REVIEW

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Telocytes inside of the peripheral nervous system – a 3D endoneurial network and putative role in cell communication

NICOLAE MIRANCEA[1)], GABRIEL VALERIU MIRANCEA[2)], ANA-MARIA MOROŞANU[1)]

[1)]*Department of Developmental Biology, Institute of Biology Bucharest of Romanian Academy, Bucharest, Romania*

[2)]*Department of General Surgery, St. Pantelimon Emergency Clinical Hospital, Bucharest, Romania*

Abstract

In this paper, we developed the hypothesis concerning the reasons to assimilate endoneurial fibroblast-like dendritic phenotype [shortly termed endoneurial dendritic cells (EDCs)] to the endoneurial telocytes (TCs). We reviewed the literature concerning EDCs status and report our observations on ultrastructure and some immune electron microscopic aspects of the cutaneous peripheral nerves. Our data demonstrate that EDCs long time considered as fibroblasts or fibroblast-like, with an ovoidal nucleus and one or more moniliform cell extensions [telopodes (Tps)], which perform homocellular junctions, also able to shed extracellular microvesicles can be assimilated to TC phenotype. Sometimes, small profiles of basement membrane accompany to some extent Tps. Altogether data resulted from scientific literature and our results strength the conclusion EDCs are really TCs inside of the peripheral nervous system. The inner three-dimensional (3D) network of endoneurial TCs by their homo- and heterocellular communications appears as a genuine cell-to-cell communication system inside of each peripheral nerve.

Keywords: peripheral nerve, endoneurial telocyte infrastructure, cell communication, nerve regeneration.

Introduction

In the last few decennial scientific published papers, very important data in biomedicine research underline the major role of the so-called stromal/interstitial cells in the parenchymal cell destiny (normal cell differentiation, apoptosis, malignant cell transformation) of that particular organ, tissue homeostasis, ageing, degenerative diseases, regeneration, etc. Stromal cells are generally defined as heterogeneous population of resident or transiently cells mostly of mesenchymal origin represented by fibroblasts/fibrocytes, pericytes, telocytes (TCs), mostly located in perivascular niches [1–5].

TCs were described as a new stromal cell phenotype in almost normal tissue types [1, 6–18] or in a variety of disorders, including basal cell carcinoma (BCC) [19], fibrotic remodeling [20], uterine leiomyoma [21], mammary carcinoma [22–25], heart failure [26], atrial amyloidosis [27], etc.

Aim

Using already published data plus some personal observations, here we debate the hypothesis that some endoneurial cell types can be assimilated to the real TC phenotype. In this respect, firstly we emphasize some general data concerning TC definition, tissue localization, immunoreactivity, and some putative roles. Then, we refer to the possible identification of the appropriately endoneurial cells to be considered as TCs.

TCs have a particular infrastructural phenotype and express abilities to establish homo- and heterocellular contacts, and perform three-dimensional (3D) stromal networks inside of almost tissues/organs

Transmission electron microscopy (TEM) is the "gold standard" method to identify and describe the real phenotype of TCs

Because to date, no specific immunomarker for TC identification is available, the origin of this newly described cell phenotype remains unclear [26]. In such circumstances, TEM analysis remains the "gold standard" technique as the best modality to discriminate the real telocytic phenotype from the other stromal cells, mostly fibroblasts/fibrocytes mimicking the TCs [2, 28].

TCs are usually defined by their ultrastructural features: a cell body where the nucleus is located and very long one to few extensions called telopodes (Tps) with alternating dilated segments (podoms) and very slender segments (podomers). Perinuclear, small profiles of rough endoplasmic reticulum (RER) and Golgi apparatus can be detected. Depending on the number of Tps, TCs can have spindle, piriform, triangular, stellate or convoluted shape [1, 2, 29, 30]. Usually, inside of podoms there are small profiles of endoplasmic reticulum (ER), mitochondria and caveolae representing Ca^{2+} uptake/release units. Inside of Tps,

cytoskeleton is represented by intermediate filaments and rarely microtubules can be seen.

The remarkable feature of TCs is the variety of their cell–cell connections with TCs or different other surrounding cell phenotypes, including by exosomes deliverance

By their abilities to establish homo- and heterocellular contacts, TCs perform 3D stromal networks inside of almost tissues/organs. It seems that such cell-contacts contribute to cell signaling by the intercellular exchange of ions or molecules [2, 31–33].

TCs are able to establish homo- and heterocellular junctions and, very interestingly, TCs have the ability to generate and deliver extracellular vesicles (EVs) including exosomes as cargo for different messenger molecules [exosomes contain messenger ribonucleic acid (mRNA), which can be shuttled from one cell to another] so that TCs are strongly involved in cell signaling both in normal conditions, as well as during complex process of carcinogenesis, including malignant cells invasivity [2, 26, 31, 34–37].

TCs form networks, interact with other cell types directly by heterocellular junctions or by deliverance of EVs, and behave as nurse cells for stem cell niches [8, 38–40].

To assure tissue homeostasis, many subtle mechanisms are involved. Tissue regeneration is one of such mechanism. Regenerative ability of adult tissues is realized by adult stem cells population resident in so-called niches where stem cells may stay in a quiescent state, induced to proliferate in a symmetric or asymmetric mode or to be determinate to differentiate, depending on the micro-environmental status. In close contact with stem cell niches there are microvessels. Stem cell niche microenvironment is mostly represented by mesenchymal stromal cells, including TCs and, their extracellular matrix (ECM) proteins [5, 41–44].

In an experimental study, Liao *et al*. (2019) reported that TCs as cardiac interstitial cells increased in their number at the border myocardial infarction zone and might be involved in exercise-mediated beneficial effects in the myocardium promoting healing and regeneration [45].

Recently, Shushan & Shoshkes-Carmel (2022) identified a special subtype of TCs inside of the intestinal subepithelial tissue without which neither epithelial stem nor the progenitor cells cannot proliferate and support regeneration of intestinal crypts, TCs being considered an important source of signals for intestinal stem cells [46, 47].

Abd-Elhafeez *et al*. (2020) consider that TCs relations with different types of immune cells [macrophages, mast cells (MCs), dendritic cells (DCs), lymphocytes] indicate their putative role in maintenance of intestinal immunity [48].

During regeneration of post-injured skeletal muscle, TCs may activate and regulate satellite muscle cells activity by invading satellite cell niche by their long Tps through local destructured basal lamina succeeded to contact the adjacent activated satellite cells [49].

Moreover, in different pathologies, TCs can be altered in their morphology and their number in surrounding stroma [19, 22–24, 50]. In this line, Sabatelli *et al.* (2022) [51] reported that in Ullrich congenital muscular dystrophy – a devastating inherited neuromuscular disorder [52] –, cluster of differentiation 34 (CD34)-positive TCs increase in their number in the interstitium of the deep fascia, Tps pass through dissoluted basal lamina and contact the sarcolemma of underlying muscle fiber aspects, which suggest a potential involvement of TCs in the pathogenesis. Disruption of the mice dermal network TCs experimentally induced by Bleomycin treatment very closely mimics systemic sclerosis [53].

Is the new cell phenotype termed telocytes identifiable inside of the nervous system?

Knowledges about their origin, infrastructural aspects and immunoexpressed specific molecules to different cell types which constitute the nervous system were progressively increased. A matter of debate arising with recently discovered cell type termed 'telocyte': is this new cell phenotype really identifiable inside of the nervous system?

The presence of TCs and their roles in the nervous tissue appears of a very great interest. The story of the TCs presence inside of the brain and the nerves is very interesting especially because of the controversial opinions resulting from the similar morphological appearance of both fibroblasts/fibrocytes and real TC phenotypes as stromal cells described inside of the nervous tissue.

The central nervous system (CNS) is represented by the brain and the spinal cord. The peripheral nervous system (PNS) consists of the nervous ganglia and nerves. Peripheral nerves are the cranial and the spinal nerves, as well as the autonomic nervous system (partially are within the CNS [54]) together with their ganglia and the associated sensory and motor endings that conduct impulses from and to the CNS [55, 56]. Ganglia's neurons have large nuclei with prominent nucleoli and are surrounded by satellite support cells [57]. A fibrocollagenous stroma together with Schwann cells (SCs) offer a support for the axons running to and from the ganglion. The nerves may be motor or sensory, myelinated or non-myelinated [58, 59]. The PNS contains two supporting cell types: (*i*) SCs, and (*ii*) satellite cells, surrounding neurons in sensory and autonomic ganglia [57, 60, 61].

Beginning with the year 2000, Dănăilă [56] identified by TEM a morphologically elongated interstitial cell type termed 'cordocytes', present inside of the human cerebro-vascular tissue, later assimilated to TC phenotype [54, 62]. Dănăilă [56] considers that TCs play important roles in the human brain, mainly concerning the protection against different internal and external aggressions leading to different cerebrovascular abnormalities [56]. In this context, mention must be made that number of TCs in human glioblastoma (the most common malignant primary brain tumor and incurable) is 10 times higher than in astrocytoma [63].

The presence of TCs in meninges and choroid plexus (two structures involved in modulation of brain function) described in direct contact with blood capillaries and putative stem cells suggested that TCs might have a role during neurogenesis stages [64, 65].

In an elegant study concerning immunohistochemistry and electron microscopy of the human trigeminal ganglion,

Rusu *et al*. (2016) identified a perineuronal cell population with long and moniliform processes intermingled with satellite glial cells and reported to be considered as TCs [9].

By their heterocellular junctions with neuroblasts and capsular satellite cells, as well as with degenerating neuroblasts described in the spinal ganglia, TCs may play an important role in regulating cell differentiation and cell death during embryonic ganglia development [66].

Like any other body tissue, nervous tissue can be affected by congenital malformations, traumatic injuries, oncological tumor resection or progressively degenerative diseases [2, 67].

Because of traumatic mechanical injuries, including accidental surgical operations, oncological alterations, or other damaging factors loss of afferent and efferent innervation of tissues becomes a serious medical problem [68]. To successfully solve this problem, development of refined neurosurgical technologies of reinnervation requires deeply knowledges concerning cellular and molecular mechanisms of nerve structure, physiology, and post-traumatic nerve repair. Just to mention, advanced studies concerning nerve stroma (non-nervous cells and ECM) contribute to the better understanding of nerve repair. In this context, investigations referred to the TCs ultrastructure, their relationships and molecular status as a stromal nerve component become in focus [2].

To get a real diagnosis, detailed knowledge of the PNS development, structure, immunohistochemistry, and ultrastructure of peripheral nerves is essential to be able to correlate all these with clinicopathological data [69].

Which cell types there are inside of a peripheral nerve?

Peripheral nerves and their principal branches consist of parallel bundles of nerve fibers (axons) and support tissue sheaths, including blood vessels [58, 70].

Peripheral nerves provide the path for all types of axons (the essential transmitting units of peripheral nerves) [55, 67, 71].

A peripheral nerve is composed of three different compartments: (*i*) epineurium – the outermost layer of connective tissue sheaths, (*ii*) perineurium, and (*iii*) endoneurium [55, 72, 73].

Each individual axon and SCs are surrounded by a connective tissue, the endoneurium [55]. A bundle of nerve fibers is surrounded by a dense connective tissue called the perineurium. The outermost layer ensheathing the entire nerve fascicles within a nerve trunk represented by a dense connective tissue termed 'perineurium'.

Knowledge of the normal peripheral nerve ultrastructure is an essential prerequisite to understand clinical relevance of the fragile balance between physiology and pathophysiology of the peripheral nerves [67, 71, 73–78].

Perineurial cell (PNC) types

The fascicles of peripheral nerve trunks are surrounded by a multilayered sheath, the perineurium, composed of several alternating cellular and connective tissue layers [79]. In fact, the perineurium encircles axon plus SC units [80]. Perineurium is formed by so-called perineurial cells (PNCs) of mesenchymal origin. PNCs are joined at their ends by tight junctions forming a cellular tube around the nerve fascicles. By forming such a physical tissue–nerve barrier, the perineurium plays a major role in maintaining the integrity of the endoneurium under physiological conditions protect axons from abrupt changes in ionic composition, preventing penetration of xenobiotic active proteins, infectious agents, as well as blood-borne cells into the nerve bundles. Ultrastructurally, PNCs appear as elongated cells accompanied by the continuous basal lamina not only on the epineurium-side but also on the endoneurium-side surface [79, 80]. Inside a PNC, there are located an elongated nucleus, few common organelles, actin and vimentin filaments, and numerous pinocytotic vesicles seen on both sides of the plasmalemma of the PNCs and occur throughout all layers of the perineurial sheath. PNCs are of mesenchymal origin [81]. During development, primary epithelia arise by shape changes of the original blastoderm epithelium but later one, secondary epithelia are formed from mesenchymal intermediates by a process termed mesenchymal-to-epithelial transition. PNCs are elongated and do not exhibit thin cytoplasmic processes, are coated by a continuous external lamina, and joined at their ends by tight junctions [82, 83]. The expression of claudin-1 proteins as immunohistochemical (IHC) marker of PNCs indicated cell-to-cell contacts represented by tight junctions (*zonula occludens*) forming a barrier function. When an immunoreaction protocol is applied, PNCs express vimentin and epithelial membrane antigen (EMA) but are negative for the S100 SC marker [83].

In the context of tissue damages, including traumatic and non-traumatic (genetic, metabolic, immune, infectious, drug-induced neuropathies) nerve injury [77], nerve mesenchymal precursor-like cells migrating from perineurium, as well as from the endoneurium into adjacent damaged tissues and contribute to tissue repair [84]. Mention must be made that, together with other mesenchymal cell types arising from endoneurium, PNCs are involved in cutaneous neurofibromas. In this line, PNCs are altered in their ultrastructure, including their associated basement membrane (BM), which is partially dissoluted and, consequently, the nerve–blood barrier is destructured so that SCs from the endoneurial space proliferate outside [85].

Endoneurial cell types

Inside the endoneurium, there are resident and imported/transitory endoneurial cell types. Concerning the cellular phenotypes composition of the healthy PNS, mention must be made that neuronal body cells are absent from the endoneurium but only their axons extend into the PNS. PNS cells of the endoneurium are mainly represented by myelinating or nonmyelinating axons, Schwann glial cells, fibroblasts, vascular endothelium with their associated pericytes [71, 74, 78, 86]. Endoneurial vessels appear as a network of arterioles, non-fenestrated capillaries, and venules [2, 71, 73, 74]. Imported/transitory endoneurial cell types can be also detected, mostly represented by macrophages, and sometimes by MCs [2, 72, 74, 78, 87–89].

There is a matter of debate concerning the origin and function, as well at which extent the stromal endoneurial cells are involved in different pathologies.

There are authors sustaining that collagen is produced by endoneurial fibroblasts while others consider the ability

of SCs to synthesize collagen (as well as laminin, both molecular components of the SC basal lamina [90], especially during regeneration following nerve section or other injury [91]).

Neural crest stem cells undergo multilineage differentiation in developing peripheral nerves. They give rise to more than just SCs. After experimental nerve damage S100 protein was expressed as a marker for SCs, while endoneurial fibroblast-like cells were S100-negative [92]. Endoneurial fibroblasts (showing high amounts of ER) do not have a basal lamina and fail to express alpha-smooth muscle actin (α-SMA) or S100β. They originated from neural crest whereas PNCs, pericytes (expressing α-SMA) and endothelial cells are not neural crest derived. SCs are associated with axons and express glial markers as S100β and a basal lamina [93].

From the so far published papers, we observed that inside of the normal or pathological diseases involving peripheral nerves there are few cellular subpopulations of endoneurial fibroblasts. Many authors were tempted to re-evaluate the fibroblasts and fibroblast-like cells. In fact, there are not yet established criteria to discriminate very well the differences between real phenotype of fibroblasts and many other fibroblast-like cell populations [2, 80, 88, 89, 94, 95]. Moreover, Röyttä *et al*. (1987) appreciated endoneurial fibroblasts as endoneurial fibroblast-like cells [96].

Distinct of the conventional fibroblasts, inside of the endoneurium a so-called endoneurial DC population was identified [69]. In this context, at the first glance, a difficulty appears to discriminate between fibroblast-like and TC phenotype. To accurate identification of the cell types present inside of the peripheral nerves besides other more or less refined methods, single cell transcriptional profiling is recommended [78, 84]. Using more and more refined technical modalities for better knowledge of morpho-functional aspects of the fibroblasts, along the time, many and interesting observations were reported but still remains difficult to set clear criteria to discriminate between genuine fibroblasts and fibroblast-like cells [80].

A re-evaluation of fibroblasts and fibroblast-like cells appears necessary to be considered when we refer to the endoneurial fibroblastic cell population. Comparing with regular fibroblasts involved in synthesis and secretion of some extracellular-type molecules, such as type I collagen, endoneurial fibroblasts, mostly termed/identified as endoneurial fibroblast-like cells seem to have more potential activities, but their embryological origin, functions and involvement in pathology/regeneration remain less understood [2, 72, 88, 89].

What are the reasons to assimilate endoneurial fibroblast-like DCs to the endoneurial TCs?

To answer this question, here we review published data about endoneurial fibroblast-like DCs or shortly termed endoneurial dendritic cells (EDCs) and also report our observations on ultrastructure and some immune electron microscopy (IEM) aspects of the cutaneous peripheral nerves. Our recent investigations concerning immuno-expression at the ultrastructural level by IEM of some molecules, such as type IV collagen, integrin, and bullous pemphigoid antigen 2 (BPAG2), by normal human cutaneous peripheral nerves strength the hypothesis that EDC behave as endoneurial TCs.

From the so far published papers, a body of evidence demonstrates that TCs are commonly referred to as TCs/CD34-positive stromal cells [17, 25]. Along the time, Tcs from the PNS have been termed endoneurial stromal cells, capsular fibroblasts, endoneurial fibroblasts, endoneurial fibroblast-like cells, EDCs, CD34-positive endoneurial cells, endoneurial mesenchymal cells [2, 15, 16].

Moreover, at least in case of some organs, IHC analyses CD34-positive TCs coexpressed platelet-derived growth factor receptor alpha (PDGFRα) positive [97]. Like vascular endothelial cells, TCs express CD34 surface glycoprotein [98].

In a very elegant study, Romano *et al*. (2020) reported that isolated TCs from the human primary skin displayed an immunophenotypic profile, as follows: cluster of differentiation 31 (CD31)-negative/CD34-positive/platelet-derived growth factor alpha (PDGFα)-positive/vimentin-positive that unequivocally differentiates them from endothelial cells (CD31-positive/CD34-positive/PDGFα-negative/vimentin-positive) and fibroblasts (CD31-negative/CD34-negative/PDGFα-positive/vimentin-positive) [36].

Indeed, the most appropriate candidate for endoneurial TC was the CD34-positive fibroblast-like DCs [99]. Mention must be made that CD34 expression is not exclusive to TCs and a combination of electron microscopic analysis and immunodetection protocols is strongly recommended [2, 28].

A quite long time ago, searching for the pattern of CD34 antigen (a transmembrane glycoprotein) immunoreactivity within normal nerve, Weiss & Nickoloff (1993) identified positive immunophenotypically and cytologically DCs among endoneurial cell population, distinct from the conventional fibroblasts and SCs [100]. Later on, Khalifa *et al*. (2000) confirmed the presence of a CD34-positive and S100-negative amoeboid with long dendritic cytoplasmic processes (non-Schwannian) cell population in normal nerves [101]. Moreover, since committed collagenous fibroblasts are immunonegative for CD34, Khalifa *et al*. (2000) concluded that this subpopulation is unlikely fibroblastic cells [101].

Concerning any consideration regarding morphological similarities of endoneurial TCs with endoneurial fibroblast-like cells, very important mentions must be made: endoneurial fibroblast-like cells may have cell prolongation to some extent mimicking TCs' prolongations, but differences are notable. Different from endoneurial fibroblast-like cells, TCs' prolongations termed Tps are much slender, often with a moniliform aspect, mitochondria being accommodated inside of dilated segments (podoms), almost lacking ER (this is restrained to perinuclear region).

In a previously published paper [19], we observed heterocellular junction between a TC and a terminal edge cutaneous nerve. There, a synaptic junction between a Tp and the presynaptic axolemma was in detail described. In this line, an advanced study was published by Mirancea (2016), which launched the hypothesis that inside of the endoneurium of a normal human cutaneous peripheral nerve some EDCs exhibiting a particular morphology (spindle or stellate in their shape) with 2–3 slender moniliform cell extensions resembling the Tps (podoms alternate with slender podomers) characteristic to the TCs able to perform homo-

and heterocellular junctions, to some extent, can be assimilated to the TC cell phenotype [2].

The new data arising from, in meantime published literature, as well as our contribution by TEM observations concerning ultrastructure of polymorphic endoneurial cell population of peripheral nerves in normal human skin, as well as in BCC (unpublished data – manuscript in preparation), emphasize the concept that EDC are really TCs. Just to mention, in this context, that in a recently published paper, Díaz-Flores *et al*. (2020) refer to our previous paper [2], where I addressed the question why and to which extent EDC can be assimilated to the TCs [16].

Using the term of 'cordocyte' as equivalent for TC, Pais & Pais (2014) reported an increased number of these interstitial cells around the dermal nerves in a case of histiocytic sarcoma [102].

Here, we emphasize some additional data which clearly demonstrate that TCs are common cells identifiable inside of the endoneurium intermingled with axons and SCs, able to perform an inner 3D network, a genuine cell-to-cell communication system inside of each peripheral nerve. In this paper, our original illustrative support documents without doubt that EDC are for sure TCs.

TCs are really identifiable inside of the cutaneous peripheral nerves

The cutaneous nervous system is a part of the PNS. All three compartments connective tissue sheaths: (*i*) epineurium, (*ii*) perineurium and (*iii*) endoneurium including axons are identifiable [55, 72, 91].

To know more about the endoneurial TCs inside of the cutaneous peripheral nerves, small fragments were processed following regular TEM technique published elsewhere [103, 104]. Moreover, for identifications of some molecules of interest, such as type IV collagen, integrin, etc., an IEM protocol was applied accordingly with Mirancea *et al*. (2001) [105], Mirancea *et al*. (2007) [103], Mirancea & Mirancea (2010) [57].

Cutaneous peripheral nerves composition is different accordingly with the three levels of the skin: epidermis, dermis, and hypodermis. Basically, subcutaneous peripheral nerve trunks exhibit two connective tissue sheaths, epineurium and perineurium. Usually, epineurium is missing for the smaller intradermal nerve branches but perineurium is present when nerves traverse the reticular region of the dermis and finally terminate as they approach the papillary region when SCs and associated neuraxons lie freely in contact with the general connective tissue [91].

Cutaneous nerves terminate either as "free nerve endings" just beneath the skin BM or in association with specialized receptors, such as the Merkel cell or the Meissner corpuscle. Mention must be made that very rarely a terminal axon may be seen in direct contact with the basal keratinocyte from the interfollicullar regions of human hairy skin. A naked axon lacks either a SC or a basal lamina. Mostly, free endings are not naked neuraxons, but small SC processes surrounded by basal lamina and containing one or more neuraxons [91].

In an extensive study concerning TCs infrastructure and their intercellular junctions inside of the tumor stroma in a human skin BCC, Mirancea *et al*. (2013) reported on the heterocellular junction between TC and a terminal edge cutaneous nerve [19].

Additionally to the literature data, we search for better knowledge of the peripheral nerve ultrastructure, here we present our personal results obtained by TEM investigations of the cutaneous nerves from the normal human skin, with focus on the endoneurial cells infrastructure. In the papillary region of the dermis, nerves are enwrapped by an epithelial sheath represented by perineurial flattened epithelial cells with a BM on both sides (Figure 1). The perineurium is one layer thick and appears to consist of a single cell process of which meet and overlap at their ends performing a plug socket homocellular junctions. Endoneurium is represented mainly by SCs and collagen. Laminated myelin sheaths enwrapped neuraxons. Very long slender cell prolongation Tp-like of so-called EDC TC with moniliform aspect represented by alternations of podomeres and podoms runs close to the perineurium. Interestingly, both ends of the telopodium become to some extent in close junction performing nanocontacts (Figures 2–4, as well as Figure 5, detailed in Figure 6). Always a continuous BM is visible around SCs.

Because as is usually the case with Tps being very slender, to some extent a Tp zone not included in the plane of section, appears interrupted (encircled area in Figure 5). Interestingly, sometimes a transcytotic process can be detected (ovoidal area in Figure 5, detailed in Figures 7 and 8).

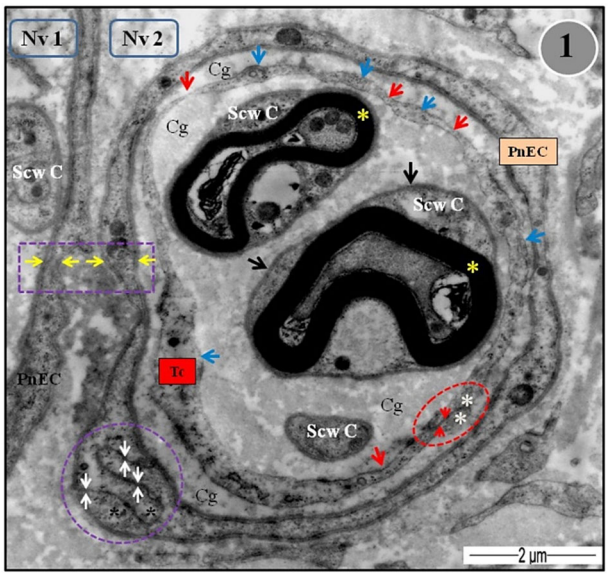

Figure 1 – ***In the papillary region of the dermis, two cross-sectioned nerves (Nv 1, Nv 2), each enwrapped by perineurial epithelial cells (PnEC) with a BM (yellow arrows) on both sides. The perineurium is one layer thick and appears to consist of a single cell process of which meet and overlap at their ends (black asterisks) performing a plug socket homocellular junctions (white arrows). Endoneurium is represented mainly by Schwann cells (Scw C) and collagen fibrils (Cg). Very long slender cell prolongation telopode-like of so-called endoneurial dendritic cell telocyte (TC) with moniliform aspect represented by alternations of podomeres (red small arrows) and podoms (blue small arrows) runs close to the perineurium. Both ends of the telopodium (white stars) become to some extent in close junction performing a close junction (red head arrows in elliptic area). Around Scw C, a continuous BM (black arrows) is detected. Myelin sheaths (yellow stars). BM: Basement membrane.***

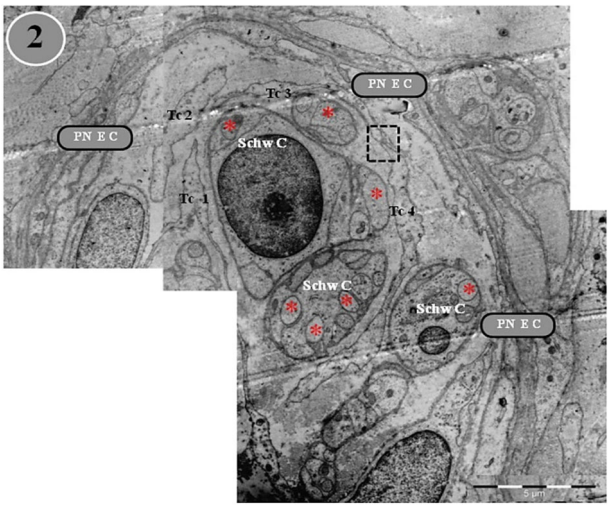

Figure 2 – ***Cross-section of a dermal nerve shows flattened perineurial cells (PN E C) and endoneurium mostly occupied by Schwann cells (Schw C) entrapping unmielinated axons (red stars), as well as by slender cell prolongations belonging to few telocytes (Tc 1–Tc 4) and collagen fibrils (Cg) can be also seen.***

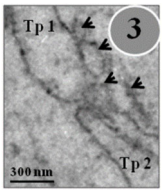

Figure 3 – ***Detail from the rectangular area depicted in Figure 2: extracellular vesicles (head arrows) released at the terminal ends of two telopodes (Tp 1, Tp 2).***

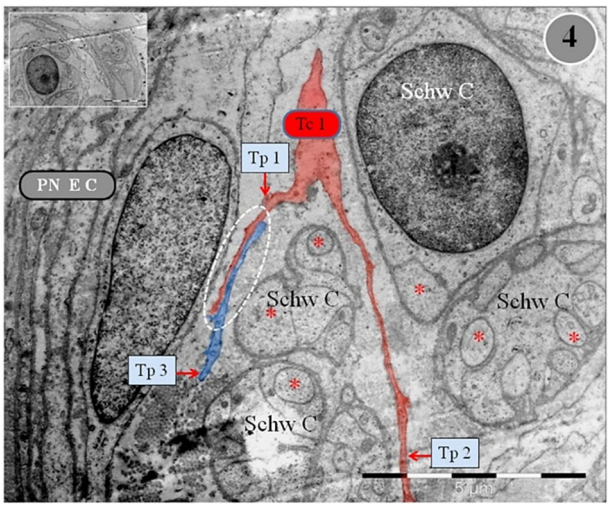

Figure 4 – ***Between Schwann cells (Schw C) there are three telopodes (Tp 1–Tp 3). Tp 1 and Tp 2 belong to one telocyte (Tc 1). Between Tp 1 and Tp 3, a homocellular junction is established (ovoidal area). Many axons (red stars) appear enwrapped by Schw C processes. PN: Perineurium.***

To know if the patches of the BM, which are visibly associated with endoneurial TCs, following the IEM protocol published elsewhere [57, 103, 105], we performed an IEM study for some molecules associated to the interface of the plasma membrane with the BM, such as type IV collagen, $\alpha6\beta4$ integrins, BPAG2 applied to the normal human skin.

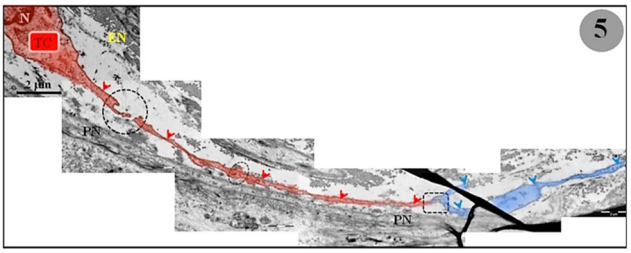

Figure 5 – ***A reconstruct from seven successive pictures shows an endoneurial nucleated (N) telocyte (TC) with a very long telopode (red head arrows) in close contact with a telopode of another TC (blue head arrows). Encircled area marks an apparent interruption of the slender telopodium belonging to the nucleated TC. Homocellular junction (rectangular area) is detailed in Figure 6. A transcytotic process (ovoidal window) will be detailed in Figures 7 and 8. EN: Endoneurium; PN: Perineurium.***

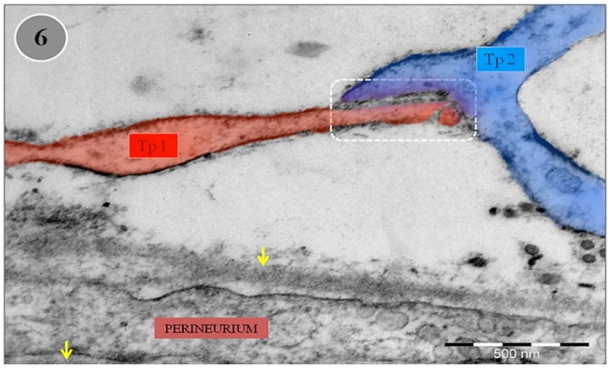

Figure 6 – ***Segment from a peripheral nerve in the human normal skin. A homocellular junction (rectangular area) was established between two telopodes (Tp 1 and Tp 2) belonging to two telocytes inside of the endoneurium. Yellow arrows: Perineurial basement membrane.***

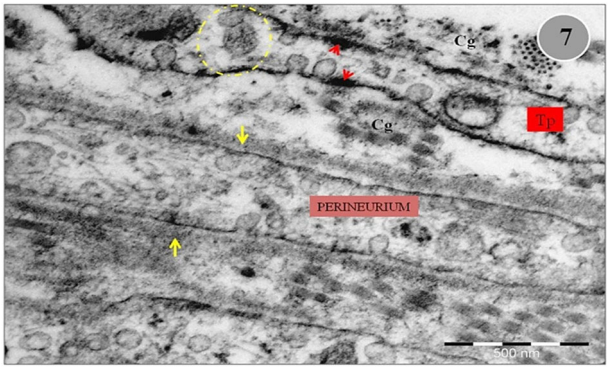

Figure 7 – ***Transcytosis by a telopode (Tp) inside of a peripheral nerve (detail for the elliptic area in Figure 5). Two patches of subplasmalemmal densities can be detected (red head arrows). Yellow arrows mark basement membrane facing both sides of the perineurial cell. See details in Figure 8. Cg: Collagen fibrils.***

Our IEM with focus to the terminal cutaneous nerves showed a very high immunoexpression for type IV collagen corresponding to the continuous BM around perineurial epithelial cells, as well as accompanying SCs inside of the endoneurium (Figures 9–14). Concerning the BM profiles of endoneurial TCs identified by TEM, indeed, limited areas of positive immunoreaction for type IV collagen associated to slender moniliform cell prolongations of EDCs *recte* Tps of the endoneurial TCs (for an overview see Figure 9 and for details see Figures 13 and 14) were detected. A strong positive immunoreaction for $\alpha6\beta4$ integrin and BPAG2 was associated with basal pole of the keratinocytes facing dermo–epidermal basal membrane at the hemidesmosomal level (not shown here) but no immunopositive signal was detected

along the endoneurial Tps even where some short profiles of basal membrane appear associated with endoneurial TCs.

Altogether our advanced observations concerning the infrastructure of the normal human cutaneous peripheral nerves strongly suggest that endoneurial fibroblasts/EDCs are a special cell phenotype different from the regular fibroblasts rich in ER involved in fibrillar collagen synthesis. By their intercellular contacts, endoneurial TCs appear as a 3D network inside/along of each peripheral nerve. In this respect, we drafted a diagrammatic representation as depicted in Figure 15.

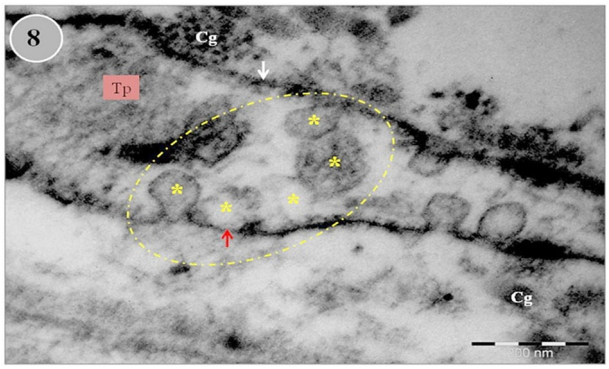

Figure 8 – *Detail for Figure 7. Inside the cytoplasm of a telopode (Tp), a tubulovesicular system represented by cargo vesicles in close contact each other (yellow asterisks in ellipsoidal areas), which connect plasma membrane facing perineurium (red arrow) to the opposite side facing endoneurium (white arrow), can be detected. Cg: Collagen fibrils.*

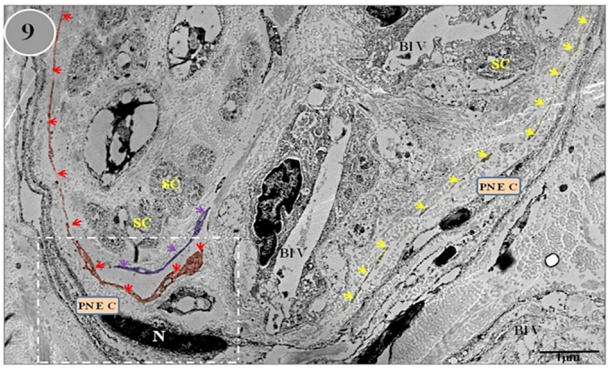

Figure 9 – *An overview from a skin peripheral nerve exhibiting few slender profiles of telopodes (red, pink and yellow head arrows) inside of the endoneurium. Perineurium is represented by perineurial epithelial cells (PN E C); one of them exhibits the nucleus (N). Rectangular area is detailed in Figures 10 and 11. Bl V: Blood vessels; SC: Schwann cells.*

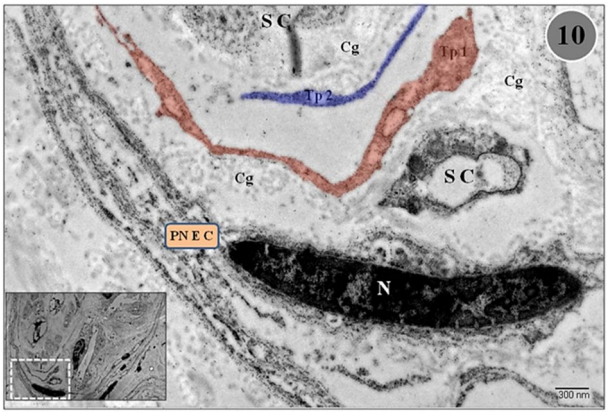

Figure 10 – *Detail for the white rectangular area from Figure 9 and depicted in inset as overview. Tp 1 and Tp 2 mark slender telopodes of two endoneurial telocytes. Cg: Collagen fibrils; N: Nucleus of a flattened perineurial cell (PN E C); S C: Schwann cells.*

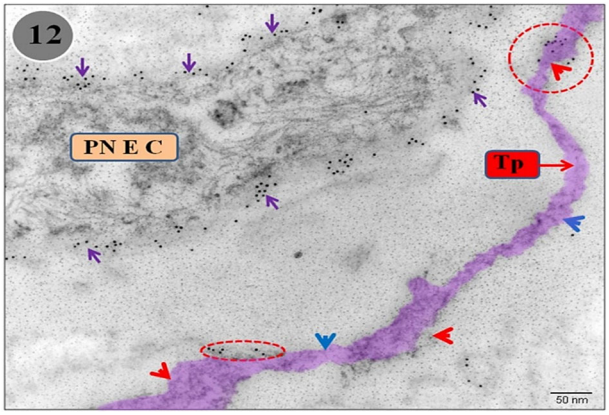

Figure 12 – *Along a moniliform telopode (Tp), represented by podoms (red head arrows) alternating with podomeres (blue head arrows), there are two small immunopositive zones for type IV collagen (elliptic and encircled areas), but strong immunopositive signal can be seen associated to basement membranes on both sides of the perineurial cell (PN E C).*

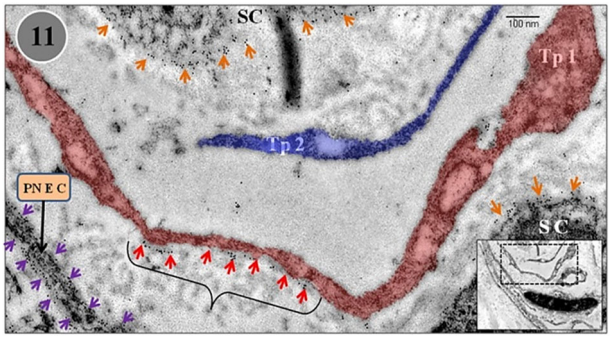

Figure 11 – *Immune electron microscopy reaction for Cg IV. Electron dense dots marked by small pink arrows represent the Cg IV corresponding to the BMs on both sides of the perineurial cell (PN E C). Brown small arrows mark Cg IV corresponding to the BM of Schwann cell (S C). A small profile of positive immunoreaction for Cg IV is marked by small red arrows along the Tp 1. Inset: an overview. BM: Basement membrane; Cg IV: Type IV collagen; Tp 1, Tp 2: Telopode 1, 2.*

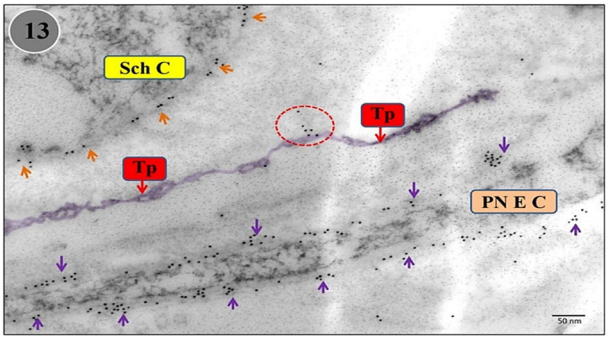

Figure 13 – *Positive immunoreaction for Cg IV is visible as electron dense dots inside of basement membrane of the Schwann cell (Sch C), as well as on both sides of the perineurial cell (PN E C). Note a very limited positive immunoreaction for Cg IV (electron dense dots inside of the red elliptic area) near a telopode (Tp). Cg IV: Type IV collagen.*

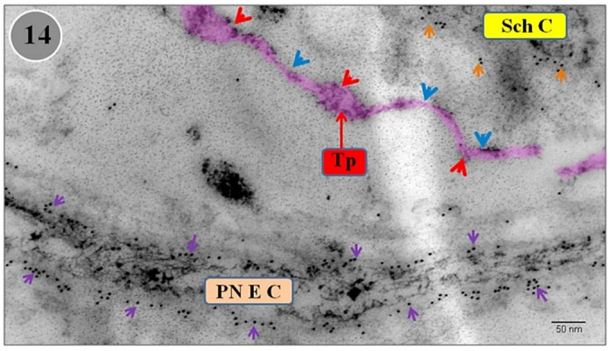

Figure 14 – ***A moniliform small profile of a telopode (Tp) represented by podoms (red head arrows) alternating with podomeres (blue head arrows) has no positive immunoreaction for Cg IV. By contrast, a strong immunoreaction for Cg IV is detected in association with basement membrane profiles (small pink arrows) of perineurial cell (PN E C) and Schwann cell (Sch C) (small brown arrows), respectively. Cg IV: Type IV collagen.***

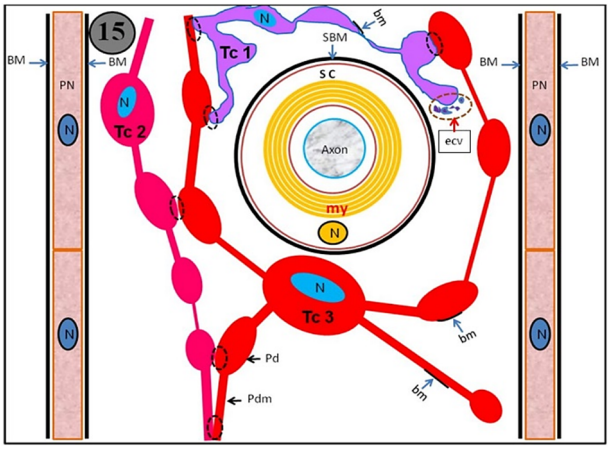

Figure 15 – ***Diagrammatic representation of a longitudinally-sectioned cutaneous peripheral nerve. Elongated perineurial cells (PN) appears with a basement membrane (BM) on both sides. Three telocytes (Tc 1–Tc 3) are depicted inside of the peripheral nerve. Two or three long slender telopodes originate from each cell body where the nucleus (N) is located. Each telopode is represented by the podomeres (Pdm) and podoms (Pd) alternations. Homocellular junctions are depicted (black dotted encircled areas) and small patches of basal lamina (bm) can be seen. Extracellular vesicles (ecv) delivered by telocyte is depicted in brown elliptic area. A myelinated (my) axon enwrapped by a Schwann cell (S C) with a continuous basement membrane (SBM).***

What about the endoneurial TCs' roles?

TCs' role is still a matter of discussion. Concerning TCs' roles, there are many published papers which demonstrate TCs' involvement in physiology and pathophysiology of different tissues/organs. Their important role is mainly related to their peculiar ability to establish both homocellular communications (a 3D network) and heterocellular communications by close contacts with other cell types (endocytes, pericytes, MCs, muscle cells, free nerve endings, etc.), and by releasing EVs, which may act as intercellular cargos with intercellular information (containing bioactive molecules) with putative role in cell signaling [2, 36]. TCs play important roles in tissue homeostasis maintenance, tissue regeneration, as well as in etiopathogenesis of different diseases (telocytopathies) [2, 19, 22–24, 106–108].

Often, TCs were described as stem cell niches component in various organs [109]. TCs are involved in crosstalk communication between stromal cells and initiate regenerative processes by supporting local stem cell niche differentiation. There is a body of evidence that TCs have a powerful potential in tissue repair and regeneration in heart, liver, lung, skin, skeletal muscle, meninges, choroidal plexus, eye, uterus, urinary system, intestine, and so far [3, 64, 106, 110]. By their role as mesenchymal precursors, resident CD34-positive stromal cells/TCs play an important role during tissue repair and tumor stroma formation [15].

Many published studies demonstrate TCs' role in tissue regeneration mostly accompanied by neoangiogenesis *via* heterocellular junctions of TCs with endothelial cells and/or pericytes, as well as *via* paracrine secretion represented by telocytic exosomes and their vascular endothelial growth factor (VEGF) or nitric oxide synthase 2 (NOS2), including micro-ribonucleic acids (miRNAs) cargo [26, 111].

In a recent experimental study, Ravalli *et al*. (2021) showed that density of TCs (which physically resides in muscle interstitium located near muscle satellite cells, nerve, and microvasculature) detected in skeletal musculature of 16 weeks sedentary rats were significantly reduced *versus* rats subjected to regular exercise [112].

Soliman (2017) showed that during the embryonic development of the spinal ganglia, TCs formed homo- and heterocellular contacts with the neuroblasts, and satellite capsular cells, and concluded that TCs may act as a major player in regulating cell differentiation and cell death during embryogenesis [66].

In our electron microscopic study concerning peripheral nerves inside of normal human skin, TCs appear in clearly close contact each other (homocellular junctions). In this context, should we consider that by their homo- and heterocellular communications could be this inner 3D network of endoneurial TCs a primitive cell-to-cell communication system inside of each peripheral nerve?

Notable peripheral nerve damage can be devastating and severe life-altering. After injury, Wallerian degeneration may occur in the distal axon. Autologous nerve grafting is considered the "gold standard" as treatment.

Different from the CNS, peripheral nerves highly exhibit ability to regenerate post-injury. So far, it is clear that an injured peripheral nerve may regenerate with or without stem cells participation. Different endoneurial cell types participate in peripheral nerve regeneration.

Peripheral nerve regeneration can be realized with stem cells participation, or other endoneurial cell types can be involved

Peripheral nerve regeneration with stem cells participation

There are many sources of stem cells used in nerve tissue engineering [113]. In response to local environmental differences, stem cells of the nervous system generate different types of mature cells [114].

Neural crest derivatives, including peripheral nerves contain stem or precursor cells with ability to be used in regenerative medicine. Some neural crest-like cells persist

in adult tissues in a nascent multipotent state and can differentiate to Schwann-like cells able to myelinate neurons [93, 115–117].

Using different cell/tissue sources, neural stem cells were obtained (they can differentiate into neurons, astrocytes, oligodendrocytes, as well as into Schwann-like cells) after transplantation can be used to repair peripheral nerve after injury [115, 117]. Myelination of axons is crucial for the repair of peripheral nerve damage, so that transplantation of Schwann-like cells derived from the neural stem cells, which promote and support neurite outgrowth, become an attractive method to be applied in clinical practice.

Peripheral nerve regeneration without stem cells participation

From so far published papers, clearly, SCs can switch to a repair-supportive differentiation state after nerve damage, remaining the major endoneurial cellular component involved in nerve regeneration [115, 118]. Following to nerve injury, an upregulation of the transcription factor c-Jun in SCs took places and amplifies a cascade of downstream changes so that SCs acquired a repair phenotype [118–120].

In an elegant study, Stierli *et al*. (2018) showed that no stem cell is required for peripheral nerve regeneration [121]. In fact, all cell types within peripheral nerves (especially SCs) proliferate efficiently following injury, independent of a stem cell population. In their experimental study, using several transgenic mice with lineage specific expression to know composition and turnover cells identified in the endoneurium of sciatic nerve, they found that most cells (cca. 70%) were positive for S100 cytoplasmic marker and recognized by electron microscopy as SCs. Following injury, all myelinating SCs can dedifferentiate to the proliferating progenitor-like SCs involved in regeneration of peripheral nerves, and switch to become non-myelinating SCs. Interestingly, among many other cell types identified inside the injured peripheral nerves, the authors identified a special cell morpho-phenotype (cca. 12.5% from the total cell population within a peripheral nerve) having long cell extensions spreading inside of the endoneurium, which make visible contacts with other cell types within the nerve (authors termed these cells as 'tactocytes'). Taking in consideration both morphological aspects (long cell prolongations) and immunomarkers profile expressed by this cell type, a question is raised: should we consider this described cell phenotype to be in fact endoneurial TCs? Because of their extensive ER, previously they were considered as fibroblasts, it seems that rather we may consider them as "activated" endoneurial TCs involved in some ECM components synthesis and deliverance required for injured nerve repair. Mention must be mad, ECM composition is very different compared with that found in uninjured peripheral nerve [121, 122].

What about the endoneurial TCs' involvement in nerve repair process?

Many roles have been hypothesized for TCs in different tissues/organs, mainly related to the maintenance and modulation of tissue homeostasis, regeneration, and tissue repair. In a very elegant and recently published study, Liao *et al*. (2021) demonstrated that cardiac TCs *via* TCs delivered exosomes and their miRNA cargo exert strong therapeutic effects by promoting cardiac angiogenesis after myocardial infarction [26]. Exosomes as small nanovesicles by their bioactive molecules are considered to have the capacity to influence tissue healing and regeneration [123]. Concerning the peripheral nerve regeneration, we can only speculate if the endoneurial TCs by their abilities to perform cell–cell contacts, but especially by delivering EVs may contribute to produce adequate ECM components to modulate nerve repair process. In such circumstances on may consider that peripheral nerves regenerate independent of a stem cell population, but other endoneurial cell types may successfully participate, namely SCs and TCs.

To our best knowledge, there is no published paper reporting clear about endoneurial TCs involvement in post-traumatic anesthesia or some diseases nerve reparation. The spindle-shaped cells with rectangular or triangular bodies of cells with slender long cytoplasmic processes were described but no assimilation with endoneurial TCs is mentioned. In a recent published study concerning a putative role of endoneurial fibroblast-like cells in the reduction and finally resolution of endoneurial edema after nerve trauma, Elbarrany & Alasmari [94] evaluate that endoneurial fibroblast-like cells might represent around 2–9% of the endoneurial cells. They reported that endoneurial fibroblast-like cells gradually modified their morphology becoming flattened with long-branching cytoplasmic processes and finally form a barrier-like cellular layer, and consequently are involved in localization of endoneurial edema following nerve crush injury. Nevertheless, if we consider that such slender cell prolongations can be also Tps of the endoneurial TCs, then mention must be made that these, similar to cordocytes assimilated with TCs described by Dănăilă [56] in the brain, have important roles, mainly concerning the protection against different internal and external aggressions [56, 62]). In this line, it is worth to note that in a recent electron microscopic investigation of peritumoral stroma in a case of human BCC (unpublished data), we identified TCs running with their Tps along the cutaneous nerves' axis also suggesting a protective role against invasive tumor cells.

To answer the question to which extent TCs are involved in post-injured nerve reparation, additionally more refined studies including *in vitro* and *in vivo* experiments using isolated TCs together with nervous cells/nerves with focus on regenerative medicine [36] must be developed.

Conclusions

Based on the so far reported data in the literature, we searched as well as on our TEM investigation of the peripheral cutaneous nerves, we concluded that cell population termed endoneurial fibroblasts/EDCs exhibiting long and slender moniliform cytoplasmic prolongations, often performing homocellular contacts and delivering EVs are really true endoneurial TCs. Moreover, to some extent, our IEM data is a plus to strength this conclusion. We appreciate the inner 3D network of endoneurial TCs by their homo- and heterocellular communications appears as a genuine cell-to-cell communication system inside of each peripheral nerve.

Note

The illustrative support used for this paper is in totality original and was performed and belongs to the corresponding author (N.M.).

Conflict of interests

The authors declare no conflict of interests.

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Corresponding author

Nicolae Mirancea, PhD, Senior Scientist grade I, Department of Developmental Biology, Institute of Biology Bucharest of Romanian Academy, 296 Independenţei Avenue, P.O. Box 56–53, Sector 6, 060031 Bucharest, Romania; Phone +4021–221 92 02, e-mail: nick_mirancea@yahoo.com

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