

Review

Satellite glial cells: Shaping peripheral input into the brain-body axis?

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SUMMARY

Satellite glial cells (SGCs) are peripheral nervous system glial cells enveloping sensory and sympathetic ganglion neuronal soma. Traditionally viewed as mere supportive cells, recent studies reveal SGCs' dynamic role in regulating sensory and autonomic processing, positioning them to shape peripheral neural signaling. This role has the potential to impact the healthy function of numerous biological processes and contribute to disease progression. Studies now implicate peripheral sensory and autonomic deficits in the etiology of many disorders, including cognitive decline in aging, neurodevelopmental disorders, or congestive heart failure. These insights highlight SGCs' potential to influence disease processes by modulating peripheral input to the brain. This review synthesizes recent findings on SGCs, emphasizing their functions beyond metabolic support. We discuss the molecular mechanisms underlying SGCs' modulation of neuronal functions, their molecular profiles, and how these change with injury and disease. We propose that SGCs contribute to shaping peripheral input in the brain-body axis.

INTRODUCTION

Satellite glial cells (SGCs) are among the most abundant cells in sensory and autonomic ganglia.^{1–3} They have been observed in all vertebrates examined so far, from reptiles to human.^{1,8} They are easily identified by their unique morphology, forming a characteristic circular pattern around neuronal soma in microscopic tissue sections^{1–3} (Figure 1). The number of SGCs per neuronal soma varies from 1 to more than 20 and is proportional to neuronal soma size, such that the ratio is relatively constant regardless of neuronal soma size.^{1–3} Beyond this unifying feature, SGCs in various types of ganglia vary in their particular morphological characteristics. In sensory ganglia (dorsal root ganglia [DRGs], trigeminal ganglia [TGs], nodose ganglia, and spiral ganglia) (Figure 2), SGCs envelop the soma of neurons that transmit signals from the skin and peripheral organs—including pain, touch, pressure, bodily position, and sound (Figure 1A). However, in spiral ganglia of the inner ear, SGCs uniquely form a few layers of myelin around the neuronal soma⁹ (Figure 1B). These sensory inputs are necessary for bodily functions and interaction with the environment. In sympathetic ganglia, which regulate various physiological processes—including cardiac output, body temperature, glycemia, and immune function under basal conditions and in response to external stressors such as cold or danger—SGCs again envelop the soma but also cover the synapses between pre-ganglionic and post-ganglionic neurons^{2,10,11} (Figures 1C and 2). Thus, not only are SGCs present at key regulatory points in the transmission of neural signals from the body's internal and external environment to and from the brain,

but their morphological variability suggests that SGCs may play distinct roles in specific circuit types.

The intimate association of SGCs with neuronal soma, which was described in early electron microscopy (EM) studies,^{1–3} led to the generally accepted view that these cells simply support the neuronal soma by providing metabolic and trophic factors. However, studies in the past 20 years have shown that SGCs dynamically regulate neuronal activity and function. For instance, SGCs in sensory ganglia modulate pain signals after various forms of neuronal insult, which have been reviewed elsewhere.^{12–14} Following nerve injury, SGCs are involved in nerve repair.^{15–17} SGCs have also been involved in regulating sensory functions linked with neurodevelopmental disorders,¹⁸ neurodegenerative diseases,^{19,20} diabetes,²¹ immune dysfunction,^{22,23} as well as autonomic functions linked to congestive heart failure.²⁴ For example, SGCs in sympathetic ganglia modulate efferent sympathetic cardiac outflow^{25,26} and are reactive in humans with heart failure and arrhythmias.²⁷

Exactly how SGCs are involved in these processes is not well understood. Studies of potential molecular and/or signaling mechanisms have been limited by the lack of precise genetic tools to target SGCs. However, recent studies have used single-cell profiling and genetic manipulations to reveal the diversity of SGCs and their complex molecular properties and functions, which vary depending on the function of the ganglion in which they are located and, therefore, the type of neurons they surround.^{8,15,16,28–30} Indeed, current literature highlights the cellular and molecular mechanisms that govern how SGCs diversify, adapt, and specialize in response to their environment.

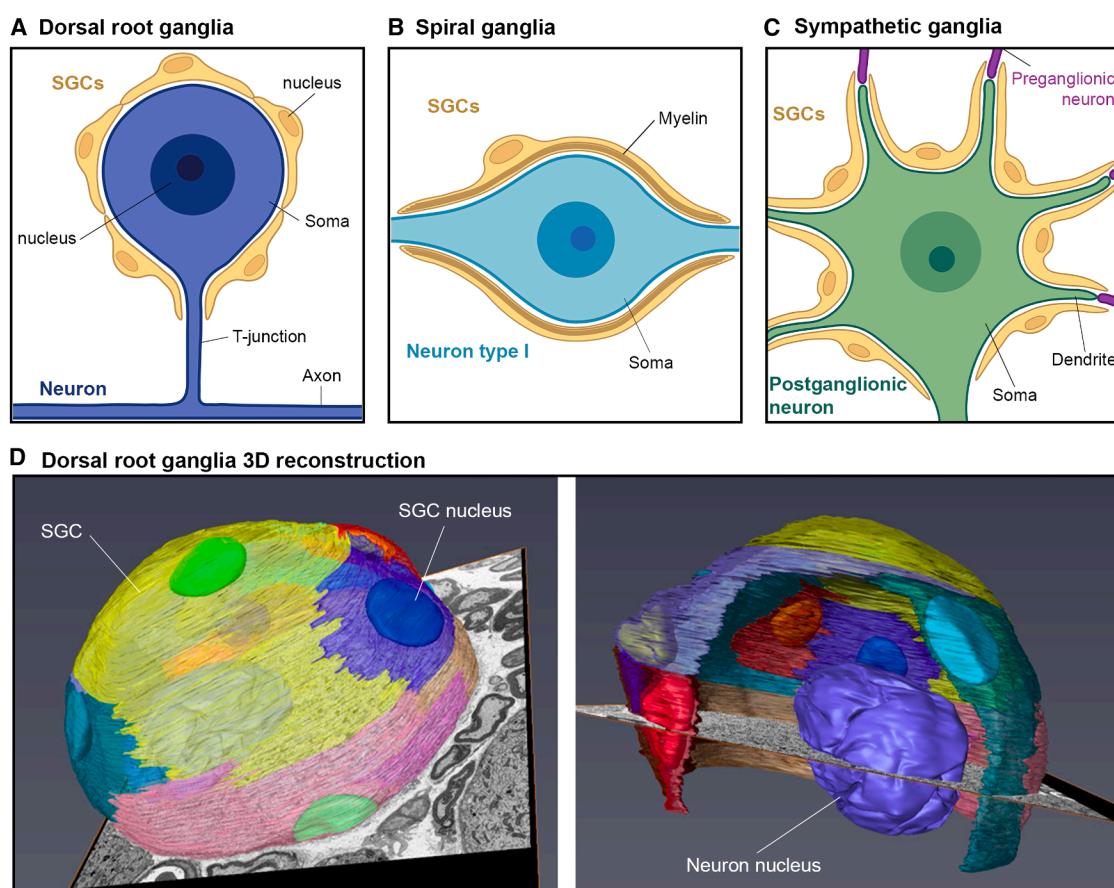


Figure 1. Morphology of SGCs in peripheral ganglia

(A–C) Schematics representing a section across a neuronal soma and its enveloping SGCs coat of (A) pseudobipolar primary sensory neuron in DRG, (B) a bipolar type I neuron in spiral ganglia, (C) a post-ganglionic sympathetic neuron in the sympathetic ganglia. (D) FIB-SEM, AMIRA software reconstruction of a mouse sensory neuron and its SGCs sheath. In DRG and sympathetic ganglia, multiple SGCs surround the neuronal soma, forming a coat that isolates the neuron from the extracellular environment. In spiral ganglia, typically one SGC generates a few layers of myelin that wrap around the soma.

Here, we review data describing the molecular features of SGCs, mechanisms by which they interact with neurons and non-neuronal cells in ganglia, and the implications of these features and interactions within the context of injury and disease. Finally, we discuss the potential involvement of SGCs in the etiology of neurodevelopmental disorders, aging, heart failure, diabetes, and immune dysfunction.

Based on our analysis of the literature to date, we propose that SGCs go beyond simply supporting the neuronal cells they contact to contribute to regulating the neural signals carrying information about the body's internal and external environment to the brain.

THE UNIQUE MORPHOLOGY OF SGCs LENDS ITSELF TO A ROLE IN SHAPING PERIPHERAL INPUT TO THE BRAIN

The most characteristic feature of SGCs is the way they surround the neuronal soma^{1,2,31} (Figure 1). The early names for these cells reflect this unique morphological feature; since first described by Gabriel Gustav Valentin in 1836, these cells were called Mantel-

zellen ("coat cells" in German), amphicyten (from the Greek amphi for "around") or capsular cells.^{1,2} The term "cellules satellites" was used by Ramon y Cajal and many others and chosen since the 1960s by Ennio Pannese, when he used EM to show that the perineuronal sheath is built of discrete, satellite cellular units around the neuron soma.¹ Since then, the term SGC has been widely accepted, to avoid confusion with satellite cells, the stem cells of the muscle.³²

To achieve this unique morphology, multiple SGCs envelop one neuronal soma in sensory and sympathetic ganglia,³ thereby forming a coat that physically isolates the soma from the ganglion microenvironment (Figure 1). In rare cases, a group of 2 or 3 somas are surrounded by a common SGC coat.² The number of SGCs increases in parallel with the neuronal soma size and age in all ganglia.^{1–3} Consistently, human sensory neurons, which are larger compared with rodent sensory neurons,³³ are surrounded by more SGCs than mouse neurons.⁷ The process by which SGCs envelop neurons appears to be complete by the time of birth, at least in rats and chickens.^{1,34} By the time most animals are adults, the outer surface of the SGCs' sheath becomes

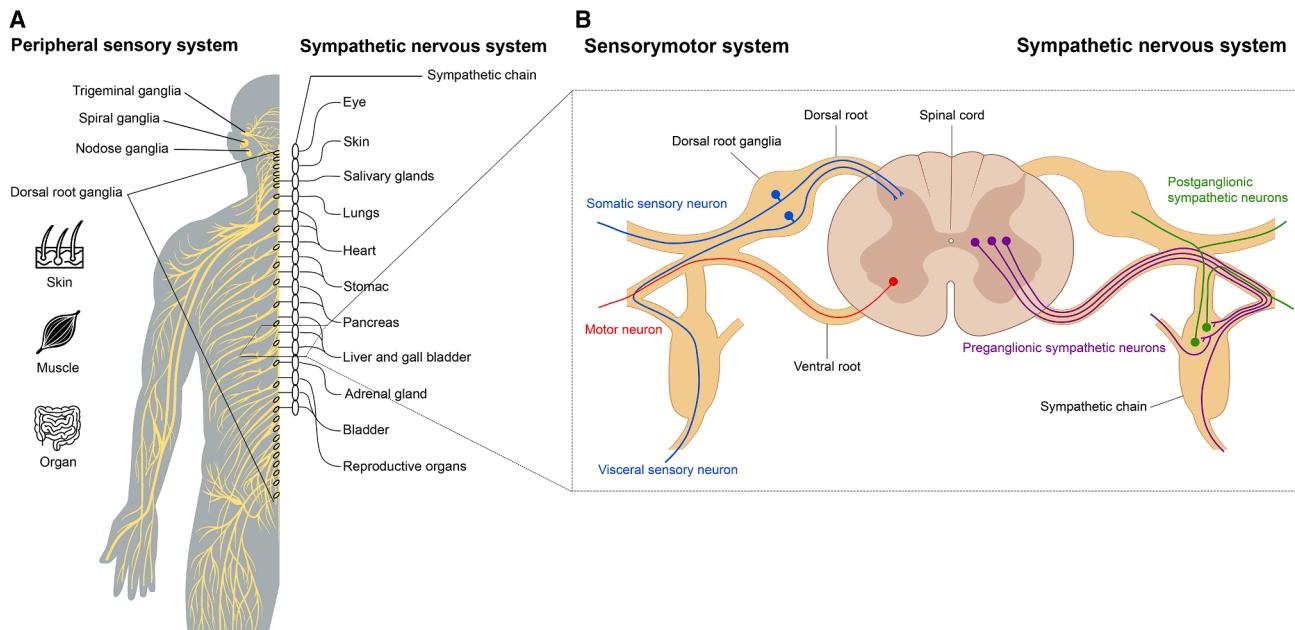


Figure 2. Organization of the peripheral sensory and sympathetic nervous systems

(A) Schematic representation of the peripheral sensory system (left) and the sympathetic nervous system (right). The peripheral sensory system includes the TG, spiral, nodose, and DRG, which relay sensory information from the skin, muscles, and internal organs to the CNS. The sympathetic nervous system, organized along the sympathetic chain, innervates various target organs, including the eye, skin, salivary glands, lungs, heart, stomach, pancreas, liver, adrenal glands, bladder, and reproductive organs.

(B) Schematic cross-section of the spinal cord illustrating the interconnections between the sensory, and autonomic components. Sensory information from the periphery is transmitted via somatic and visceral sensory neurons (blue) through the DRG into the spinal cord via the dorsal root. Motor neurons (red) exit the spinal cord via the ventral root. The sympathetic nervous system is represented by pre-ganglionic sympathetic neurons (purple), which project from the spinal cord to synapse onto post-ganglionic sympathetic neurons (green) within the sympathetic chain, which in turn send signals to target organs. Partially created in Biorender.

covered by a basal lamina, although the cellular origin of this is not known.² The inner surface facing the neuronal soma is contacted by dendrite-like projections extending from the neuron soma, enhancing contact surfaces between the SGCs and the neuron.³⁵ In the end, the gap between the neuron soma and SGCs is only ~20 nm, similar to the width of a synaptic cleft.^{3,36–38}

In some areas in the brain, astrocytes can also extend around and directly contact the neuronal soma, wrapping it partially or fully with their own cellular extensions to form a close physical connection.³⁹ This is one of the reasons for which SGCs have been compared with astrocytes of the central nervous system (CNS).⁴⁰ However, whereas each astrocyte contacts a very large number of neurons and synapses, individual SGCs only contribute to surrounding one (or at most three) neuronal soma. Interestingly, as astrocytes are interconnected via a network of gap junctions, which increases their ability to impact a global population of neurons,⁴¹ there is evidence that SGCs surrounding the same neuron (and occasionally those surrounding different neurons) are also directly connected via gap junctions,^{12,42} suggesting a more global effect of SGCs on a given neuronal population is possible.

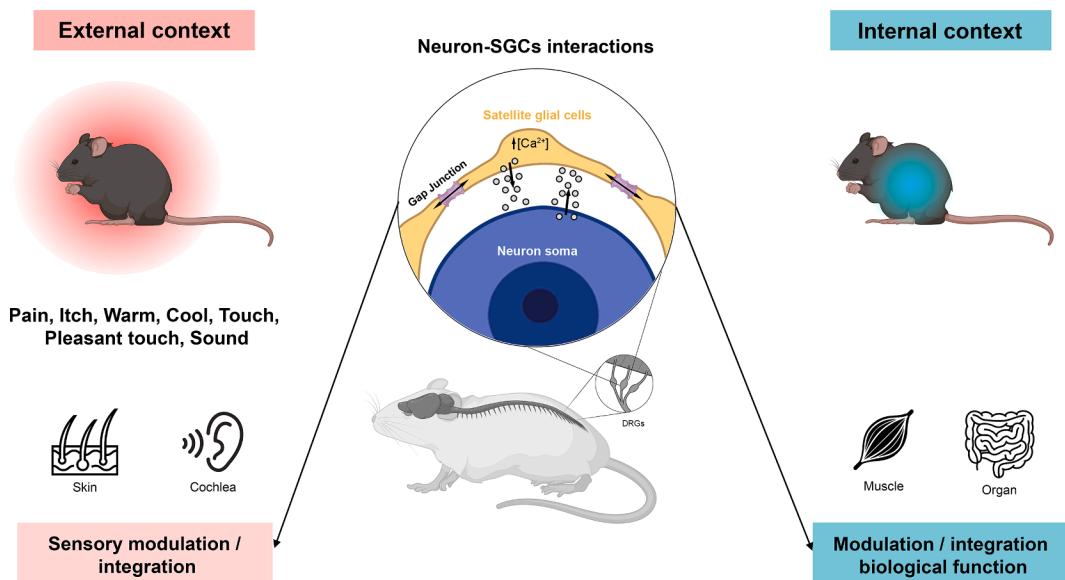
ESTABLISHED ROLE FOR SGCs IN POTASSIUM BUFFERING

Similar to the neurons in the CNS, activity in peripheral sensory and sympathetic neurons leads to accumulation of extracellular

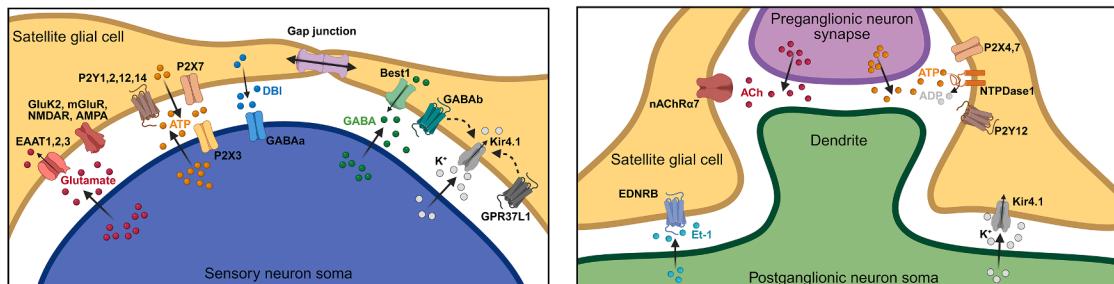
potassium. Potassium homeostasis is thus a critical process that determines neuronal excitability and axonal conduction. A role for SGCs in potassium homeostasis has been clearly established in the literature.⁴³ Inwardly rectifying potassium channels (Kir), which maintain the extracellular potassium ion concentration in peripheral ganglia (Figure 3), are the major ion channels expressed in SGCs; their expression is often used to label SGCs.^{44–48} Electrophysiological analyses show that SGCs in mouse TG and DRG have high potassium conductance, which is almost exclusively dependent on Kir4.1 expression.⁴⁹ While mouse and human SGCs primarily express Kir4.1, human SGCs also express Kir3.1.⁷ Rat SGCs exhibit low levels of both Kir channels but higher expression of the small-conductance calcium activated SK3 channels^{7,44} (Table 1). Interestingly, astrocytes also express Kir4.1 channels in mice and humans.⁵⁰ Their role in potassium buffering in the CNS is well established⁴³ and represent another reason why SGCs have been compared with astrocytes.⁴⁰

Changes in Kir4.1 expression have functional consequences both at the level of the neuron the SGCs contacts, and further downstream at the level of sensory perception. Many studies indicate that nerve damage downregulates Kir4.1 expression in SGCs, and silencing Kir4.1 in SGCs in rat TG has been associated with the development of painful behaviors.^{44,49,66} In sympathetic ganglia, deleting Kir4.1 from SGCs amplifies neuronal activity based on enhanced c-Fos immunoreactivity in sympathetic

A



B



C

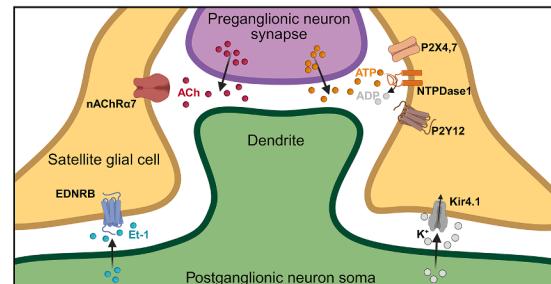


Figure 3. SGCs respond to internal and external physiological changes

(A) SGCs play a critical role in regulating the transmission of sensory information from the periphery to the CNS, thereby establishing a functional connection between the body and the brain. Primary sensory neurons, covered by their SGCs, are the main receptors for sensory inputs that convey information about the animal's state in relation to the outside world, such as sensations of touch, pain, temperature, and sound (left). Due to their presence in the autonomic nervous system, sympathetic neurons and their SGCs are the first to respond to circulating signals, metabolic state, organ or muscle status, and convey information about the animal's body condition (right). SGCs receive from and send signals to the neurons they surround, modulating sensory and biological functions (in the middle). (B) Schematic representation showing the communication between SGCs and the soma of the sensory neurons. Glutamate is released from neurons and subsequently binds to glutaminergic receptors and transporters expressed by SGCs. ATP communication is bidirectional. Both neurons and SGCs can release ATP and both express purinergic receptors. SGCs have also been shown to release DBI, which acts on neuronal GABAergic receptors. Both neurons and SGCs can secrete GABA. Activation of GABA_B or GPR37L1 on SGCs modulates the activity of the Kir4.1 potassium channel on the surface of SGCs and is involved in the regulation of extracellular potassium.

(C) Schematic representation showing the communication between SGCs and sympathetic neurons. The release of ACh by the pre-ganglionic neurons activates the cholinergic receptors on the surface of the SGCs. Communication also relies on ATP, released by the pre-ganglionic fibers. This ATP can bind to purinergic receptors on SGCs, and/or be converted to ADP by ectonucleoside triphosphate diphosphohydrolase (NTDase) on the surface of SGCs. The post-ganglionic neuron also communicates with SGCs via endothelin 1 (ET-1) and activation of the endothelin receptor type B (EDNRB) receptor on SGCs. SGCs have been shown to regulate extracellular potassium via the Kir4.1 potassium channel. Partially created in Biorender.

neurons, similar to the effect observed in SGC-ablated mice.⁴⁶ Deleting Kir4.1 from SGCs also affects the expression of nora-drenergic enzymes in sympathetic neurons, highlighting its role in regulating neuronal maintenance and survival.⁴⁶ There are also data indicating that Kir4.1 function in SGCs can be regulated by surface receptors. Activating GABA_B receptors on SGCs in TG enhances Kir buffering function, which in turn may help maintain extracellular potassium levels following neuronal excitation during sensory processing, including nociceptive

transmission.⁶⁷ G-protein-coupled-receptor-37-like 1 (GPR37L1), a GPCR enriched in SGCs in mouse and human DRGs,^{7,68} co-localizes with Kir4.1 in mouse SGCs and with both Kir3.1 and Kir4.1 in human SGCs.⁶⁸ GPR37L1 has long been viewed as an orphan receptor, but recent studies suggest at least two ligands, prosaposin⁶⁹ and the bioactive lipid maresin 1 (MaR1).⁶⁸ MaR1 binding to GPR37L1 enhances Kir3.1- or Kir4.1-mediated potassium influx in SGCs and regulates the surface expression of these potassium channels.⁶⁸ Whether

Table 1. Gene and protein markers for SGCs in various sensory and sympathetic ganglia

	Sensory ganglia				Sympathetic ganglia	
	Dorsal root ganglia	Trigeminal ganglia	Spiral ganglia	Nodose ganglia	Superior cervical ganglion	Stellate ganglia
<i>Apoe</i>	yes ^{7,8,16,28}	yes ^{8,51–53}	ND	ND	yes ²⁸	yes ³⁰
<i>Ednrb</i>	yes ^{8,16,28,54}	yes ^{8,51}	yes ^{29,47}	ND	yes ²⁸	ND
<i>Epas1</i>	yes ^{8,16,28}	yes ^{8,51}	yes ²⁹	ND	yes ²⁸	ND
<i>Fabp7</i>	yes ^{7,8,16,28}	yes ^{8,51,53,55}	yes ^{29,47,55}	yes ⁵⁶	yes ^{28,46,48,57,58}	yes ³⁰
<i>Gja1</i>	yes ^{7,8,16,28,45,46,59,135}	yes ^{8,51,53}	yes ^{29,58}	yes ⁶⁰	yes ^{28,48}	yes ⁶¹
<i>Glul</i>	yes ^{7,8,16,28,29}	yes ^{8,51}	yes ²⁹	yes ⁵⁶	yes ^{28,49,62}	yes ⁶¹
<i>Igfbp6</i>	no ^{8,16,28,29}	no ^{8,51}	yes ²⁹	ND	no ²⁸	ND
<i>Kcna2</i>	yes ^{8,16,28}	yes ^{8,51}	ND	ND	no ²⁸	ND
<i>Kcnj10</i>	yes ^{7,8,16,28,45,46,59}	yes ^{8,51,53}	yes ^{29,47,63}	ND	yes ^{28,48,49}	ND
<i>Ptpz1</i>	yes ^{8,16,28}	yes ^{8,51}	yes ²⁹	ND	yes ²⁸	yes ³⁰
<i>S100b</i>	yes ^{8,16,28}	no ^{8,51}	yes ^{29,47}	ND	yes ^{28,48,64}	yes ²⁷
<i>Shank2</i>	yes ^{8,16,28}	no ⁸	ND	ND	no ²⁸	ND
<i>Slc12a2</i>	yes ^{8,16,28}	yes ^{8,51}	ND	ND	yes ²⁸	ND
<i>Slc1a3</i>	yes ^{8,16,28,45,59}	yes ^{8,51}	yes ²⁹	yes ⁶⁵	no ²⁸	ND
<i>Srgn</i>	no ^{8,16,28,29}	no ^{8,51}	yes ²⁹	no ⁵⁶	no ²⁸	ND

prosaposin binding to GPR37L1 also regulates potassium channel function has not been tested. However, given that prosaposin can alleviate sensory neuropathy,⁶⁹ it is possible that one of the underlying mechanisms of that effect is via Kir4.1. These studies highlight the central roles that SGCs play in potassium homeostasis, and hence in protecting against pain (in sensory neurons) and regulating noradrenergic function (in sympathetic ganglia).

EVIDENCE OF A ROLE FOR SGCs AS A BARRIER BETWEEN NEURONS AND THE CIRCULATORY SYSTEM

Tracer studies

A common feature of neurons within peripheral ganglia is that they reside outside the blood-brain barrier (BBB), leaving them exposed to the circulatory milieu. Since SGCs completely envelop neuronal soma, some have proposed that they serve as a barrier to limit diffusion of circulating molecules into the neuronal microenvironment. Previous studies using injected tracers (lanthanum, horse-radish peroxidase [HRP], or fluorescently labeled albumin) combined with EM have yielded conflicting observations about the barrier properties of SGCs in sympathetic ganglia.^{36,70–76} In some studies, there was no evidence of tracer accumulation in the space between neurons and SGCs, suggesting that the glial sheaths act as an impermeable barrier.⁷⁶ However, other groups report that systemic injection of tracers results in tracer accumulation along the neuronal surface and that the capillaries in sympathetic ganglia are fenestrated.^{70–72} Some of the inconsistencies can be attributed to differences in the amounts of tracer injected and circulation times. For example, large doses of HRP are toxic and induce vascular permeability.⁷⁷ Notably, systemic or direct ganglionic injections of wheat germ agglutinin labeled HRP in adult rats resulted in different patterns of tracer accumulation in the superior cervical ganglia (sympathetic) versus TGs (sensory) in the same animals.⁷⁶ In sympathetic ganglia, the tracer was excluded from the space be-

tween neurons and SGCs, whereas in TG, the tracer lined the membranes of neurons and SGCs, indicating that SGCs act as a diffusion barrier in sympathetic but not in sensory ganglia. These tracer studies suggest that there may be ganglion-specific differences in the ability of the SGCs to act as protective barriers between neurons and the circulation.

Morphology and gene expression

The unique sheath-forming morphology of SGCs suggests a barrier-forming role for these cells. The extent to which the sheath formed is complete and/or resilient to permeating factors is still being determined, and as discussed above, may depend on the ganglia. Ultrastructural studies reveal that SGCs in sympathetic ganglia are more tightly packed compared with sensory SGCs.⁷⁶ This tight packing may be important for forming the tight junctions between SGCs in sympathetic ganglia (no such connections are observed among SGCs in sensory ganglia), which may in turn facilitate a more continuous glial sheath and more complete diffusion barrier.⁷⁶ Further support for a barrier role is based on recent single-cell RNA sequencing analyses revealing that SGCs express genes implicated in BBB integrity, including *Vcam1*, *Tgfb2*, *Iqgap2*, *Mfsd2a*, and *Aqp*.^{15,16,28} Further functional analysis using SGC-specific conditional knockout mice are warranted to assess the role of these proteins in SGCs.

Vascular interactions

SGCs share some functional similarities with astrocytes in the CNS, including their ability to influence the neuronal microenvironment and neuronal activity and to act as selective barriers between neurons and the circulatory system.^{12,15,16} Astrocytes notably have specialized morphologies with endfeet processes that make contacts with vascular endothelial cells, which contributes to a tight BBB.⁷⁸ However, it is unclear whether or to what extent SGCs interact with the vasculature and how any interactions affect vascular permeability in sensory or sympathetic ganglia.

A role for SGCs in viral infection

By enveloping neuronal cell bodies, SGCs may also form a functional barrier to restrict local diffusion of certain viruses from the neuron into the ganglia parenchyma and the circulation. Herpesvirus, varicella-zoster virus, and swine hemagglutinating encephalomyelitis virus can infect the peripheral nervous system (PNS), gaining access at free nerve endings in organs and reaching the neuron soma in sensory ganglia.^{12,23} After the primary infection, viruses can become latent but retain the ability to reactivate and cause diseases, such as herpes zoster or cold sores. The mechanisms of viral latency and whether SGCs are infected remain poorly understood.¹² The hemagglutinating encephalomyelitis virus was shown to replicate within rat sensory neurons and accumulate in lysosome-like structures within SGCs,²³ suggesting that SGCs may limit the spread of virus to the DRG environment. Moreover, SGCs were shown to express interferon-induced transmembrane proteins (IFITMs),⁷ which generally work to restrict viral infections, though a subset of IFITMs can enhance infections by specific coronaviruses.⁷⁹ Furthermore, a subset of SGCs expressing an immune cell character has been observed in multiple species, from rodents to human,^{6,15,28,30,80} suggesting that they may be able to respond to neuronal viral exposure. A better understanding of immune and cell biological properties of SGCs is needed to help elucidate a potential role for SGCs in viral infection.

COMMUNICATION BETWEEN SGCs AND NEURONS: CRITICAL ROLES OF NEUROTRANSMITTERS AND NEUROMODULATORS

Sensory neurons have a unique pseudounipolar morphology with a single axon that bifurcates within the ganglion; one axon extends along peripheral nerves to innervate target tissue and the other proceeds centrally along the dorsal root into the spinal cord (Figure 2). Sensory cell bodies in DRG were once thought to be uninvolved in sensory transmission,⁸¹ mostly because action potentials are generated at the periphery in the target tissue and propagate along peripheral and then central axons to reach the spinal cord, simply passing through the neuronal soma along the way.⁸¹ However, intracellular electrophysiological recordings and modulation of ion channels in sensory neurons indicate that the soma is involved in sensory transmission from the periphery to the spinal cord.⁸² Additionally, hyperactivity within nociceptor soma may contribute to hyperalgesia priming and driving anxiety-related hypervigilance.^{83,84} Because SGCs are so close to neuronal cell bodies in these areas, any neurotransmitters or other signaling molecules released from sensory neuronal soma are likely to affect SGCs. Indeed, and as detailed below, we now know that SGCs and neurons communicate via neurotransmitters and neuromodulators to affect neuronal activity. Several studies report evidence of neurotransmitter release with distinct kinetics from DRG somas, via calcium-dependent exocytosis⁸⁵ or depolarization.⁸⁶ In this section, we will review and discuss current knowledge regarding the molecules and mechanisms involved in SGCs-neuron communication (Figure 3).

Glutamate

Glutamate is the excitatory neurotransmitter found in sensory pathways.⁸⁷ Activation of these neurons leads to neurotransmitter

release at nerve terminals. In addition, extra synaptic transmission, which includes the release of neurotransmitter by neuronal cell bodies, occurs in peripheral ganglia.⁸⁸ By combining membrane capacitance, calcium measurements, and patch-clamp experiments, it has been shown that calcium-dependent exocytosis of glutamate occurs from the soma of both DRG and TG neurons in response to depolarization.^{85,89} There are now data supporting the idea that SGCs are directly impacted by glutamate release, including the observation that bath application of glutamate to mixed DRG cultures triggers calcium responses in both neurons and SGCs.⁸⁹ SGCs take up glutamate either via transporters or receptors. There are studies of the role of glutamate transporters expressed by SGCs (EAAT1, EAAT2, and EAAT3) in uptake of glutamate released by neuronal soma in mixed DRG cultures.^{89,90} In addition, SGCs express various kainate and glutamate receptors (glutamate ionotropic receptor kainate type 2 [GluK2], glutamate metabotropic receptor [mGluR], N-methyl-D-aspartate receptor [NMDAR], and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid [AMPA]).^{89,91–93} Brief NMDA pulses applied to SGCs-enriched cultures trigger transient increases in calcium levels, which are inhibited by specific NMDA receptor blockers MK-801 and AP5.⁹¹ Moreover, NMDA injections *in vivo* into lumbar DRG induce hyperalgesia, while AP5 injection attenuates prostaglandin E2-induced hyperalgesia.⁹⁴ Associated *in vitro* studies of cultured DRG neurons indicate that NMDA-induced sensitization relies on NMDA receptors in SGCs.⁹⁴ These findings underscore the functional role of glutamatergic receptors in SGCs, though details of the signaling pathways downstream of glutamate signaling in SGCs are not fully understood.

GABA

In TG, neuronal soma release GABA in response to elevated extracellular potassium.⁹⁵ This suggests that GABA acts as another non-synaptic neurotransmitter that modulates somatic inhibition of TG neurons via GABA_A and GABA_B receptors.^{95,96} In DRG, sensory neurons express GABA_A,⁹⁷ and some nociceptors are capable of synthesizing and releasing GABA in response to mechanical or chemical stimulation.^{98,99} There is also evidence from a reptile DRG model that SGCs themselves are a source of endogenous GABA.⁴ While SGCs lack Gad, the main enzyme involved in classical GABA synthesis, they do express MaoB, an enzyme of the alternative putrescine pathway of GABA biosynthesis.⁴ GABA released via bestrophin 1 channels in SGCs tonically activates GABA receptors in sensory neurons.⁴ On a functional level, *in vivo* patch-clamp data in rat TG show that GABA released from sensory neuronal soma acts on GABA_B receptors in SGCs, affecting Kir4.1 activity and thus contributing to the regulation of extracellular potassium levels.⁶⁷ In DRGs, SGCs contribute to regulating GABA_A activity in neurons via the release of diazepam-binding inhibitor (DBI), which is expressed in SGCs of mice, rats, and humans.¹⁰⁰ Using viral approaches to manipulate DBI levels in SGCs, Li et al.¹⁰⁰ demonstrated that knocking down DBI in SGCs results in robust mechanical hypersensitivity with no major effects on other sensory modalities. Conversely, overexpression of DBI in SGCs reduces sensitivity to mechanical stimulation and alleviates mechanical allodynia in neuropathic and inflammatory pain models. They further demonstrate that DBI acts as an endogenous unconventional agonist

and positive allosteric modulator of GABA_A receptors within the DRG.¹⁰⁰ This study used intra-ganglionic delivery of an adeno-associated virus (AAV) with the GfaABC1D promoter to manipulate DBI levels in SGCs. This approach successfully targets SGCs, since promoter selection, rather than the capsid tropism of the AAV serotype, determines selective gene expression in SGCs following intra-ganglionic AAV delivery.¹⁰¹ However, because glial fibrillary acidic protein (GFAP) is also expressed in Schwann cells (SCs) in the DRG,¹⁶ future studies need to include careful characterization of cellular identity to ensure efficiency and specificity of SGC targeting. Together, these findings underscore the pivotal role of GABA as a non-synaptic neurotransmitter in modulating sensory neuron activity while highlighting the contributions of modulators of GABA signaling like DBI to pain modulation.

ACh

In sympathetic ganglia, acetylcholine (ACh) released from pre-ganglionic axon terminals leads to increased calcium signaling in SGCs, glial activation characterized by increased GFAP expression, and enhanced electrical coupling between SGCs.¹⁰² The effects of ACh were attenuated by atropine, suggesting that SGCs express muscarinic ACh receptors. Further, immuno-EM analyses indicate the presence of nicotinic ACh receptors, especially the $\alpha 7$ subunit, in sympathetic SGCs.¹⁰³ In co-cultures with sympathetic neurons, SGCs enhance cholinergic neurotransmission,⁶⁴ suggesting a regulatory pathway through which SGCs may enhance ACh release from pre-ganglionic axons to ultimately modulate SGC activity. In TG and DRG, low levels of the ACh receptors $\alpha 7$ subunit (*Chrna7*) are observed in SGCs.⁸ Clearly, further studies are needed to fully define the contribution of cholinergic/nicotinic signaling in neuron-SGC interactions and determine whether these pathways operate within sensory ganglia.

ATP

Neuron-SGC communication in sensory and sympathetic ganglia involves ATP signaling.^{11,38} Neuronal membrane depolarization triggers ATP release from DRG neuron soma, which can occur through both calcium-dependent and -independent mechanisms.^{85,104–106} ATP is primarily effluxed through Pannexin 1 channels expressed in medium to large-sized sensory neurons in DRG, leading to extracellular ATP accumulation.^{107,108} ATP release can also be vesicular following the arrival of an action potential. Double voltage-clamp whole-cell recordings reveal that ATP released from the DRG neuron soma communicate with SGCs via purinergic receptors.^{106,109} Using sniffer patch methods and DRG explants, Zhang et al.¹⁰⁶ showed that P2X7 receptor-mediated ATP action in SGCs triggers tumor necrosis factor alpha (TNF- α) release, which then goes on to sensitize DRG neurons, establishing a bidirectional activation loop. However, since P2X7 is expressed in macrophages in addition to SGCs,^{16,110} the measured release of TNF- α in DRG explants cannot be affirmatively attributed to SGCs. In addition to P2X7, P2Y1, and P2Y2 receptors in SGCs play key roles in glial-neuron interactions *in vitro*.^{111,112} ATP released by neuron soma or SGCs can also impact neurons via P2X3 receptors. Activation of P2X3 receptors on small nociceptive neurons in DRG *in vivo*

triggers prolonged SGC activation (monitored by Ca²⁺ signals *in situ*). In the late activation phase, large neurons were also activated, and this response was reduced by the Pannexin1 blocker probenecid, suggesting a paracrine ATP action in neuron coupling *in vivo*.¹¹³

ATP is also released by innervating cholinergic pre-ganglionic axons in sympathetic ganglia,^{114–116} which are in contact with SGCs (Figure 1C). This extracellular ATP can be rapidly metabolized by cell-surface ectonucleotidases, which are expressed in sympathetic SGCs.^{116,117} Indeed, single-cell RNA sequencing data from SGCs reveal several transcripts that are involved in ATP sensing, hydrolysis, and removal of breakdown products in sympathetic SGCs, including the purinergic receptors *P2rx4*, *P2rx7*, and *P2ry12*, and *Entpd1*, an ectoenzyme which catalyzes ATP hydrolysis to ADP, as well as adenosine kinase (*Adk*),²⁸ which is best-known for mediating astrocytic uptake of extracellular adenosine in the brain.¹¹⁸ These data further support the idea that neuron-SGCs bidirectional communication involve ATP signaling.

Other signaling molecules

In addition to classical neurotransmitters and neuromodulators, SGCs respond to other signaling molecules. Nitric oxide (NO) released from neurons increases cyclic guanosine monophosphate (cGMP) synthesis in SGCs, which increases GFAP expression and gap junctional coupling of SGCs in cultured DRG.^{37,119} Endothelin-1 released by sympathetic neurons can bind endothelin receptors expressed by SGCs,²⁸ resulting in a reduction in gap junction-mediated coupling between glial cells.¹²⁰ Purinergic and endothelin signaling between neurons and SGCs is conserved across different peripheral ganglia.

SGCs also communicate with neurons through the release of inflammatory molecules, a topic that has been reviewed broadly³⁶ and in detail in the context of diabetic neuropathy.²¹ In brief, the release of interleukin (IL)-1 β , TNF- α , and chemokine ligand 2 (CCL2) by SGCs can be triggered by inflammation or nerve injury, or by directly activating P2RY14 receptors in SGCs. Inflammatory signaling stemming from SGCs may have several consequences on neurons, such as an increase in IL-1R1 receptor activity and an increase in their excitability.^{66,106,121,122}

Gaps in our knowledge and future directions

The data presented above support the idea that SGCs and neurons communicate with each other through many different types of signaling molecules. However, the evidence available to date relies on studies of mixed DRG cultures or DRG explants. Thus, while highly suggestive of mechanisms involving signaling molecules released by SGCs, the results cannot rule out signaling molecules released from other sources (e.g., SCs, fibroblasts, or other non-neuronal cells). Furthermore, earlier *in vitro* studies suggested that SGCs retain their characteristics for only about 24 h in culture before undergoing major phenotypic changes, including leaving the neuronal cell soma, dividing, and becoming spindle shaped.¹²³ These changes are likely due to SGCs losing their adhesive contacts with neurons over time in culture, which likely leads to changes in their molecular properties. However, the field may now have a reliable experimental model of SGCs

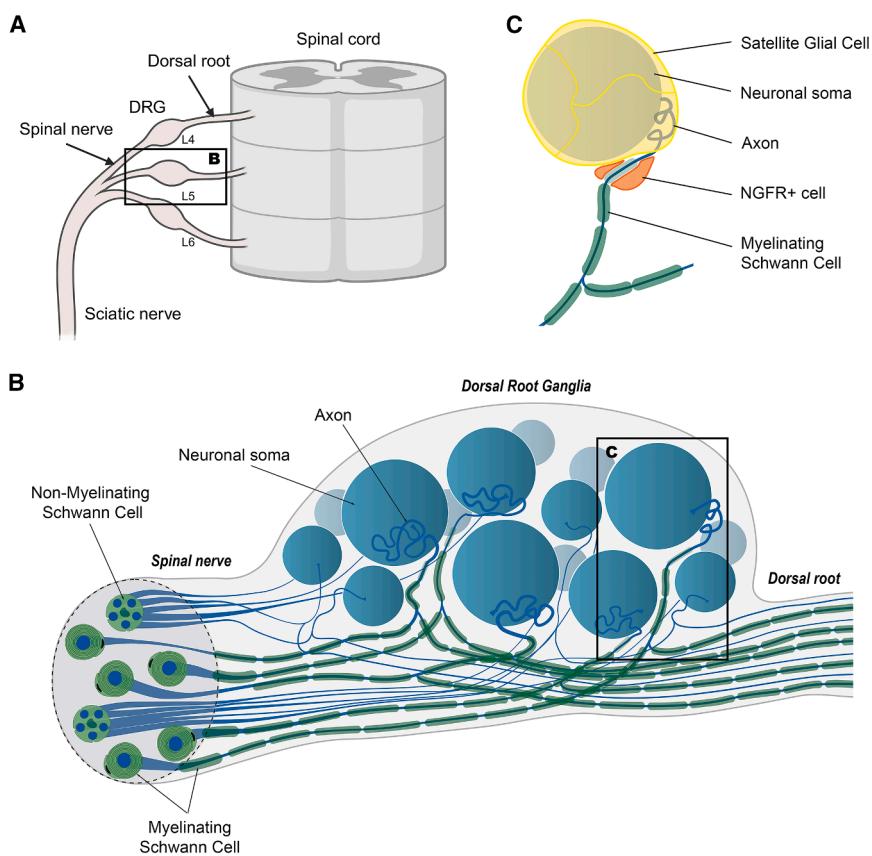


Figure 4. Glial cell heterogeneity and morphology of the periaxonal sheath

(A) Schematic representation of three lumbar DRG. Each DRG is connected to the spinal cord via the dorsal root and to the sciatic nerve via spinal nerve.

(B) Illustration of the morphological complexity of sensory neurons and their axons in DRGs, adapted in part from Ramon y Cajal (1909).¹³⁷

(C) The convoluted axon that emerges from the soma is in contact with SGCs. Further away, the axon is then enveloped by a SC that makes thin myelin, followed by other SCs that make the regular thick myelin sheath.¹⁴¹ The first SC is covered by a specialized glial cell that expressed nerve growth factor receptor (NGFR). Partially created in Biorender.

that would make it possible to identify molecules secreted specifically by SGCs. A recent study described a new protocol for culturing SGCs that resulted in cultures enriched in the expression of SGCs markers (*Glul*, *Gja1*, and *Ednrb*) and de-enriched for SC markers, fibroblasts, and other non-neuronal cells.¹²⁴ These cultured SGCs respond to an endothelin receptor type B (ETBR) agonist with calcium elevation,¹²⁴ similarly to acutely dissociated SGCs.^{120,125} Since ETBR is highly enriched in SGCs in the DRG,¹²⁶ nodose, TG, and sympathetic ganglia,^{120,125} the functional response to ETBR activation is a suitable metric for validating the health and purity of SGCs cultures from different ganglia. So far, this culture model was successfully used to demonstrate that SGCs release DBI,¹⁰⁰ and it could be used to corroborate data from the mixed culture models presented above and to identify new molecules released by SGCs. This new approach has the potential to rigorously and systematically explore the signaling molecular landscape shared by SGCs and the neurons they contact.

DIVERSITY WITHIN SGCs SUGGESTS SPECIALIZED ROLES ACROSS SYSTEMS

Given the different functions of sensory and autonomic ganglia and the different types of neurons they harbor, it is not surprising that the role of SGCs differs based on where they are and what type of neuron they contact. These differences can be appreciated in terms of the cells' developmental origins, anatomical

and morphological features, and molecular expression patterns.

Developmental origins

We know relatively little about the developmental origin and trajectory that results in the unique morphology of SGCs. In most rodent sensory and sympathetic ganglia, SGCs are generated during development from multipotent neural crest cells and boundary cap cells, which migrate from the neural tube to form sensory and sympathetic ganglia.^{127–133}

There are, however, differences in the developmental origins of SGCs across gan-

glia. Notably, in TG, SGCs have a dual origin; they are derived from both cranial neural crest cells and trigeminal ectodermal placodes.^{134–136} Whether this difference in origin is reflected in the functional properties of SGCs in TG vs. DRG awaits further studies.⁸

Anatomical and morphological differences

Differences in the anatomical and morphological features of SGCs suggest they are adapted to specific roles depending on what type of neurons they contact. For example, while the majority of SGCs contact the neuronal soma exclusively, some SGCs extend their envelope to the initial axon segment, a convolution of the axon near the cell soma known as the Cajal initial glomeruli.^{137,138} SGCs around the initial glomeruli form a structure called the periaxonal sheath^{1,139–141} (Figure 4). Using EM, Ennio Pannese proposed that SGCs surrounding axons form a separate layer and do not contact the neuronal soma.¹ However, this idea could not be proven without three-dimensional ultra-structure imaging. Using array tomography combined with correlative light and EM, Koike et al. report a specialized glial cell type in rats that surround the glia-covered initial axon segment.¹⁴² These specialized cells express p75NTR (*Ngfr*), but not the SGC markers *Kir4.1* or *GFAP* (expression of the SGC marker *Fabp7* or the non-myelinating SCs (nmSCs) marker *Scn7a* was not examined). Precise cell annotation from single-cell datasets may make it possible to characterize this cell type in more detail. However, these methods lack consistency, even

for major glial cell types in the PNS. For example, studies in the DRG have identified SGCs, myelinating SCs (mSCs), and nmSCs,⁸ while other studies describe SGCs and SCs, but do not differentiate nmSCs.^{15,28} Other studies in sympathetic ganglia classified all glia as SCs.¹⁴³ This apparent discrepancy may be due to the lack of precise molecular markers that differentiate nmSCs from SGC subtypes or may come down to differences in tissue dissection techniques. According to EM studies in the 1970s, axons tend to bundle together after the T-junction bifurcation,¹³⁹ which means Remak bundles generated by nmSCs may only be present in the axon-rich region after the axon bifurcation in the nerve or root, but not in the soma-rich region (Figure 4). Thus, nmSCs in the DRG may resemble nmSCs in the nerve but would lack the ability to sort and bundle axons. Correlating precise anatomical location with molecular signatures of different glial cell types will require further studies.

There are also several significant morphological differences among SGCs across ganglia. For example, in rat⁹ and human^{144,145} spiral ganglia, the soma of type I bipolar neurons are surrounded by a few layers of myelin produced by SGCs (Figure 1B). This type of myelination is not observed in SGCs in any other ganglia and is distinct from the classical thick myelin layer produced by SCs around axons.¹⁴⁶ This morphological specialization may be in response to the need for speed and precision to transmit sound,¹⁴⁷ though this hypothesis has not been directly tested. Sensory neurons in the DRG also transmit multiple types of sensory information at different speeds. The neurons themselves display morphological adaptations, e.g., large, myelinated axons in mechanoreceptors and proprioceptors and non-myelinated axons among pain-transmitting, slow-conducting axons. To date, no difference in SGC morphology has been reported in DRG. However, whether their molecular and/or functional properties are tuned to the conduction velocity of sensory neurons they contact remains to be determined.

Molecular expression differences

In most studies, SGCs are identified by the expression of marker genes like *Glul*, *Gfap*, *Kcnj10/Kir4.1*, *Gja1*/connexin 43 (Cx43), *ApoE*, and *Plp1*^{16,28,59,100} (Table 1). Results from single-cell RNA-seq studies have identified new markers for SGCs, including *Fabp7*.¹⁶ Such studies have also begun to shed light on the similarities and differences in molecular expression profiles of SGCs both within and across ganglia.

Across ganglia

In a recent study using the droplet sequencing (Drop-seq) technique,¹⁴⁸ Mapps et al. compared the transcriptional profile of SGCs in DRG and sympathetic ganglia (superior cervical ganglia) using a similar number of cells.²⁸ The authors classified SGCs into five transcriptionally distinct populations. Three clusters were common across ganglia, while two were specialized in their respective ganglia.²⁸ The three common populations were enriched for genes related to extracellular matrix (ECM) interactions, immediate-early genes, and immune-related genes.²⁸ Interestingly, a cluster enriched for the expression of immune-related genes was also identified in stellate ganglia, which is part of the sympathetic chain,³⁰ and in DRGs.¹⁵ Sensory SGCs were enriched for transcripts associated with glutamatergic ma-

chinery, consistent with their association with glutamatergic sensory neurons. While ACh is the major neurotransmitter in sympathetic ganglia, this study did not detect SGC transcripts that could be directly involved in cholinergic signaling. This contrasts with previous observations that SGCs in freshly isolated sympathetic ganglia, but not nodose or TG, respond to ACh by increasing intracellular calcium.¹⁰² Further studies with greater sequencing depth may be able to resolve whether sympathetic SGCs express cholinergic genes.

Several studies have shown that sensory SGCs are enriched for genes related to cholesterol biosynthesis compared with sympathetic SGCs.^{16,17,28} One SGC cluster in the stellate ganglia was also enriched in cholesterol pathway.³⁰ Downregulation of the cholesterol pathway appears to reflect a feature of aging in SGCs.^{30,54} Based on these data, it is tempting to speculate that SGC-derived cholesterol is involved in maintaining neuronal cell soma, similar to the role of cholesterol derived from astrocytes (likely to be important for neuronal health and synaptogenesis).¹⁴⁹ It may also hint at a role in mediating changes to sensory function in neurodegenerative diseases, as at least one study has linked dysregulation of cholesterol homeostasis to Alzheimer's disease (AD) onset and progression.¹⁵⁰

Other genes enriched in sensory SGCs compared with sympathetic SGCs include *Cx43/Gja1* and endothelin B receptor/*Ednrb*. Cx43 forms gap junctions between SGCs surrounding the same neurons.¹⁵¹ In pathological conditions such as nerve injury, Cx43 is upregulated, leading to an injury-induced upregulation of gap junctions between SGCs surrounding adjacent neurons. The resulting neuron-neuron electrical coupling via SGCs represents a possible mechanism of pain-related neuronal plasticity.^{36,42} An increase in Cx43 expression in SGCs after nerve injury also correlates with an increase in axon regeneration capacity.⁵⁴ The mechanisms regulating Cx43 expression in SGCs are not fully elucidated. In astrocytes, endothelin signaling inhibits the expression of Cx43 and reduces gap junction coupling.^{152,153} Similarly, in cultured SGCs from TG, nodose, and sympathetic ganglia, endothelin-1 reduces gap junction coupling.¹²⁰ Conversely, blocking endothelin B receptor increases the expression of Cx43 in SGCs after nerve injury *in vivo* in both adult and age mice.⁵⁴ Whether endothelin signaling regulates the Cx43 gap junction or hemichannel function in SGCs and the consequences of such regulation on sensory neuron function has not yet been investigated. Overall, these single-cell sequencing approaches reveal that there are fewer genes specific to sympathetic SGCs compared with sensory SGCs. Whether sensory SGCs have additional specialized properties that are tuned to the properties of sensory neurons and their function remains to be determined.

Among sensory ganglia

Even within sensory ganglia, there are notable differences in the molecular profiles displayed by SGCs, which may relate to the different sensory modalities that each sensory ganglia needs to transmit. In the cochlea, two types of spiral ganglion neurons, bipolar and pseudobipolar, transmit ear-to-brain signals at high speed and precision.¹⁴⁷ Within the DRG, more than a dozen morphologically and physiologically distinct sensory neuron subtypes report internal and external environmental

features.^{154–157} Here, we present data highlighting the specialization of SGCs within specific sensory ganglia.

In spiral ganglia, SGCs surround both types of spiral ganglion neurons (bipolar and pseudounipolar), but their morphology is significantly different. SGC surrounding bipolar spiral ganglion neurons generate multiple layers of myelin,⁹ whereas SGC surrounding pseudounipolar neurons, which represent only 5% of all spiral ganglia neurons,¹⁵⁸ resemble SGCs in the DRG (Figure 1B). Overall, SGCs in cochlea have a different molecular expression profile compared with SGCs in DRG. These differences not only highlight the uniqueness of the SGCs populations in each ganglion but also key differences between the myelinating SGCs of the cochlea and SCs, which myelinate axons throughout the periphery. One study profiled proteolipid protein 1 (PLP1)-expressing glia in the cochlea and DRG during development at the single-cell level and found that while SC showed consistent gene expression profile in both ganglia, SGCs in each ganglion were distinct.²⁹ Unique marker genes were identified in cochlear SGCs, such as *Igfbp6*, which can bind to the single-span membrane protein prohibitin 2 (Phb2) in spiral ganglion neurons, suggesting specific SGC-neuron communication in the cochlea. Consistent with SGCs myelinating the soma of bipolar spiral ganglion neurons, several myelin-related genes were enriched in spiral ganglia SGCs. However, the myelination gene profile differs from SC myelination,²⁹ reflecting the different myelination process and/or structure.¹⁴⁶ Genes known to repress myelination, such as *Ednrb*, *Ptpz1*, are enriched in SGCs in DRG and in sympathetic ganglia,²⁸ suggesting that myelination is actively suppressed in sensory and sympathetic SGCs.²⁹ Other important differences between SGCs in DRG and cochlea may be related to neuronal firing properties. This is evidenced by the selective enrichment of specific genes involved in neurotransmitter reuptake and release as well as synapse formation and function.²⁹ These studies support the idea that SGC characteristics are tuned to the neuron they surround, whereas SC characteristics may be more constant across ganglia.

In the DRG, SGCs are transcriptionally heterogeneous, with at least four distinct clusters identified in single-cell RNA-seq studies.^{15,28} Another recent study in DRG defined two major subclusters of *Fabp7*-positive SGCs, defined by the expression of *Gja1* and *Entpd2*, an ecto-ATPase.⁵⁹ Current data support the idea that each SGC subtype may not be dedicated to a particular neuron but rather that multiple SGCs subtypes surround a given neuron.^{16,59} Future studies using spatial transcriptomics or proteomics will be needed to bring further evidence to the organization of SGCs subtypes around neuronal soma.

However, interesting hypotheses about the function of some SGC subtypes can be drawn from these transcriptomic data. *Aldh1l1*, a marker typically used to label astrocytes in the CNS, is expressed by a subtype of SGCs that has the most similarities to astrocytes,¹⁵ consistent with ALDH1L1-eGFP mice driving eGFP expression only in a subset of SGCs.¹⁵⁹ Both TrkA-positive and TrkA-negative neurons were found to be surrounded by an *Aldh1l1* expressing SGCs,¹⁵ and *Aldh1l1*-expressing SGCs did form the typical circular pattern observed with *Fabp7*.^{16,28} This *Aldh1l1* positive cluster of SGCs also expresses aquaporin-4 (AQP4) in mouse,¹⁵ rat, and human.⁷ AQP4 is a water channel expressed on astrocytic endfeet in the brain¹⁶⁰ and controls water

exchange across the blood-brain interface. In porcine DRG, AQP4 is expressed in SGCs surrounding small and medium sized neuronal soma, but not large neurons.⁵ The precise subcellular localization of AQP4 within SGCs has not been examined in detail. Whether SGCs expressing AQP4 have increased water permeability compared with other SGCs and favor water uptake from nearby capillaries remains to be determined.

Sensory neurons located in the TG and DRG are the primary sensors of noxious or potentially damaging stimuli for the head and body, respectively. They are also key drivers of chronic pain states.¹⁶¹ In spite of their different embryogenic origins and processing capabilities, DRG and TG neurons are surprisingly similar to each other in both mice and humans.^{8,162} However, several genes were found to be exclusively expressed in neurons of each ganglion, and others were differentially enriched such as *Pvalb*, *Calca*, *Dcn*, and *Rxfp1* neurons.⁸ These differences in neuronal properties suggest that SGCs in DRG and TG may also have special properties for fine modulation of nociceptive responses.

Across species

A small number of studies have investigated the molecular characteristics of SGCs in different species. At the functional level, gap junction coupling and expression of connexins in SGCs is conserved in all vertebrates examined, from reptiles to human.^{1–6,8,15} SGCs in all species express Kir4.1, key to their role in potassium buffering.^{7,8} However, there are species-specific differences in the expression of another potassium channel, SK3/*Kcnn3*; expression is enriched in rats compared with mice and human.^{7,44} While key features of SGCs in DRG related to axon repair are conserved in humans, mice, and rats, however, human SGCs display a greater variety of ion channels and receptors compared with rodent SGCs.⁷ The specialization of human SGCs may relate to the observation that at the cellular level, glial cells in the CNS display more differences in the human evolutionary lineage than neurons.¹⁶³ Further studies are needed to explore SGCs across other species and other ganglia.⁸ Sex as a variable will also be a critical factor to consider when examining molecular features of SGCs. A recent study unraveled that the SGCs transcriptome differs between males and females in mouse DRG, and this could render SGCs in males (both mice and human) more susceptible to the degenerative actions of the chemotherapeutic agents.¹⁶⁴

THE WAYS SGCs CONTRIBUTE TO INJURY AND DISEASE

Despite being located in the periphery, SGCs are well positioned to contribute to the pathology of various brain diseases and post-injury sequelae in the CNS. This is because there is accumulating evidence that in many cases, such conditions are initiated in the periphery. For example, while sensory defects in neurodevelopmental disorders have been largely attributed to sensory processing abnormalities in the brain,¹⁶⁵ many core sensory and cognitive deficits may arise from earlier abnormalities in sensory inputs that drive subsequent abnormal development of cortical circuits.^{166,167} Impaired sensory perception, including a diminished sensory response to touch, smell, and sound also

occurs with normal advancing age. Dysfunction or loss of peripheral sensory axons can result in reduced sensory inputs to the brain and lead to pathological disturbances in the brain itself.¹⁶⁸ Olfactory loss is among the first clinical signs of neurodegenerative diseases including AD and Parkinson's disease.^{168,169} Impaired balance, which relies in part on proprioception, is affected in the very early stages of AD.¹⁷⁰ In the last decade, epidemiologic studies have also linked hearing loss to increased risk of dementia including AD.^{171–174} Hence, sensory dysfunction may be a pivotal factor that upregulates cognitive and memory dysfunction. Interestingly, we also know that SGCs are altered structurally and functionally with aging, as well as within some pathological contexts, including inflammation, chemotherapy-induced neuropathic pain, and nerve injury.^{175,176} SGCs in sympathetic ganglia may also contribute to disease pathologies and brain-body relevance. SGCs in sympathetic ganglia influence heart rate, a property thought to be intrinsic to sympathetic neurons,^{30,46} and are reactive in humans with heart failure and arrhythmias.²⁷

While there have been no studies directly linking SGCs to changes in brain circuits and functions, their close relationship with peripheral neurons suggests the need for further research into potential SGC-dependent mechanisms of CNS disease. Addressing this gap may reveal new ways to treat peripheral neuropathy and perhaps mitigate downstream effects on the brain.

Pain processing

SGCs have been studied in the context of pain responses and are known to modulate pain thresholds, which has been reviewed extensively elsewhere.^{14,37,177–180} The role SGCs play in buffering potassium (true in all SGCs across all ganglia) may be particularly relevant to their role in pain processing in health and disease. One recent study linked the stabilization of Kir4.1 at the surface of SGCs with relief from neuropathic pain.⁶⁸ Specifically, the authors find that GPR37L1 interacts with Kir4.1 to stabilize its surface expression, and that upregulation of GPR37L1 in SGCs (via intra-ganglionic injection of an AAV9 with *Fabp7* promoter) is sufficient to rescue neuropathic pain in a model of paclitaxel-induced neuropathy.⁶⁸ They show that the mechanism of rescue is via increasing expression of Kir4.1 and, thus, increasing potassium influx.⁶⁸ Interestingly, GPR37L1 mutations are associated with chronic pain in humans.⁶⁸ This mechanism may be significant in other ganglia as well; both *Gpr37L1* and *Kcnj10* are expressed in SGCs in TG,^{8,68} suggesting that this mechanism may play a role in migraine pain. Moreover, GPR37L1 is expressed by SGCs in nodose ganglia in mice,⁶⁸ suggesting a role for this receptor in sympathetic tone. Indeed, Kir4.1 ablation in SGCs in the sympathetic ganglia results in increased pupil dilation and heart rate, indicative of enhanced sympathetic tone.⁴⁶

ATP signaling in the DRG plays a crucial role in pain perception, acting on purinergic receptors in sensory neurons and SGCs.¹² A critical balance between exo-ATPase activity and purinergic receptor function in SGCs has been implicated in maintaining neuronal function and modulating pain processing.¹² Recent studies unravel a new layer of regulation of purinergic receptors, and hence, pain, via the ECM. The calcium-binding protein 2 (SMOC2), which is secreted by fibroblasts and incorporated into

the basement membrane enveloping SGCs, interacts with the P2X7 receptor on SGCs, suppressing its activity and the coupled activation of adjacent DRG neurons and dampening pain signaling.¹⁸¹ Another critical ECM component is the tissue inhibitor metalloproteinase 3 (TIMP3) expressed in the DRG of humans and mice, specifically in a subtype of SGCs. Research has shown that knockdown or blockade of TIMP3 (via antibody treatment) increases pain sensitivity, particularly in response to mechanical and thermal stimuli.⁵⁹ Consistent with this, TIMP3 expression is reduced in both DRG tissue and in cultured SGCs in a chemotherapy (paclitaxel)-induced neuropathic pain model.⁵⁹ In human DRG, differential expression of ECM genes produced by both fibroblasts and nociceptors was observed in samples with pain compared with no pain, reinforcing the importance of ECM components and metalloproteinases in neuropathic pain.¹⁸²

Nerve injury and repair

SGCs are sensitive to neuronal stressors. Morphological and molecular changes in SGCs have been observed in pathological conditions such as inflammation, chemotherapy-induced neuropathy, and nerve injuries.^{183–185} In some cases, such changes can result in pain or other sensory dysfunctions. In line with this, GFAP is currently the only widely used marker for SGCs reactivity following nervous system chemical or mechanical injury.^{183,186} One study used a rat model of peripheral nerve injury to determine the mechanisms by which SGCs react to nerve injury and express GFAP. They found that blocking electrical activity at the site of injury in the nerve with the sodium channel blocker tetrodotoxin (TTX) or bupivacaine prevents GFAP expression in SGCs,¹⁸⁷ suggesting that backpropagation of electrical activity along the axon to the neuronal soma is required to communicate injury to SGCs. However, important discrepancies between species and experimental models prevents the use of GFAP as a universal marker for SGCs reactivity.^{188,189} While GFAP is upregulated in both rat and mouse in an inflammation model, only rat demonstrated robust increase in GFAP in SGCs following sciatic nerve injury.¹⁸⁷ This is consistent with single-cell RNA-seq studies showing only few SGCs expressing *Gfap* after nerve injury in mice.^{15,189}

Recent studies have used single-cell transcriptomics to better understand the response of SGCs to nerve injury. These studies have revealed that mechanical nerve injury induces numerous transcriptional changes in SGCs. In addition to *Gfap*, genes involved in lipid metabolism and peroxisome proliferator activated receptor alpha (PPAR α) signaling are upregulated in response to mechanical nerve injury in SGCs.^{16,17} Using a transgenic mouse line specifically targeting SGCs in the PNS (*Fabp7-creER* line), the authors selectively deleted fatty acid synthase (*Fasn*) in SGCs and found that axon regeneration was reduced, highlighting that lipid-dependent pathway operating in SGCs regulate nerve repair.¹⁶ The precise molecular mechanisms downstream of lipid signaling in SGCs that regulate axon growth capacity remains to be established, but a possible mechanism is via the secretion of ApoE. Peripheral nerve injury results in increased expression and secretion of apolipoprotein E (ApoE), a PPAR α target gene, by non-neuronal cells in the nerve^{190,191} and ApoE was shown to be involved in the provision of lipids required for axon growth and regeneration.^{192,193}

Another way by which SGCs can assist with nerve repair is via their stemness properties, replenishing neurons lost to injury. Indeed, in adult rodents, 20%–50% of sensory neurons die after sciatic nerve injury, but the number recovers to normal level over time.^{194–198} These studies suggest that adult neurons lost to mechanical or chemical insult can be replaced by newly born ones. While the presence of cells with stemness potential¹⁹⁹ in the adult DRG has been controversial, multiple *in vitro* studies and more recently *in vivo* studies now support the idea that a pool of DRG stem cells can self-renew and give rise to new neurons.^{194–198} The stemness potential of adult DRG was initially assessed *in vitro*, based on explant cultures in which cells emerge from the explant and proliferate to form multipotent spheres that give rise to neurons, glial cells, and myofibroblast.^{200,201} These stem cells have been proposed to be SGCs.^{197,198,200} In support of SGCs stemness potential, recent molecular analyses of SGCs revealed that adult SGCs retain expression of genes related to glial progenitor and pluripotency, such as *Nestin*, *Foxd3*, *Sox2*, and *Sox10*.^{15,197,202} Furthermore, cultured SGCs can differentiate into nociceptive-like neurons under certain culture conditions.²⁰² *In vivo*, in adult mouse DRGs, *Nestin*-positive SGCs can differentiate into new SGCs under homeostatic conditions, or into sensory neurons after nerve injury,¹⁹⁷ suggesting that adult SGCs multipotency is strongly modulated by the environment.^{200,203} Together, these studies indicate that similar to the subventricular zone and the dentate gyrus in the CNS,¹⁹⁹ DRG harbor stem cells that can maintain DRG homeostasis. However, many questions remain to be answered. What are the signaling mechanisms that regulate SGC stemness potential under physiological and pathological conditions? Do all SGCs retain stemness potential or is there a unique SGC subtype that possesses stemness? Future studies are needed to understand the origin and mechanisms by which the progenitor properties of SGCs are regulated in homeostasis and under injured conditions, and the extent to which such processes support greater plasticity of the somatosensory system.

ASD

Recent studies indicate that neuron-SGC signaling is disrupted in mouse models of autism. For example, in a mouse model of syndromic autism spectrum disorder (ASD), disruption of SGCs covering the soma of spiral ganglia neurons contributes to auditory nerve dysfunction and ASD-related phenotypes.²⁰⁴ Changes to the peripheral auditory system may thus contribute to auditory hypersensitivity and intolerance of ordinary environmental sounds commonly seen in ASD patients.²⁰⁵ This is similar to what is observed in studies of mouse models of fragile X syndrome, in which SGCs covering the soma of neurons in the DRG are disrupted,¹⁸ suggesting that altered neuron-glia communication may contribute to sensory deficits in this condition. Indeed, somatosensory deficits, including hypersensitivity to auditory, visual, and tactile stimuli,²⁰⁶ are among the most common features of ASD. Increasing evidence suggests that sensory hypersensitivity may contribute or even cause behavioral alterations such as poor eye contact, anxiety, and impaired social interactions.²⁰⁷ These sensory deficits have been thus far largely attributed to alterations in cortical sensory processing.¹⁶⁵ However, core cognitive and sensory deficits may arise from an earlier abnormality in sensory inputs that

drive subsequent abnormal development of cortical circuits.^{166,167} Thus, the findings that neuron-SGCs signaling may also be disrupted in ASD suggest that SGCs signaling mechanisms may be a key part of early cortical circuit development.

Neurodegenerative diseases

A role for SGCs in the pathophysiology of some neurodegenerative conditions has already been shown definitively, including in Friedreich ataxia (FA), amyotrophic lateral sclerosis (ALS), chemotherapy-induced neuropathy, and aging.^{2,19,20,208} FA is an autosomal recessive neurodegenerative disease whose first symptom is degeneration of the proprioceptive sensory neurons of the DRG.¹⁹ In human with FA, SGCs proliferate and form gap junctions and abnormal layers around the neurons.¹⁹ A recent study using a mouse model of FA suggests that proprioceptor dysfunction could potentially initiate and exacerbate the SGCs responses observed in FA patients.⁴⁵ This study demonstrated that proprioceptor dysfunction is sufficient to induce sequential changes in SGCs and macrophages, mirroring the temporal signatures of FA ganglionopathy progression.⁴⁵

ALS is the most common neurodegenerative disease affecting motor neurons. However, the condition also leads to sensory system impairment.²⁰⁹ A small percentage (20%) of cases have a familial origin linked to mutations in specific causal genes such as SOD1.²⁰⁹ SGCs have been identified as a key pathophysiological target in the superoxide dismutase (SOD1) transgenic murine model of ALS, highlighting the pathogenic role of glial cells in motor neuron disease. Histological analysis of SGCs in the SOD1G93A mouse model reveals abnormal accumulation of SOD1, which is associated with nitro-oxidative stress and the formation of lipid droplets within these cells.²⁰ These changes lead to the progressive development of a lysosomal storage disorder, and, in some cases, vacuolar degeneration in SGCs. This may not only contribute to sensory disturbances in ALS but, due to its impact on spinal cord sensory-motor circuits, may also play a role in motor dysfunction in the anterior horn.²⁰

SGCs are also impacted in mouse models of chemotherapy-induced neuropathy.^{177,183} Thinking and memory problems can develop in cancer patients during and after chemotherapy,²¹⁰ the mechanisms of which are not fully understood. However, the effect of chemotherapy on the brain is likely to be indirect, since most chemotherapy drugs are non-brain targeted and usually fail to cross the BBB.^{211,212} Inflammatory neurotoxic agents released in the periphery are believed to be the primary contributors to chemotherapy-induced neuropathy, but alteration to SGCs, and thus sensory input to the brain is another possible mechanism that warrants future study.¹⁶⁴

Finally, there are reports of age-related changes in SGCs morphology²⁰⁸ and SGCs gap junction coupling.^{54,151,213} Reduced SGCs volume and coverage of the neuronal soma^{54,208} combined with altered gene expression⁵⁴ suggest that SGCs may contribute to age-dependent decreases in sensory and autonomic functions, which in turn promote pathological disturbances in several brain areas. In some cases these disturbances precede cognitive decline and memory dysfunction¹⁶⁸ and are considered a risk factor for cognitive decline.^{171–173}

Thus, it is tempting to speculate that SGCs, by regulating the transmission of peripheral information, contribute to shaping

neuronal circuits in the brain. A better understanding of how SGCs regulate neuron function may thus provide avenues to not only treat peripheral dysfunctions but also alleviate the subsequent alterations in cognitive functions.

CONCLUDING REMARKS

SGCs are pivotal players in the development, function, and pathology of the PNS. Their tight physical connection to neuronal soma, along with their ability to respond to internal and external physiological changes, allows them to significantly shape the function of neuronal networks within the PNS. SGCs share fundamental characteristics across species as well as across the different types of ganglia. As ongoing research continues to explore the full scope of their molecular and functional diversity, we are likely to learn of more ways SGCs regulate PNS functions and how they can in turn influence CNS functions. To support this progress, we need to continue to innovate tools that allow for specific and targeted manipulations of SGCs. In addition to *in vitro* models of SGCs, precise genetic tools to target SGCs specifically *in vivo* are needed. Indeed, while several genetic mouse lines have been used to manipulate SGCs in DRG and sympathetic ganglia (summarized in Birren et al.¹²⁸), none of these lines exclusively target SGCs. For example, the *Fabp7-creER* mouse line has become a useful tool to specifically manipulate SGCs in the DRG and sympathetic ganglia, labeling >90% of these populations without affecting SCs.^{16,28} However, *Fabp7* is also expressed in astrocytes,²¹⁴ limiting the use of this line to analysis of the PNS. While *Pip1-cre* and *S100b-cre* lines can be used to target most SGCs in DRG and spiral ganglia,^{29,42,159,215} these lines are generally used to target SCs. Intersectional genetics approaches may make it possible to target SGCs specifically and exclusively. Such new tools would allow researchers to directly test whether and how SGCs impact brain circuits and function. In addition, extending studies of SGCs to human tissue in donors with different medical histories may allow identification of new ways to treat human nerve injuries and other pathological conditions of the PNS. Ultimately, deepening our understanding of how SGCs contribute to sensory, sympathetic, and auditory system function is critical to the development of novel therapeutics to treat peripheral neuropathies and sensory disorders.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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