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Unveiling the significance of peripheral nervous system glia: implications for nervous system disorders and therapeutic interventions

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ABSTRACT

Glial cells are indispensable components of the peripheral nervous system (PNS), exerting diverse regulatory functions crucial for neuronal health and function. From myelination and synaptic modulation to immune regulation, glia actively participates in maintaining PNS homeostasis and responding to pathological insults. Further elucidating the roles of glial cells in peripheral nerve disorders holds promise for developing targeted therapeutic interventions to alleviate symptoms and improve patient outcomes. This article reviews the multifaceted functions of PNS glia in shaping nervous system function and their intricate involvement in various neuropathologies, including peripheral neuropathies, neuroinflammatory conditions, and gastrointestinal disorders. Understanding the underlying mechanisms of glial dysfunction

offers opportunities for developing targeted therapeutic interventions aimed at preserving nerve function, attenuating neuroinflammation, and restoring gastrointestinal homeostasis. The expanding research on PNS glia underscores their indispensable roles and highlights the potential of therapeutic strategies targeting glial dysfunction in revolutionizing the management of nervous system disorders, offering hope for improved patient outcomes and quality of life.

Keywords: Schwann cells, satellite cells, enteric glia, glial dysfunction, nervous system disorders, therapeutic strategies

INTRODUCTION

The peripheral nervous system (PNS) constitutes a fundamental component of the broader nervous system, serving as a vital communication network between the central nervous system (CNS) and the body's organs and tissues. Within the PNS, an intricate network of glial cells plays a pivotal role in orchestrating essential functions crucial for neuronal health and maintaining physiological balance [31]. While neurons have traditionally been spotlighted as the primary actors in neural function, recent insights have illuminated the significant regulatory roles of PNS glial cells. Once perceived as merely supportive, glial cells are now recognized as indispensable contributors to PNS health and function. Despite neurons historically monopolizing neuroscientific investigation, mounting evidence underscores the pivotal roles of PNS glia in modulating neuronal activity, preserving axonal integrity, and coordinating immune responses. Glial dysfunctions in the PNS, particularly involving Schwann cells and satellite cells, can lead to impaired nerve signal transmission and support. This contributes to conditions such as peripheral neuropathies, where damaged glial cells fail to maintain proper myelination and neuronal health, resulting in muscle weakness, pain, or sensory disturbances [16, 31]. This review comprehensively examines the multifaceted contributions of PNS glia to nervous system function, elucidating their involvement in various disorders, and exploring emerging therapeutic strategies aimed at addressing glial dysfunction [16, 31, 40].

TYPES OF GLIAL CELLS IN THE PERIPHERAL NERVOUS SYSTEM

In the PNS, the main glial cells are Schwann cells, satellite cells, and enteric glia (Fig. 1). These cells differ from each other and are classified based on morphology, distinct locations in the nervous system, function, development al origin, and unique molecular composition [30].

Schwann cells

Schwann cells are glial cells named after Theodor Schwann, the founder of modern histology. They are considered some of the largest and structurally most complex cells in the human body [15]. During their developmental, Schwann cells occur as: Schwann cell precursors, immature, non-myelinating Schwann cells, and mature, myelinating Schwann cells [18]. As the main type of glia in the peripheral nervous system, they participate in the formation of the myelin sheath, transmission of nerve impulses, and secretion of various neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), nerve growth factor (NGF), and neurotrophin-3 (NT-3), as well as extracellular matrix components that provide a favorable microenvironment for neuron survival and axon growth [20] (Fig. 2). During development, Schwann cells promote neuron survival and participate in the formation of their axons. At the same time, they coordinate the architectural development of developing nerves, including blood vessels and nerve fibers, epineurium, perineurium, and endoneurium [6].

Satellite glial cells

Satellite glial cells are found in the sensory ganglia of the PNS as well as in the autonomic ganglia, where they form a tight sheath around neuronal bodies [2, 13]. They are the most numerous glial cells in the sensory ganglia, and therefore, they are believed to play an important role in sensory functions [12]. Satellite cells constantly and completely surround ganglionic neurons in the form of one or, less commonly, two or three concentric layers, collectively forming morphological and functional units with them (Fig. 3). Satellite glial cells are small, flattened, and interconnected by gap junctions. Close relationships between them and ganglionic neurons also enable mutual communication, in which one of the main messengers is nitric oxide [24]. These glial cells are functionally like astrocytes, as both astrocytes and satellite cells, being the main homeostatic glial cells, seem to perform similar functions [2].

Enteric glia

The last type of glia present in the peripheral nervous system is enteric glia [37]. It is a large population of non-myelinating peripheral glial cells derived from neural crest precursor that colonize the gastrointestinal tract during embryonic development [11]. Enteric glia constitutes a population of cells associated with the perikarya and processes of enteric neurons along the entire length of the gastrointestinal tract (Fig. 4). It is one of the most dynamic components of the enteric nervous system signaling. Rapid bidirectional communications between enteric glia and neurons regulates gastrointestinal reflexes and communications between neurons outside the nervous system and interneurons that innervate the gastrointestinal tract [37]. Enteric glia actively participates in immune responses in the intestine. Thus, it is essential for maintaining gastrointestinal functions and has a significant impact on the physiology and pathophysiology of the intestine [11].

GLIAL DYSFUNCTION AND NERVOUS SYSTEM DISORDERS, PERIPHERAL NEUROPATHIES

Glial cells in the peripheral nervous system (PNS) fulfill critical roles in maintaining neuronal health and function. Dysfunction of these cells is linked to the development of a range of nervous system disorders, including peripheral neuropathies, neuroinflammatory conditions, and gastrointestinal disorders. A deeper understanding of the mechanisms underlying glial dysfunction could pave the way for targeted therapeutic interventions designed to preserve nerve function, reduce neuroinflammation, and restore gastrointestinal balance. Diseases or injuries often disrupt the normal functioning of glial cells and the axons of neurons. For instance, demyelination or dysmyelination of Schwann cells is a hallmark of various peripheral neuropathies, influenced by genetic factors (such as Charcot–Marie–Tooth disease), autoimmune responses (like Guillain–Barré syndrome), metabolic disturbances (observed in diabetic neuropathy), or mechanical stress, all of which can lead to sensory and motor deficits. Beyond demyelination, dysfunction in the axonal support mechanisms provided by Schwann cells can result in axonal neuropathies, which are characterized by axonal degeneration and impaired nerve conduction. In conditions like diabetes mellitus, peripheral nerve damage is commonplace, with Schwann cell dysfunction significantly contributing to sensory neuropathies. These are typically marked by neuropathic pain, sensory loss, and the development of foot ulcerations. Additionally, hereditary forms of axonal neuropathies, such as hereditary sensory and autonomic neuropathy (HSAN), arise from genetic mutations that disrupt Schwann cell-neuron interactions, leading to pronounced sensory and autonomic dysfunctions [3, 28, 30]. Aberrant satellite cell function contributes to

sensory neuropathies, such as diabetic neuropathy, characterized by neuropathic pain and sensory loss. In autoimmune neuropathies like chronic inflammatory demyelinating polyneuropathy (CIDP), Schwann cells mount immune responses against peripheral nerves, exacerbating demyelination and nerve dysfunction [14].

Enteric glia, which outnumber neurons in the enteric nervous system, play a fundamental role in supporting their function and survival. There is also evidence that enteric glia may have multiple immune functions and thus participate in gut homeostasis. Therefore, interest has been raised in its involvement in immune disorders [22, 36]. Enteric glia may participate in pathological conditions through several mechanisms. For example, these cells may present disease-associated antigens to modulate gut acquired immunity and are able to indirectly or directly penetrate the epithelial layer and effect its integrity [8, 23]. They could also respond to pro-inflammatory cytokines from other immune cells and enhance inflammation. Studies confirm the hypothesis that enteric glial cells act as immunomodulatory cells in the enteric nervous system [34]. Their role has been identified in gastrointestinal diseases such as inflammatory bowel disease, celiac disease, or autoimmune enteropathy [22]. Dysregulated enteric glial cell responses contribute to gastrointestinal disorders, including inflammatory bowel diseases and irritable bowel syndrome, affecting gut motility and epithelial barrier integrity. Inflammatory conditions affecting the gastrointestinal tract, such as Crohn's disease and ulcerative colitis, are associated with dysregulated enteric glial cell responses and neuroinflammation within the enteric nervous system (ENS). Altered glial-neuronal signaling and immune activation contribute to gastrointestinal symptoms, including dysmotility, visceral hypersensitivity, and inflammation. Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain, bloating, and altered bowel habits. Dysfunctional enteric glial-neuronal communication and aberrant glial activation within the ENS contribute to visceral hypersensitivity and gastrointestinal dysmotility, implicating enteric glial dysfunction in the pathophysiology of IBS [33].

Glial diversity and function in the PNS

Schwann cells are integral to the process of myelinating peripheral nerve fibers, whereby they form insulating layers of myelin around axons. This myelination process serves to expedite the propagation of action potentials, thereby enhancing nerve conduction velocity and preserving signal fidelity. Additionally, Schwann cells play a multifaceted role beyond myelination. They provide metabolic support to axons by supplying nutrients and eliminating waste products, thereby ensuring the sustained function and integrity of the neuronal fibers.

Moreover, Schwann cells are actively involved in axonal maintenance and repair mechanisms, thereby promoting neuronal survival and functionality. Furthermore, Schwann cells secrete a variety of neurotrophic factors, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). These trophic factors are instrumental in fostering neuronal survival, promoting axonal growth, and facilitating synaptic plasticity. Their contributions are particularly crucial during nerve development, regeneration following injury, and the ongoing maintenance of neuronal circuits [27, 35].

Satellite cells, on the other hand, envelop neuronal cell bodies within sensory and autonomic ganglia, establishing intimate associations with neurons. This unique organization is not found elsewhere in the nervous system. In addition to providing structural support, satellite cells regulate the microenvironment surrounding neurons, thereby modulating neuronal excitability and neurotransmitter release. They are actively involved in maintaining ion concentrations around neuronal cell bodies, ensuring the optimal ionic milieu necessary for proper neuronal function. This regulatory role is facilitated through the expression of various ion channels and transporters by satellite cells, which influence neuronal excitability and synaptic transmission. Moreover, satellite cells contribute to neurotransmitter recycling within ganglia, aiding in the clearance of neurotransmitters released during synaptic transmission. This function is essential for maintaining synaptic efficiency and preventing the accumulation of neurotransmitters, thereby ensuring the fidelity of neuronal communication within the ganglia. Satellite cells in sensory ganglia are activated by various types of nerve injuries and inflammatory conditions. Activation includes, among other things, expression of acidic fibroblast growth factor, stronger coupling of satellite cells with each other and neurons via gap junctions, increased sensitivity to ATP, or increased synthesis and release of cytokines. There is evidence that changes in satellite cells contribute to chronic pain by increasing neuron al activity [14, 17, 29].

Enteric glial cells are integral components of the enteric nervous system (ENS), regulating gastrointestinal functions such as gut motility, secretion, and epithelial barrier integrity. They modulate synaptic transmission within the ENS by regulating the release and uptake of neurotransmitters, including acetylcholine, serotonin, and ATP. They influence neuronal excitability and synaptic plasticity, shaping gut motility and sensory responses. These cells participate in immune regulation within the gut, interacting with immune cells and secreting cytokines and chemokines in response to inflammation or injury. They contribute to the maintenance of gut immune homeostasis and participate in mucosal immune responses [33, 37].

Interactions and crosstalk

Glial cells in the PNS are not merely passive support structures but are dynamic participants in the regulation of nervous system function. They form elaborate networks with neurons and other types of glial cells, through which they play critical roles in signal reception and integration. These cells are essential for the modulation of neuronal activity and for coordinating physiological responses across the nervous system. Neurons communicate with glial cells by releasing neurotransmitters and neuromodulators that can drastically alter glial behavior and functionality. In response, glial cells secrete their own repertoire of signaling molecules, such as cytokines and chemokines, which in turn influence neuronal excitability and regulate synaptic transmission. This complex interplay of signals between neurons and glial cells is crucial for the maintenance and modulation of neural circuits [10, 38]. Furthermore, this bidirectional communication is pivotal in several key aspects of neurophysiology including neuronal development, where glial cells play essential roles in guiding the formation of neuronal connections and in synaptic pruning — a process vital for the development of efficient and effective neural networks. During synaptic plasticity, glial cells respond to neuronal activity by adjusting the synaptic environment, thus influencing the strength and efficacy of synaptic transmission. This capacity of glial cells to modulate synaptic strength is crucial for learning and memory. Glial cells also contribute to the maintenance of the homeostatic balance of ions and neurotransmitters in the extracellular space. They help in the reuptake of neurotransmitters and metabolic products, thereby preventing neurotoxicity and maintaining the chemical environment necessary for optimal neuronal function. The involvement of glial cells extends to the neural circuit function, where they respond to changes in neuronal activity by modulating the availability of nutrients and oxygen and by removing waste products. This ensures that neurons have the resources required for sustained activity during periods of heightened demand, such as during prolonged phases of learning [4, 7].

Therapeutic strategies targeting glial dysfunction

Therapeutic strategies targeting glial dysfunction in peripheral nerve disorders include a broad spectrum of approaches, such as promoting remyelination, immunomodulation, glial cell replacement, and the application of emerging technologies. Advancements in glial biology, combined with these innovative therapeutic modalities, are poised to transform the treatment of nervous system disorders and enhance patient outcomes. Traumatic injury to

peripheral nerves poses a significant clinical challenge, often leading to substantial functional impairment and permanent disability. Despite advancements in medical techniques, the functional recovery following peripheral nerve repair frequently remains unsatisfactory. This underscores the urgent need for novel therapeutic or supportive strategies to aid recovery. Severe peripheral nerve injuries may result in the loss of Schwann cells, which are crucial for regeneration. In conditions of chronic axonal injury, denervated Schwann cells gradually lose their capacity to support neuronal growth. Consequently, the depletion of healthy Schwann cells becomes a major obstacle in nerve regeneration, sparking a growing interest in cell therapy as a potential solution [25].

Cultures of Schwann cells have shown beneficial results in experimental models of traumatic injury to peripheral nerves with regeneration and remyelination [5, 32]. Myelin loss is a hallmark of several peripheral neuropathies, contributing to impaired nerve conduction and axonal degeneration. Therapeutic approaches aimed at promoting remyelination by Schwann cells represent a promising strategy for restoring axonal integrity and function. Small molecules, growth factors, and gene therapy techniques can be employed to stimulate Schwann cell proliferation and differentiation, fostering the generation of new myelinating cells and facilitating remyelination [21].

Modulating signaling pathways crucial for Schwann cell development and myelination, such as the neuregulin-1/ErbB signaling pathway, holds promising therapeutic potential for promoting remyelination in demyelinating neuropathies. The transplantation of Schwann cells or Schwann cell precursors, sourced either from autologous or allogeneic origins, represents a compelling strategy for delivering myelinating cells to nerve injury sites and fostering remyelination [35].

In autoimmune neuropathies characterized by misguided immune activation against peripheral nerves, immunomodulatory therapies aim to temper glial-mediated immune responses and alleviate neuroinflammation. Corticosteroids, immunosuppressive agents (e.g., azathioprine, methotrexate), and intravenous immunoglobulin therapy are commonly employed to mitigate inflammatory responses and attenuate Schwann cell-mediated immune reactions, particularly in conditions like chronic inflammatory demyelinating polyneuropathy (CIDP). Monoclonal antibodies targeting specific immune cell populations or pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) inhibitors or interleukin-6 (IL-6) antagonists, offer targeted strategies for modulating immune-mediated neuroinflammation [39].

Stem cell-based therapies hold considerable promise for replenishing dysfunctional glial populations and promoting nerve repair in peripheral neuropathies characterized by glial cell loss or dysfunction. Delivery of exogenous glial progenitor cells, derived from embryonic, induced pluripotent stem cells (iPSCs), or tissue-resident progenitors, offers a means to replenish depleted glial populations and support remyelination in demyelinating neuropathies. Patient-specific iPSCs can be differentiated into glial lineage cells and subsequently transplanted into the injured nervous system, providing a personalized approach for cell replacement therapy in peripheral nerve disorders [19, 41].

Gene editing technologies, such as CRISPR-Cas9, show promise for correcting genetic mutations responsible for glial dysfunction in inherited neuropathies, offering potential cures or disease-modifying treatments. Nanoparticle-based delivery systems can be harnessed to target therapeutic agents specifically to glial cells, thereby enhancing drug delivery efficiency and minimizing off-target effects. Additionally, biomaterial scaffolds and tissue engineering approaches can be employed to create supportive microenvironments for transplanted glial cells, facilitating their integration into host tissues and augmenting therapeutic outcomes [1, 9, 26].

An enhanced understanding of PNS glial cells and their functions offers a promising strategy for addressing a range of disorders arising from disruptions in PNS homeostasis. Furthermore, elucidating the role of PNS glial cells in immune system regulation provides critical insights that could significantly influence the treatment of prevalent human diseases. This comprehensive approach to studying glial cells underscores their potential as therapeutic targets in neurology and immunology, highlighting the necessity for further research into their complex roles within the PNS.

ARTICLE INFORMATION AND DECLARATIONS

Author contributions

AW — writing manuscript, literature review, linguistic correction, supervision; I K-M — writing manuscript; AŻ — literature review; MK — literature review; JW — content-related supervision, linguistic correction; GW — literature review, linguistic correction; KB — writing manuscript, literature review.

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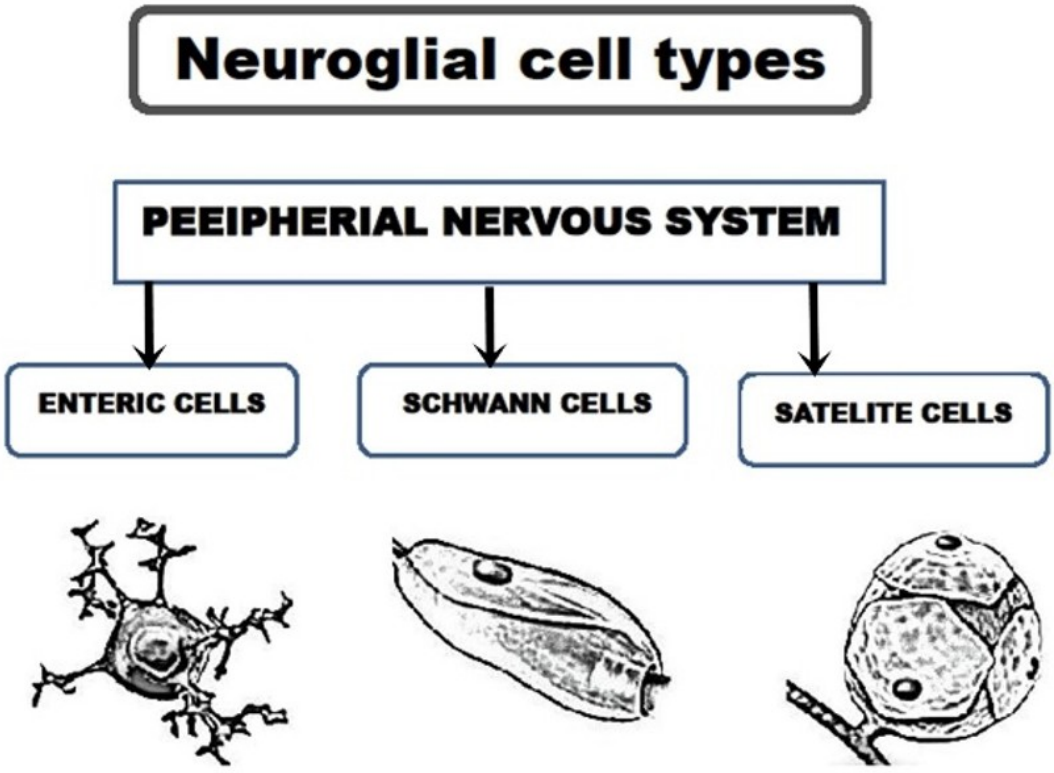

Figure 1. The diagram shows the types of glial cells in the peripheral nervous system (PNS). **Intestinal cells:** These cells line the walls of the intestines, facilitating nutrient absorption, digestion, and maintaining a protective barrier against harmful substances. **Schwann cells:** Found in the peripheral nervous system, Schwann cells insulate nerve fibers by forming

myelin sheaths, which enhance nerve signal transmission. **Satellite cells:** These cells surround neuron cell bodies in the peripheral nervous system, providing structural support, regulating the microenvironment, and aiding in repair and regeneration after injury.

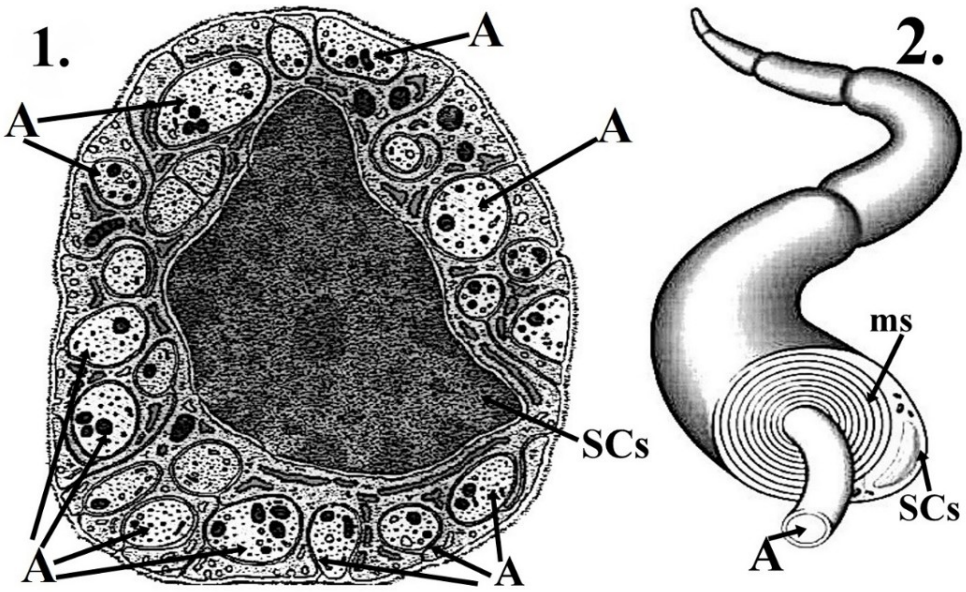

Figure 2. The illustration shows an unmyelinated fiber (**1**) and a myelinated fiber (**2**). In unmyelinated fibers of the PNS, axons (A) lie in groove-like invaginations of the Schwann cell (SCs) cytoplasm (Schwann sheath). In myelinated nerve fibers, the axon (A) is surrounded by a myelin sheath (ms) produced by the Schwann cell (SCs).

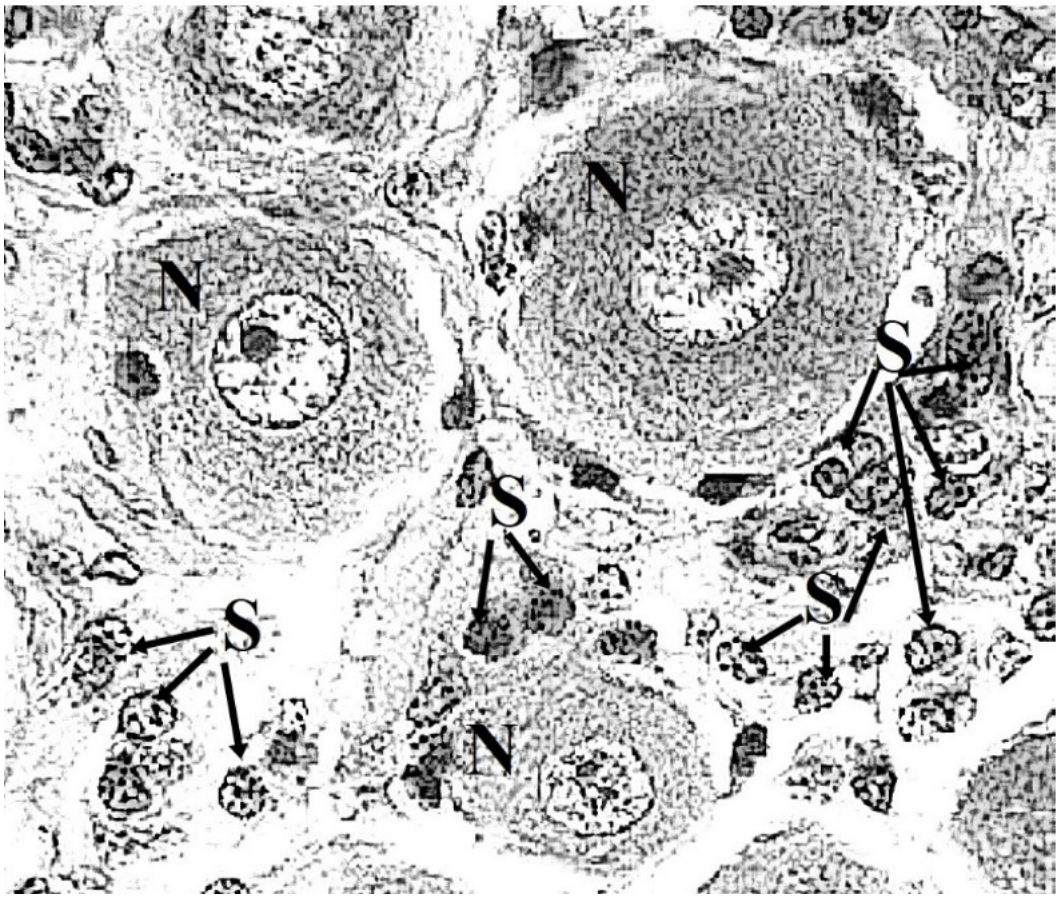

Figure 3. The illustration shows satellite cells (S) surrounding ganglion neurons (N).

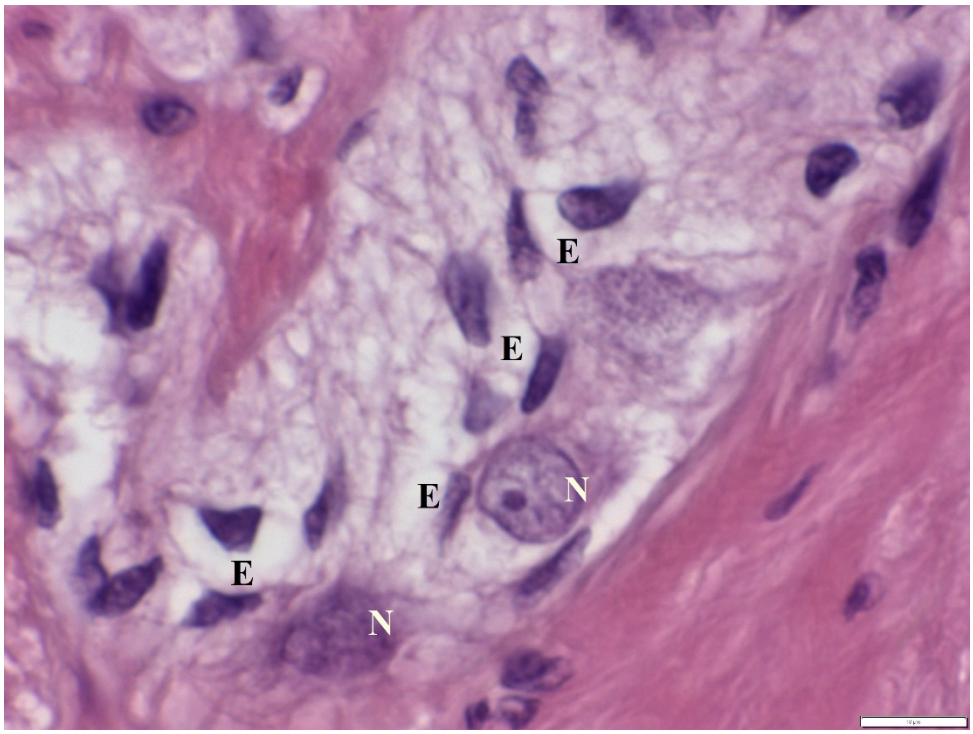

Figure 4. The micrograph of the rabbit small intestine reveals enteric glial cells (E) surrounding the perikaryons of neurons (N) within the myenteric plexus, situated between the circular and longitudinal layers of the tunica muscularis. H&E stain, scale bar 10 μm. Magnification: 60×.