REVIEW

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The intriguing perineurial cells – an updated overview of their origin, structure, functions and implication in pathology

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Abstract

The paper overviews the uniquely intricate and distinct perineurium that envelops nerve fibers in bundles. It consists of perineurial cells (PCs), connective tissue, and blood vessels. The perineurium creates a microenvironment for efficient signal transmission, protects and maintains neuronal structure and function, and facilitates neuronal repair. PCs are a unique type of myofibroblasts essential for maintaining nerve homeostasis. They act as an effective blood–nerve barrier (BNB), protecting against toxins, infections, and mechanical trauma. Despite their crucial function, the origin, ultrastructure, molecular structure, and functional roles of PCs remain a mystery, making them a fascinating area of study.

Keywords: perineurial cells, perineurium ultrastructure, origin, markers, blood–nerve barrier, peripheral nerves.

Introduction

The peripheral nervous system (PNS) is an intricate mesh of neurons surrounded by various cell types, each contributing to the system's proper functioning. These include supporting glial cells such as Schwann, satellite, perineurial cells (PCs), and endoneurial cells. Their supportive roles create a microenvironment essential for efficient signal transmission, protect and maintain neuronal structure and function, and facilitate neuronal repair and regeneration after injury. Understanding the roles and interactions of these cells is important for diagnosing and treating peripheral nerve (PN) disorders and injuries. While less studied than cells of the central nervous system (CNS), PCs form a sheath that has been studied in various animals and humans using different investigative techniques. This is due to the fundamental lack of understanding of their involvement in repairing damaged nerve conductors and the need to decipher the molecular pathways that promote the regeneration of damaged nerves [1].

PNs are uniquely intricate and distinct organs comprising nerve fibers, connective tissue (CT), and blood vessels. The CT is further divided into three main components: the epineurium, perineurium, and endoneurium, which contribute to the complex nature of these nerves (Figure 1). These connective structures extend along the entire length of the nerve, including its branches, and consist of collagen fibers grouped in bundles, elastic fibers (that allow elongation during movement), reticulin fibers, and numerous cell types such as fibroblasts, macrophages, mast cells (MCs), and supporting glial cells, as mentioned earlier.

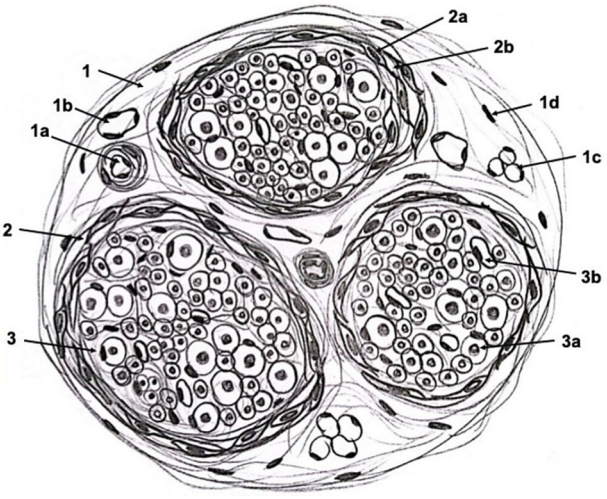

Figure 1 – ***Diagram of a peripheral nerve. 1: Epineurium; 1a: Artery; 1b: Vein; 1c: Adipose cells; 1d: Fibroblast in the CT of the epineurium; 2: Perineurium; 2a: PCs in concentric layers; 2b: CT matrix between PCs; 3: Endoneurium; 3a: Myelinated nerve fiber covered by Schwann cell; 3b: Capillary in the endoneurium. CT: Connective tissue; PCs: Perineurial cells.***

The epineurium, which surrounds the entire nerve as a dense CT capsule, primarily consists of collagen fibers and vessels that supply blood to the nerve [2].

The perineurium, derived from the loose CT septa of the epineurium, subdivides the nerve into multiple fascicles. Thin, concentric layers of PCs, arranged in a tight palisade-like epithelioid structure [3, 4], form a complete sleeve around the axon bundles of the fascicles. These layers, composed of PCs and tight endothelial cells (ECs), create a permeable but selective barrier [5]. The perineurium maintains intrafascicular pressure, allowing axon movement, and transmits this pressure to the endoneurium, which generates pressure within the axons [6].

The endoneurium, the innermost sheath, encircles the nerve fibers within the fascicles, with each fiber-containing axon–Schwann cell complex [7, 8]. The endoneurium comprises two layers of fragile CT: an external longitudinal layer and an internal, less organized one. It forms an uninterrupted sheath that extends from the surface of the CNS to the level of the peripheral synapse. In the endoneurium, separate collagen fibers are surrounded by endoneurial fluid, similar to cerebrospinal fluid (CSF) [9]. The diameter of the collagen fibrils in the perineurium and endoneurium, primarily composed of type III collagen, is smaller than those in the epineurium [10].

PCs, a unique type of myofibroblasts, are crucial in maintaining nerve homeostasis. They are the only connective structure that acts as an effective barrier, protecting axons and their associated Schwann cells from toxins, infections, and mechanical trauma. Despite their essential role, PCs' origin, ultrastructure, molecular structure, and functional roles remain poorly understood, making them a fascinating area of study [8].

Origin

The embryonic origin of PCs, a topic of intense and ongoing debate, adds a layer of complexity to their study. Recent research has proposed various theories about the origin of PCs. Due to their shape, PCs were traditionally classified as fibroblasts, suggesting a mesodermal origin. This phenotype of PCs, characteristic in neural leprosy, expresses cluster of differentiation (CD)34 immunoreactivity and the nerve growth factor receptor (NGFR), suggesting a possible origin from activated pericytes [11]. However, unlike fibroblasts, PCs possess unique characteristics that distinguish them. They lack a significant amount of rough endoplasmic reticulum (RER) but express basement membrane-specific genes, have a double basal lamina, and are connected by tight junctions [8]. These unique features make the study of PCs a significant and intriguing area of research.

Some authors suggest that PCs are epithelioid myofibroblasts [12, 13] and express CD29 as a mesenchymal marker [14].

Trevisan *et al*. [15] suggest that PCs could be satellite glia expressing the Jedi-1 [platelet endothelial aggregation receptor 1 (PEAR1)/multiple epidermal growth factor (EGF)-like domains 12 (MEGF12)] phagocytic receptor. Other studies on motor nerves in *Drosophila*, zebrafish, chicken, and mice reveal that satellite glia originate either from the neuroectoderm of the CNS, oligodendrocyte precursors (Olig2+ precursors), or the neural tube's transcription factors Nkx2.2+ perineurial glia. These Nkx2.2+ precursors, a subset of peripheral glia, contribute to the formation of the perineurium of spinal nerves [16], guide axons, and direct motor nerve development [8, 17].

Structure

The perineurium is organized into concentric sheets of collagen fibers, PCs, and other cell types. It can be divided, similar to Pacini's corpuscle, into three zones: the inner zone (characterized by the epithelioid palisade arrangement of PCs, where cell junctions are more pronounced), and the intermediate and outer zones (which connect the perineurium to the epineurium) [18]. The concentric epithelioid layers of PCs are separated by a CT matrix containing fibronectin and collagen. Small capillaries can be found between the PC layers or squeezed between the myelinated axons [3, 19].

Due to their position, PCs have a double basal lamina (occasionally discontinuous) that can be up to 500 nm thick in larger nerves. This lamina contains type IV collagen, laminin $\beta 2$ chain, and negatively charged heparan sulfate proteoglycans [7, 8, 19]. Numerous electron-dense tight junctions are present between the PCs' twisted and interlacing cellular extensions [20].

The cytoplasm contains inconspicuous organelles, including mitochondria, the Golgi apparatus, and the RER, which becomes more prominent under reactive conditions. Microfilaments of actin and vimentin are attached to electron-dense cell membrane plaques [10, 21]. Additionally, active transcytosis is suggested by the presence of pinocytotic plasmalemma vesicles or caveolae [20], which are more numerous in the outermost layers of internal PCs [3, 7, 8]. Flattened, large, and predominantly oval nuclei, with a dark peripheral zone of heterochromatin encircling a centrally located, medium-dense euchromatin, are typical of PCs [3].

The thickness of the perineurium, and thus the number of PCs, decreases toward the nerve's termination. It varies between 15 layers (in the largest fascicles of the sciatic nerve) and 1–2 layers (in the smallest peripheral fascicles) [7]. Interspersed with PCs are different types of cells, including macrophages, MCs, and a heterogeneous population of cells with long, interdigitating telopodes and mesenchymal stromal cell properties, known as telocytes (TCs) [22]. TCs typically flank the layers formed by the PCs [22]. Still, they can also be found in other regions, such as the vegetative nervous system, various ganglia, the olfactory nerve, and the outer compartment of Pacinian corpuscles [22]. Immunophenotypically, TCs differ from fibroblasts and Schwann cells, as they express CD34 and platelet-derived growth factor receptors alpha/beta (PDGFRα/β) in PNs [22].

Studying Pacini's corpuscle could provide insights into the origin and function of PCs. Pacini's corpuscle is a cutaneous end-organ with sensory function and an "onion bulb" structure. The peri-axonal cells of this corpuscle are arranged in three distinct compartments: the inner core, outer core, and capsule. The outer core and the capsule are made of concentric, flattened lamellae, which are continuous with the perineurium [23]. These lamellae are composed of perineurial myofibroblast-like cells, considered terminal glial cells. A fluid-filled space between the cell layers contains a complex molecular extracellular matrix

(ECM). The outer core lamellar cells' origin, development, and protein profile are similar to those of PCs [24].

Markers

Adult human PCs show reactivity for epithelial membrane antigen (EMA) and vimentin while lacking reactivity for CD57 (Leu 7) and S100 protein (Schwann cell markers) [21, 25]. In rat PC cultures, the cells were positive for the CD29 mesenchymal marker and negative for CD31, CD34, and CD57 [14].

PCs express markers of junctional proteins [*e.g.*, *zonula occludens*-1 (ZO-1), occludin, claudin-1, a persistent feature, claudin-3, claudin-19, and tricellulin] [7, 26, 27], markers of adherens junction proteins (*e.g.*, E-cadherin and N-cadherin) [28], junctional protein associated with coronary artery disease [JCAD [18], epidermal growth factor receptor (EGFR) [18], markers of gap junctions (*e.g.*, α-1 protein, connexin 43) [29], and markers of the basal lamina and cell–matrix adhesion molecules (*e.g.*, β5 integrins and α2 integrin *in vitro*, and α3 integrin *in vivo*, which recognize various collagen subtypes, and structural glycoproteins such as fibronectin and laminin] [30]. Molecules can also be actively transported across the human and rat perineurium *via* aquaporin 1 (AQP1) [31, 32] or distinct membrane receptors, such as glucose transporter type 1 (Glut1) [7, 33]. Another transporter, the monocarboxylate transporter 1 (MCT1), is colocalized with Glut1 in the perineurium but not in the endoneurial capillaries. Under conditions of reduced glucose utilization, only PCs can transfer other nutrients (*e.g.*, ketone bodies and lactate) *via* MCT1 [10].

Other genes and immunohistochemical (IHC) markers identified for PCs include the LY6/PLAUR domain containing 2 (*Lypd2*), netrin G1 (*Ntng1*), monooxygenase DBH like 1 (*Moxd1*), keratin 19 (*Krt19*), and deleted in lymphocytic leukemia 7 (*Dleu7*) marker genes (gene signatures shared with ECs), and solute carrier family 2 member 1 (Slc2a1)/Glut1, secreted frizzled-related protein 5 (Sfrp5), netrin 4 (Ntn4), mesothelin (Msln), myelin protein zero like 2 (Mpzl2), p53 apoptosis effector related to peripheral myelin protein 22 (PMP22) (Perp; a desmosome protein), and the integrin subunit beta 4 (Itgb4) and integrin subunit alpha 6 (Itga6) integrins [34]. In specific locations, such as the olfactory nerve, PCs have been immuno-localized with $P75^{NTR}$ neurotrophin receptor, vimentin, and the SRY-box transcription factor 10 (SOX10) [35].

The outer lamellar cells of Pacini's corpuscle and the PCs are immunohistochemically positive for EMA and Glut1 [23, 36].

Functions

Blood–nerve barrier

The PCs, linked through tight junctions, form a barrier between the nerve fibers and the extrafascicular tissue, contributing to the blood–nerve barrier (BNB) [3, 4]. This barrier consists of two main structural and functional components: the endoneurial microvessels' ECs (the endothelium) and the PCs. The perineurial barrier is organized as follows (from outside to inside): (*i*) the basal lamina surrounding each cell layer; (*ii*) the tight junctions between the cells; and (*iii*) active transcytosis transport through the PCs membrane [3, 7].

The internal perineurium is the primary diffusion barrier between the endoneurium and the epineurium (extrafascicular tissue). While understanding of both the endoneurial microvascular endothelium [3, 7] and PC–cell junctions is still incomplete, it is believed that the BNB, in a strictly functional sense, is primarily based on the microvascular endothelium. However, the perineurial tight junction proteins also play a significant role in regulating the function of the perineurial barrier [18]. The complexity of this barrier creates a specialized microenvironment that helps maintain the homeostasis of the endoneurium. It controls the interstitial fluid flow between the endoneurium and the epineurium, acting as a critical interface [3]. Maintaining endoneurial homeostasis establishes an immune-privileged compartment, protecting Schwann and endoneurial cells from potential harm caused by external toxins, infections, and ionic flux [3, 7]. As a result, treatment options for neurosensory disturbances are limited by the restricted permeability of the endoneurium and perineurium microvessels, which protect the endoneurial microenvironment from the entry of nonspecific molecules [18].

Additionally, the BNB acts as a molecular barrier, preventing the diffusion of molecules larger than 12 nm in diameter (*e.g.*, analgesic drugs) [7, 8, 19]. The ECM between the PCs contributes to this barrier by allowing the PCs to adjust to external stretching forces and regulate endoneurial pressure [7]. Furthermore, endoneurial fluid protects the delicate axons, further supporting the function of the BNB [9].

Normal development of nerves

Studies in *Drosophila* have shown that the normal development of motor nerves relies on the proper development of PCs, oligodendrocytes, and Schwann cells [37]. Therefore, PCs and Schwann cells must interact through Notch cascade signaling [38–40]. The regular expression of developmental genes, such as YIPPEE-like 3 (*YPEL3*) [37] and the alpha1 collagen (*Col1a1*) gene [20], is also essential.

During nerve development and in response to injury, PCs and endoneurial Schwann cells reciprocally depend on each other. Schwann cells require PCs for migration across the injury site, a process facilitated by several signaling mechanisms, including Ephrin B2/Ephrin signaling [8, 41, 42]. PCs need Schwann cells for proper development and response to injury [43, 44]. This bidirectional signaling is crucial for forming columns of Schwann cells that guide regenerating axons across the gap between nerve stumps [39, 41].

In the repair process and nerve development, glial cell line-derived neurotrophic factor (GDNF) secretion by endoneurial Schwann cells induces tight junction specialization in the innermost PCs [3]. PCs also modulate myelin production by Schwann cells and, together with macrophages, coordinate early phagocytosis and debris clearance at the nerve injury site [17, 43]. Additionally, PCs can influence the development of neuromuscular junction [17].

The interaction between PCs and Schwann cells is

further suggested by their shared expression of the NGFR [11, 45], which induces PC maturation [46]. In humans, Schwann cell signaling through the Desert Hedgehog (*Dhh*) gene and its receptor, patched 1 (PTCH1) protein, contributes to regulating the cellular ensheathment formed by PCs and the complete formation of the perineurium. This is supported by the fact that mutations in the human *Dhh* gene cause neuropathy [40, 47].

Nerve regeneration

PCs and Schwann cells are the two major cell types that play critical roles in PN regeneration [4, 48], contributing to axon guidance (by creating a glial bridge across the injury site), phagocytosis, debris clearance, and more.

In animal models of severe spinal cord injury repair, reactive fibroblast-like scarring cells form tightly packed cellular septa connected to the adjacent perineurium. These cells exhibit highly uniform ultrastructural features, such as oval nuclei aligned in the same orientation and tight junctions between their overlapping processes. They are intensely positive for ZO-1 and vimentin but negative for glial fibrillary acid protein (GFAP) and S100, a profile suggesting a reactive perineurial origin [20]. This reparative process may occur in a hyperplastic manner, particularly in the context of prior fibrosis or skin injuries, creating potential diagnostic pitfalls. Perineurial involvement can be confirmed using panels of IHC markers, such as pan-cytokeratin (CK), S100, and EMA, as PCs are CK and S100 negative but EMA positive [49].

Following PN injury, multiple cellular interactions occur involving macrophages, neutrophils, nerve fibroblasts, ECs, PCs, and Schwann cells. These cells regulate each other's recruitment and migration to form a bridge during nerve regeneration [50]. PCs are primarily involved in the earliest regenerative steps of the fibrotic scar response [50–52]. They first migrate along the fibrin and form a tube, attempting to bridge the severed, non-repaired nerve stumps [4, 20, 50, 53], before completing axonal fragmentation and clearance, extending processes into the injury site [8]. Their interaction with the surrounding ECM, which contains components like collagen, fibronectin, and fibrin, influences the migration of all regenerative cells, including reactive perineurial, endothelial, and Schwann cells [48].

In these reactive conditions, the expression of PCs is modified. Their integrin expression modulates adhesion to the ECM [54], while junctional molecule expression [such as claudins, occludins, and vascular endothelial (VE) cadherins] decreases. PCs also express the human natural killer-1 (HNK-1) neural migration marker, contributing to the disruption and leakiness of the BNB and facilitating cellular migration [55]. Additionally, PCs upregulate the expression of axon guidance molecules like semaphorin 3A (SEMA3A), a chemorepellent, and semaphorin 3F (SEMA3F) [20, 56–58], as well as the *Col1a1* gene [59].

Numerous exchanges occur between the fibroblasts of the endoneurium, epineurium, and PCs within the uninjured nerve and during repair. Signals from the epineurium and PCs may stimulate early blood vessel regeneration [34]. Furthermore, TCs can synthesize collagen, phagocytize myelin debris, and participate in inflammatory and immune responses, increasing numbers following nerve injury [22].

Perineurial barrier: implication in pathology

It is hypothesized that the perineurium's normal homeostatic function extends to eliminating lipid and protein waste, restoring the PN fiber's normal microenvironment [60–62]. Perineurial glia is essential during nerve development, maintenance, and repair. Therefore, alterations in PCs and BNB lead to increased permeability and could contribute to various peripheral neuropathies [8].

Many disorders are associated with the distortion of BNB, causing inflammation, demyelination, and nerve degeneration. The most important are diabetes [27], but also coronavirus disease 2019 (COVID-19) [63], neurotropic viruses [64, 65], vasculitis, leprosy, borreliosis, sarcoidosis, lymphomatosis, eosinophilia-myalgia syndrome, toxic oil syndrome, tumors and metastasis, and other rarer conditions [66]. However, the mechanism through which these diseases act is different. In *diabetic polyneuropathy*, for example, the BNB is destabilized due to several factors: specific downregulation of claudin-1 messenger ribonucleic acid (mRNA) expression in the perineurium (distinct from traumatic nerve injury); weakened macrophage shielding of the vessels; increased expression of inducible nitric oxide synthase (iNOS) in the perineurium [27]. In *severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection*, cells in the sciatic nerve, lung, and skeletal muscle strongly express angiotensin-converting enzyme 2 (ACE2), particularly around nerve bundles, that contributes to the neuropathic manifestations of COVID-19 [63]. *Neurotropic viruses*, such as varicella-zoster and herpes simplex, disrupt the perineurial barrier by infecting PCs [28, 64]. Interleukin-6 (IL-6), a key mediator of inflammation, facilitates this disruption, allowing viruses and immune cells to breach the perineurium, causing nerve injury [28]. In infected primary adult human PC cultures, virus-induced changes occur in expression patterns, including the downregulation of programmed death-ligand 1 (PD-L1) and major histo-compatibility complex I (MHC-I), depending on the virus type. This results in the induction of proviral factors that enhance viral infection and promote an amyloidogenic extracellular environment [65, 66].

Both perineurial and endoneurial compartments are altered in *leprosy*, with a proliferation of PCs infiltrating the endoneurium. Collagen fibers replace nerve fibers; the PC phenotype is changing to fibroblastic (possibly originating from activated pericytes) along the fibers [11]. The perineurial microenvironment is altered in neoplastic invasion, such as pancreatic adenocarcinoma. In this process, upregulation of rearranged during transfection proto-oncogene (*RET*) expression and a high abundance of bone marrow-derived macrophages expressing the RET ligand GDNF have been observed [67]. In hyperplastic neurogenic processes, neurofibromas, and nerve tumors (*e.g.*, adenocarcinomas with perineural invasion), TCs, including TCs/CD34+ Schwann cells, interact with other cells (*e.g.*, lymphocytes, macrophages, MCs, and Schwann cells) [22]. The complex cell interaction in the perineurial microenvironment leads to diagnostic challenges. Hence, the importance of immuno-histochemistry panels of markers that can target PCs.

For example, perineuriomas, benign tumors derived from PCs (that account for about 1% of PN neoplasms),

are similar to reactive Schwann cell-derived processes and inherited polyneuropathies [68]. IHC markers, such as EMA, low-affinity NGFR (p75NTR), α-smooth muscle actin, and CK, identify PCs in these tumors [65, 69]. Some intestinal perineuriomas, particularly the polypoid type, express markers of PCs (EMA, claudin-1, Glut1, type IV collagen) and the B-Raf proto-oncogene (*BRAF*)*V600E* mutation [70]. Further studies of the anatomic localization and characteristics of perineuriomas could contribute to a better understanding of the embryological origins of PCs [71].

Malignant PN sheath tumors with perineurial differentiation display varied histopathological features, including fibrosarcoma-like areas and pleomorphic and spindle cell zones. These tumors are negative for S100, CD34, and smooth muscle actin but positive for EMA, Glut1, and claudin-1, making these markers useful for diagnosis [7, 72–77].

Targeting the molecular mechanisms that can disrupt BNB may result in new therapies. Here are a few examples from current research. Inhibiting microRNA-21-5p (miR-21), whose expression is increased in PCs, has a potential analgesic effect in neuropathic pain [78, 79], as seen in patients with area-specific pain disorders or mice following nerve injury. Moreover, therapeutic use of miR mimics (*e.g.*, miR-183-5p/3p) could downregulate claudin-1, selectively opening the BNB to facilitate anesthetic delivery [80]. In addition, therapeutic focus on claudins and barrier sealing could stabilize nerve damage and reduce pain in diabetic neuropathy [27]. Furthermore, in a cultured system of nerve fibrosis, L-alanyl-L-glutamine (L-Ala-L-Gln) efficiently suppresses hypoxia-mediated fibrotic processes [81]. L-Ala-L-Gln was reported to protect from sepsis, play an immunomodulatory role in fibrosis and stress, modulate several profibrotic factors, and significantly reduce the expression of profibrotic and cell adhesion-inducing factors [82].

Conclusions

The perineurium has a unique structure and function that remains underexplored. Identifying the cells within an intact PN, understanding the characteristics of the perineurial barrier, and studying the changes that occur after nerve injury could lead to new tissue engineering strategies for nerve repair. Moreover, identifying biologically relevant perturbations or gene variants involved in nerve development may enable the identification and treatment of peripheral neuropathies, tumors, or rare congenital diseases in human patients.

Conflict of interests

The authors declare that they have no conflict of interests.

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