury (54, 60), inflammation (24) and acute herpetic neuralgia (25), a condition associated with chronic pain. Interestingly, it has been proposed that the cytokine TNF α may be responsible for the reduction of Kir4.1 expression levels in SGCs in chronic pain conditions (25). Mechanistically, it is suggested that decrease of Kir4.1 in SGCs results in reduced buffering of K⁺ leading to a high concentration of extracellular K⁺ and increased neuronal excitability, as predicted by the conventional model of neuronal ionic bal-

ance or Hodgkin-Huxley model (64). However, it has been reported that reversal potentials of K⁺ in SGCs are unaltered after inflammation (26). It is also important to note that nerve injury-induced Kir currents in SGCs are transiently reduced and return to control level in 7 days, but the increased neuronal excitability persists (54). This may suggest that Kir4.1 and buffering of K⁺ likely participate in the development, but not in the maintenance of chronic pain.

Regulation of Cytokine Release

Cytokines injected or released into DRGs enhance the excitability of sensory neurons and elicit pain behaviors (65,66). SGCs exhibit similar characteristics to immune cells and are able to react and produce pro-inflammatory cytokines, such as the interleukins IL-1 β , IL-6, and TNF α . Immunohistochemistry demonstrated that SGCs express both TNF α and TNF α receptor 1 (TNFR1) (25, 67). It has been suggested that TNF α enhances ATP-induced depolarization and increases firing of DRG neurons leading to chronic pain (49). Although increased expression in TNF α is observed in SGCs and increase in TNFR1 is found in both neurons and SGCs after nerve injury (68), the inhibitor of TNF α synthesis thalidomide is only effective in preventing and not treating nerve injury-induced pain behaviors (69). This suggests that TNF α signaling mainly directs the development of chronic pain. However, TNF α can elicit the phosphorylation of the extracellular signal-regulated kinase (ERK) in SGCs, and its persistence is often associated with the maintenance of chronic pain after nerve injury and temporomandibular joint inflammation (70, 71).

Interestingly, the matrix metalloproteinase 9 (MMP9) has been shown to regulate phenotypic remodeling and proliferation of peripheral glial cells such as Schwann cells via ERK (72). MMP9 has been shown to increase in DRGs after nerve injury (73), as well as after acute exposure to morphine (74). In particular, we have demonstrated that acute morphine upregulates GFAP and IL-1 β in SGCs through the expression and induction of MMP9 (30). MMP-9 release from neurons results in increased expression and re-

lease of IL-1 β by SGCs, which in turn activates IL-1 β receptors in sensory neurons masking the morphine-evoked analgesia. Peripheral inflammation also increased the expression levels of IL-1 β in SGCs and IL-1 receptor in nociceptive neurons (75). IL-1 β is known to increase the excitability of sensory neurons via enhancing sodium currents and suppressing potassium currents (66, 76, 77). This suggests a modus operandi by which SGCs control neuronal excitability and pain via the release of IL-1 β . Concordantly, blocking IL-1 β signaling decreased the neuronal excitability after peripheral inflammation (76) and enhanced the analgesia evoked by acute morphine exposure (30).

Little is known about the role of other cytokines in SGC function and control of pain. However, SGCs are activated by monocyte chemoattractant protein 1 after tissue and nerve injury (78-80) and IL-6 is increased in SGCs after nerve injury, and both can modify the neuronal excitability in DRGs leading to the development of chronic pain. Interestingly, both pathogenic and protective functions have been recently observed in microglia and astrocytes, and are often directed by the progression of the injury and the presence of particular pro- and anti-inflammatory cytokines (7, 81). For instance, SGCs constitutively express the 27 kDa heat shock protein, neurotrophins, and their receptors after nerve injury that may be implicated in protective and regenerative functions (82, 83). However, the effects of anti-inflammatory cytokines on SGCs are still to be explored and whether protective functions are really present in SGCs remains an intriguing open question.

Conclusions and Future Directions

Emerging evidence suggests that SGCs are activated after tissue and nerve injury, playing an important role in the development of chronic pain. We have answered the question “How do satellite glial cells control chronic pain?” arguing that SGCs tightly control the excitability of sensory neurons via the regulation of neurotransmitters, cytokines, ion buffering, purinergic signaling, and gap junctions (Figure 2). However, our knowledge of SGCs is still limited compared to our understanding of sensory neurons and other

glial cells, and outstanding questions still need to be addressed.

For instance, does SGC activation represent the consequence rather than the primary cause of pain? Several mutations have been reported in the *Scn9a* gene decoding the sodium ion channel Nav1.7 in sensory neurons resulting in loss-of-function and loss of acute pain, as well as in gain-of-function and paroxysmal pain syndromes (84). No mutations specific to SGCs have yet been identified and it is an open question how much SGC dysfunction contributes to pain. Interestingly, the specific silencing of Cx43 or Kir4.1 in SGCs of naïve mice resulted in spontaneous and stimuli-evoked pain behaviors (24, 60), suggesting a causative role for SGCs. Minor changes in SGCs accumulating over years could also lead to neuronal perturbation and pain syndromes. For instance, it has been reported that aging is associated with increased gap junctions and SGC coupling, which are important for the excitability of DRG neurons (18) and may explain the development of chronic pain states which are rather frequent in senescence (85). This topic merits to be studied in depth.

Another important question is whether SGCs can be pharmacologically and specifically targeted to alleviate pain. In contrast with sensory neurons and other types of glial cells, there has been no high throughput transcriptional analysis of SGCs and many known SGC proteins and therapeutic targets are shared with other glial cells (4). Although the phosphorylation of ERK appears to be an important intracellular pathway for the activation of SGCs and their functions, studies and identifications of intracellular pathways specific to SGCs are hampered by the fact that this phosphorylation also occurs in other neuronal and glial cells in chronic pain conditions (71, 86-88). Cell-specific, promoter-driven altered mice are currently the best approach to define specific proteins and study specific functions in astrocytes, microglia, and Schwann cells. Although mice carrying the proteolipid protein 1 (*Plp1*) promoter have been used to drive genetic modifications in SGCs (18), *Plp1* promoter also induces modifications in oligodendrocytes and Schwann cells and currently no specific SGC promoter exists. The identification of such a promoter would be highly beneficial for the identifi-

cation and understanding of the intracellular pathways and molecular mechanisms underlying the biology of SGCs, as well as for their efficient and specific pharmacological targeting.

Finally, it is worth noting that all the evidence presented in this review is from animal studies. It is well-known that rodent and human astrocytes are quite different (4). Are rodent and human SGCs different too? In the past few years, several laboratories have extended their research of DRG neurons from animal models to human DRG samples, showing a remarkable resemblance between mouse and human sensory neurons (89-92). Preparation of human DRG samples contain both neurons and SGCs (93), so can we use these samples to study human SGCs?

Given the importance of SGCs in the animal model of chronic pain, future studies are warranted to investigate the molecular and functional characteristics of human SGCs, which will certainly refine and accelerate our drug discovery for a better and more efficient treatment of clinical pain.

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