Editorial

Fibromyalgia: a satellite gliopathy?

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The mechanisms leading to fibromyalgia have not been elucidated, and the prevailing theory considers "central sensitisation" the main driver of fibromyalgia pain (1). The International Association for the Study of Pain (IASP) defines central sensitisation as "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input". This IASP definition makes clear that in central sensitisation, "peripheral neurons are functioning normally; changes in function occur in central neurons only" (2).

An alternative theory views fibromyalgia as a stress-related, sympathetically maintained neuropathic pain syndrome. This latter hypothesis posits that the paravertebral dorsal root ganglia (DRG) are located at the epicentre of fibromyalgia pain (3, 4). Various stressors can induce DRG phenotypic modifications, leading to chronic pain. DRG have unique pro-algesic physio-anatomy in which metabolically active satellite glial cells (SGCs) closely interact with pain-sensing neuronal soma. Similar SGC-neuron interactions are also observed in the paravertebral sympathetic ganglia (5). Sympathetic nervous system dysfunction may explain the multisystem symptoms of fibromyalgia (6). This article reviews the unique pronociceptive physio-anatomy of SGCs as well as emerging evidence suggesting that DRG SGCs may play an important role in fibromyalgia pain. Our literature review strategy included searching the PubMed database with the key words "satellite glial cells" in quotation marks and linking the words "fibromyalgia" with "satellite glial cells".

The unique pain-inducing physio-anatomy of satellite glial cells

SGCs are located in the peripheral nervous system. SGC precursors originate in the neural crest and are closely related to Schwann cells. SGCs completely wrap around each of the pain-sensing neuron cell bodies located in the DRG (Fig. 1). The gap between SGCs and the encased neuronal cell body is approximately 20 nm, which is similar to that of the synaptic cleft in the central nervous system; this closeness allows bidirectional neuron-SGC interplay (5, 7). SGCs maintain contact with other SGCs or with enclosed neurons via mainly cadherin 19 and connexin 43 (8). Gap junctions allow cytoplasmic communication between adjacent SGCs; therefore, activated SGCs may respond as syncytia (5).

Upon activation, SGCs upregulate and/or release different bioactive molecules, including glial fibrillary acidic protein, S100 protein, glutamate synthase, inwardly rectifying K channel subunit 4.1 (Kir4.1), adenosine triphosphate (ATP), and a variety of cytokines. SGCs in the DRG are activated by nerve injury and by different types of inflammatory and/or stressful conditions, leading to chronic pain (5, 7). SGCs can act as immune cells expressing macrophage markers, including MHC type II and CD40 (5). Apart from the DRG, no other body region displays this tight anatomical and physiological interplay between inflammatory immune-competent cells and pain-transmitting nerves.

Satellite glial cell functional diversity

Single-cell RNA sequencing data reveal the functional diversity of DRG SGCs (9-12). Most SGCs express high levels of ApoE protein and other lipid-related genes, providing metabolic support to neurons (10, 11). Other SGC subgroups are enriched in genes related to glutamate metabolism, including genes encoding glutamate transporters and glutamine synthetase, which interact with glutamatergic sensory neurons (10, 11).

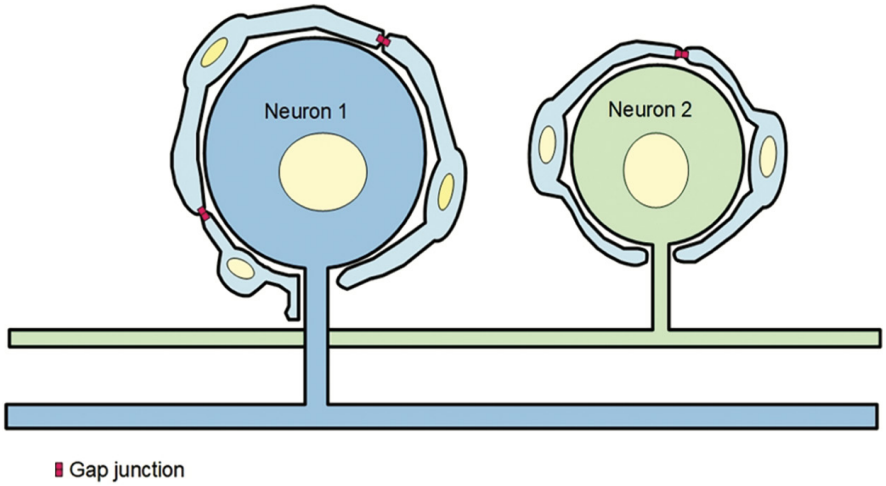

Fig. 1. Satellite glial cell tightly encase pseudo-unipolar dorsal root ganglion pain-transmitting neurons.

SGCs also express immune signalling genes, including interferon, antibacterial and antiviral genes (10).

The role of satellite glial cells in chronic pain

After trauma and/or inflammation, DRG SGCs display different pain-promoting changes, including enhanced gap junction coupling with the encased neuron, downregulation of the Kir4.1 channel, upregulation of glial fibrillary acidic protein and increased ATP sensitivity. Upon activation, SGCs release pronociceptive cytokines, including substance P, interleukin 1β, and tumour necrosis factor-α. These cytokines can activate nociceptive neurons (13). In addition, environmental stress can stimulate SGCs, and several murine models have demonstrated that stressors such as chronic restraint or water avoidance facilitate allodynia via overproduction of substance P and interleukin-1β in SGCs as well as reduced Kir4.1 expression (14-16).

SGCs may play a role in sympathetically maintained pain. DRG SGCs but not neurons express G_s-coupled β2 adrenergic receptors. Different stressors induce sympathetic sprouting in the DRG. Norepinephrine can induce SGCs activation through cyclic adenosine monophosphate response element-binding protein (CREB) phosphorylation. DRG sympathetic sprouting induces β2 adrenergic receptor overexpression in SGCs, leading to CREB phosphorylation and visceral hypersensitivity (17, 18).

Satellite glial cells in the sympathetic ganglia

There is a direct anatomical connection between the DRG and the paravertebral sympathetic ganglia (3). Similar to what is observed in the DRG, SGCs also wrap-up neurons in the sympathetic ganglia. SGCs play important roles in both the development and maintenance of sympathetic function. A main difference between SGCs in the sympathetic ganglia and in the DRG is the presence of synapses in the sympathetic ganglia, where SGCs overlay synapses and may control synaptic transmission (4). SGCs modulate cholinergic transmission between sympathetic neurons (19). Nerve injury increases interactions between the sympathetic ganglia and nearby DRG. Damage causes sympathetic fibre sprouting in the DRG and SGC activation with immune cell infiltration in the adjacent sympathetic ganglia (5). These alterations may lead to sympathetically maintained pain.

Unfolding evidence of the role of dorsal root ganglion satellite glial cells in fibromyalgia pain

Several lines of investigation support the longstanding proposal that the DRG are located at the epicentre of fibromyalgia pathogenesis (3, 4, 20). The DRG house the small nerve fibre soma, and there is a clear link between fibromyalgia and small-fibre neuropathy. The animal model is clear; diverse stressful impulses, including physical stress, lead to DRG phenotypic changes with the ensuing chronic pain development (4). Recent investigations have proposed that DRG SGCs are important players in fibromyalgia development: Mice receiving immunoglobulin G from patients suffering from fibromyalgia display mechanical and cold hypersensitivity accompanied by reduced intraepidermal nerve fibres, and immunoglobulin G is exclusively deposited in mouse DRG SGCs (21). Furthermore, patients suffering from fibromyalgia with high anti-SGC IgG levels had greater pain intensity and a worse disease status than patients with low anti-SGC IgG levels did (22).

Using primary cell cultures, our research group measured the acute effects of human serum on nociceptive DRG cells. The results revealed that serum taken from fibromyalgia sufferers induces more intense and widespread stimulation of DRG SGCs than does that from healthy individuals. This new information has been published in an abstract form (23), but it has not yet been printed in a peer-reviewed journal.

Future research

Focusing on DRG opens new avenues for fibromyalgia research. Advanced imaging techniques could be used to estimate DRG glial metabolic activity. Ground-breaking research has revealed the presence of anti SGCs antibodies in patients suffering from fibromyalgia, and defining the antigenic specificity of these antibodies is important. Acute stimulation of DRG pronociceptive cells may be able to define which fraction of patient serum is responsible for glial cell kindling.

Concluding remarks

Longstanding research has proposed DRG as an important player in the pathogenesis of fibromyalgia (3, 4, 20). New information suggests that DRG SGCs are able to transform different emotional, physical, infectious and/or autoimmune stressors into biochemical signals that can activate primary pain-sensing neurons. The search for peripheral pain generators in persons suffering from fibromyalgia may lead to the development of precision analgesics free from the current opioid addictive side effects.

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