

Telocyte – a particular cell phenotype. Infrastructure, relationships and putative functions

NICOLAE MIRANCEA

Institute of Biology Bucharest of Romanian Academy

This paper is dedicated to the 150th anniversary of the Romanian Academy.

Abstract

Here we review on the infrastructure, relationships and putative role of a new cell phenotype termed telocyte. Ultrastructural and immunochemical characteristics of telocytes, their identification in different tissues, homo- and heterocellular telocyte's contacts and considerations concerning their putative role in normal as well as pathological conditions are largely presented. A special section of the paper is devoted to our opinion/hypothesis concerning the possibility that, to some extent, endoneurial fibroblast dendritic phenotype (existed in the peripheral nerve endoneurium) can be assimilated to the telocyte or, at least to the telocyte-like. In this respect, we report about a body of evidence that endoneurial fibroblasts dendritic cells share some infrastructural characteristics with telocyte phenotype. Telocytes involvement in pathology, tissue engineering and regenerative medicine is also debated.

Keywords: telocytes, infrastructure, cell signaling, endoneurial telocyte-like, regenerative medicine.

☞ Definition of the telocyte as particular cell phenotype. Telocyte – a new cell phenotype identified as stromal (interstitial) component

The telocyte (TC) is a new interstitial (stromal) cell phenotype identified, described and introduced in scientific literature by Popescu's group, firstly termed interstitial Cajal-like cell, then replaced with the name of telocyte [1–3]. Interstitial cells of Cajal (ICCs) are very heterogeneous in appearance. ICCs are characterized as cells with numerous mitochondria, abundant intermedium filaments and gap junctions, which connect the cells with each other and with smooth cells. They are different from neurons, smooth muscle cells and fibroblasts, having a pacemaking activity and regulatory roles in gastrointestinal muscle movement [4]. Like ICCs, TCs have a mesenchymal origin, but with specific ultrastructural characteristics [5]. Now is clearly established that telocytes (TCs) are not Cajal-like cells [6].

Morphology of TCs (cell body and telopodes)

Ultrastructural (US) characteristics remain currently the modality for precisely identification of TCs. So far, a specific immunohistochemical (IHC) marker has not yet been found, but several IHC markers have been found that have variable expression in TCs from different tissues [7, 8].

In Figure 1 is depicted a diagrammatic representation of the ideal morphological aspect of a telocyte and its relationships with microenvironment [9].

A TC is defined as a special interstitial cell (phenotype), having a relative small cell body with 1–5 (more frequently 2–3) specific very long (several tens to

hundreds of micrometers) and slender cell extensions named telopodes with moniliform aspect (alternation of dilated segments termed podoms and thin segments termed podomers (often less than 200 nm thickness). TC shape is pending to the numbers of its cell extensions: piriform for one telopode, spindle for two telopodes, triangular for three telopodes and stellate for more telopodes [5]. TC cell body is occupied by an ovoidal euchromatic nucleus (clusters of heterochromatin are attached to the inner membrane of nuclear envelope) and some endoplasmic rough reticulum and Golgi apparatus. Usually, podoms accommodate mitochondria, endoplasmic reticulum and caveolae (Ca²⁺ uptake/release units). Moreover, telocytes have the ability to make and deliver extracellular vesicles [3, 6, 10, 11]. Briefly, telocyte is a cell with telopodes [12]. Indeed, the identification of TC is mostly based on recognition of their telopodes [13]. Some telopodes may branching with a dichotomous pattern.

TC immunophenotypes

Transmission electron microscopy (TEM) remains a golden method for identifying TCs. So far, not a single immunomarker can be considered specific for detecting TCs [5, 14]. However, in order to discriminate between telocytes and fibroblasts or other elongated interstitial cell type, some immune labeling was done both *in vivo* and in isolated and cultured cells. For example, an *in vitro* study of isolated interstitial cells from the heart tissue and cultivated showed that TCs were positive for CD34/c-kit, CD34/vimentin and CD34/PDGFR- β (platelet-derived growth factor receptor-beta), while fibroblasts were only vimentin and PDGFR- β positive [15]. Moreover, when compared, TCs were different from pericytes: TCs were CD34 positive and α -SMA (alpha-smooth muscle actin)

weak positive while pericytes were CD34 negative but α -SMA positive [15]. Cardiac TCs were double positive for CD34/PDGFR- α in primary culture [16].

It is considered that different likely organ-specific immunophenotypes of TCs might exist [5]. Taken in consideration that TCs express c-kit/CD117, vimentin, VEGF (vascular endothelial growth factor) and CD34, while most interstitial and tissue stem cells do not express c-kit/CD117, it was suggested the last immunophenotype to be considered as an immunomarker for TCs identification [17]. More recently it is accepted to consider that CD34 is the most reliable TC marker, while c-kit has been excluded for some organs [8]. Endoneurial fibroblasts are CD34 positive [18].

There is a body of evidence as infrastructural characteristics, immunohistochemical data, gene profiles, proteome features and miRNA (micro-ribonucleic acid) signature [3, 16] supporting the telocyte as a distinct and interesting cell phenotype, different from other types of interstitial cells.

Identification and distribution of TCs. Where are TCs located?

TCs are located in the stroma of many tissues/organs. So far, telocytes have been widely identified in many tissues and organs. Telocytes are stromal cells present in all normal, but also in altered tissues.

Many laboratories adopted the term and concept of telocyte and described this cell phenotype in different normal tissues as heart [19–20], trachea and lungs [21–23], human trigeminal ganglion [24], skin [25], urinary system [7–26], myometrium [27], fascia lata [28], serosae as pleura [29] and mesentery [5, 30], spleen [31], testes [32], dura mater [33] or altered tissue by different diseases,

including cancer: in basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) [10], mammary carcinoma [34].

Faussone Pellegrini & Popescu [5] consider that in adulthood most of the TCs have the morphology of fibrocytes. Skin telocytes and fibroblasts are two distinct dermal cell populations [35].

In an elegant study concerning interstitial cells within human adult trigeminal ganglia, using TEM and immunolabeling for CD117/c-kit, Rusu *et al.* [24] concluded that trigeminal neurons envelopes mostly consists of satellite glial cells, but are also combined with interstitial Cajal-like cells and/or telocytes.

As a general observation, mostly TCs occupy a strategic position. Often TCs are located around the capillaries, in very close vicinity or in direct contact with stem cells/progenitor cells, nerves, mast cells [8, 10, 12, 33, 36].

Ultrastructural aspect of TCs

A TC has a small cell body where an ovoidal nucleus is located and two or more (maximum five) long cell prolongations termed telopodes [12]. Each telopode starts abruptly from the cell body as slender, sometimes folded, convoluted cell extension [5, 8, 12] with moniliform aspect: thin segments less than 200 nm thickness termed podomers alternate with dilated segments termed podoms (Figure 1). As a general rule, inside of perinuclear cytoplasm, a (rough) endoplasmic reticulum and, eventually, dictyosomes of Golgi apparatus are located (Figures 2 and 3). Usually, podoms accommodate mitochondria, some endoplasmic reticulum profiles and caveole (Ca^{2+} uptake/release units). Inside of telopodes, microfibrils as cytoskeleton (mostly represented by vimentin, and scarce microtubules) can be identified [10].

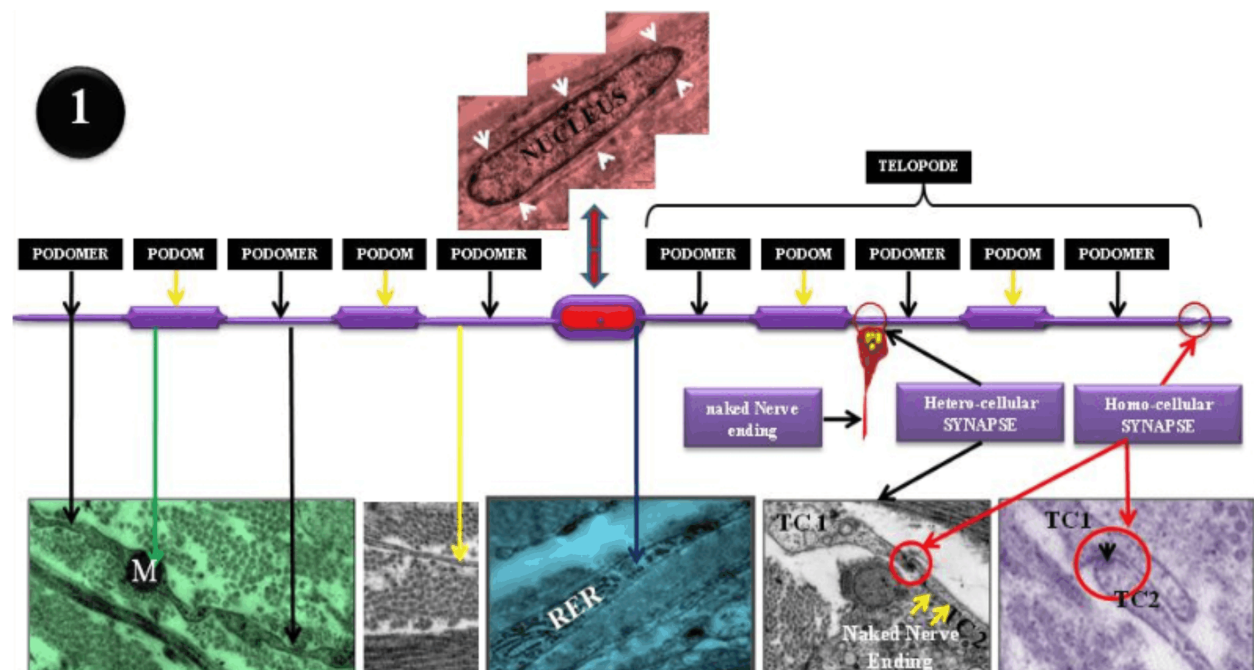


Figure 1 – Diagrammatic representation of the telocyte morphology and infrastructure phenotype. Two long telopodes originate from the cell body where the nucleus is located. Each telopode is represented by alternations of podomer–podome. Synapses as homo- or heterocellular junction are depicted (encircled areas) between the telocyte and another adjacent cell. RER: Rough endoplasmic reticulum; M: Mitochondria; TC1: Telocyte 1; TC2: Telocyte 2. (Original).

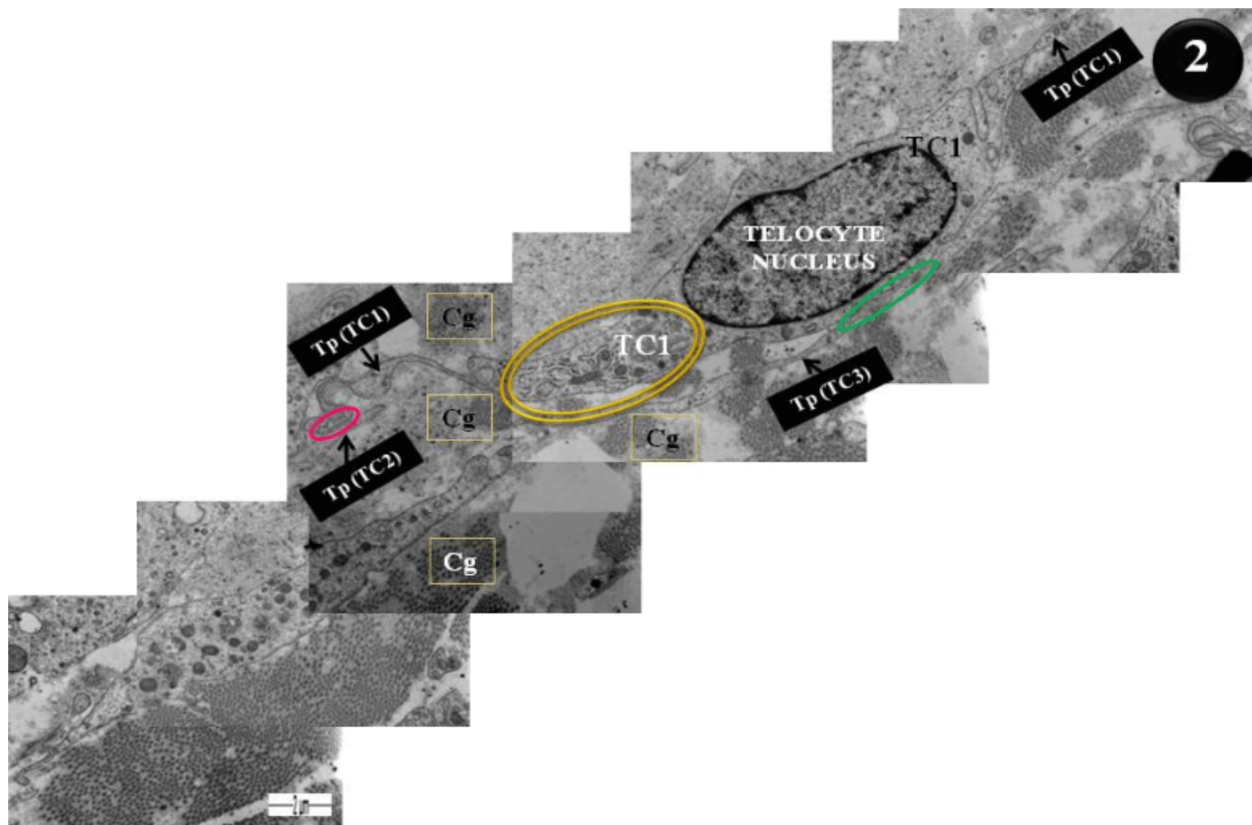


Figure 2 – A nucleated telocyte (TC1) with two telopodes. One telopode [Tp(TC1)] exhibits an alternation of podomers and podoms and become in contact (red ellipse) with a telopode of another telocyte [Tp(TC2)]. Near the nucleus of TC1, rough endoplasmic reticulum and a dictyosome of Golgi apparatus are located (yellow elliptic area) detailed in Figure 3. A very long telopode of the telocyte 3 [Tp(TC3)] become in contact with body cell of TC1 (green ellipse) (see detail in Figure 3). Fibrillar collagen (Cg) can be seen around all three telocytes. (Cutaneous BCC – basal cell carcinoma).

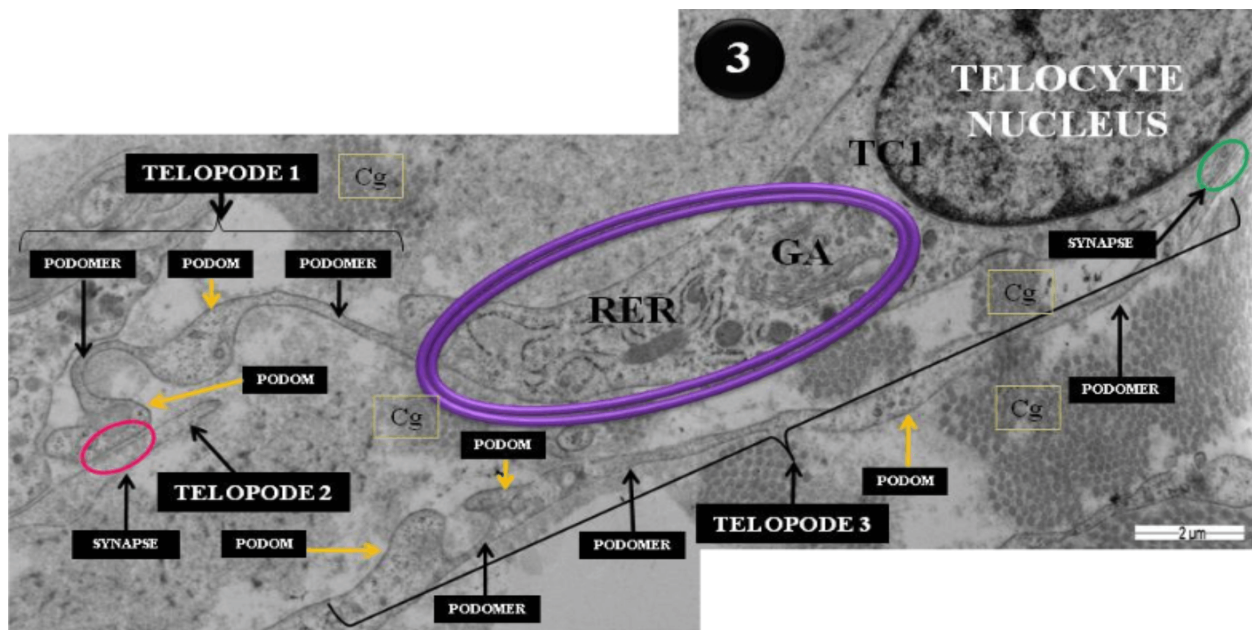


Figure 3 – Detail for Figure 2. Red elliptic area indicates a homocellular contact between the telopode 1 and telopode 2, while green elliptic area indicates a homocellular contact between telopode 3 and the cell body of telocyte 1 (TC1). RER: Rough endoplasmic reticulum; GA: A dictyosome of Golgi apparatus; Cg: Collagen. (Cutaneous BCC).

☐ Telocyte's contact. Intercellular communications of telocytes

Concerning TCs, two main characteristic must be emphasized: their ability to connect each to other or with resident/non-resident cells from the tissue stroma

(interstitium), strategic position of some telocytes inside of tissue being either in close vicinity or in direct contact with (putative) stem cells/progenitor cells or with nerves or immunocytes, very often overlapping capillaries [8, 10].

Now is well documented that by their slender and long cell extensions TCs are able to realize (1) direct cell–

cell communications/junctions, either (a) homocellular junctions or (b) heterocellular junctions, as well as (2) indirect cell–cell communications mediated by shedding membrane vesicles/microvesicles [10].

Sometimes, TCs also may be in contact with some anhist components of the stroma (connective extracellular matrix) as collagen or elastic fibers/fibrils.

Homocellular junctions

Telocytes establish homocellular contacts by their end-to-end telopodes or telopode become in direct contact with cell body of another telocyte (Figures 2–4; Figure 6, inset d; Figure 9).

Homocellular junctions/contacts are made by simple apposition of plasmalemmas of the two contiguous cells or by complex junctional areas resembling various types of the junctions' adherens termed *puncta adherentia minima*, *manubria adherentia* [8].

A special mention must be made about the junction termed nexus (gap junctions) also performed by TC, knowing that this type of contact allow the exchange of small molecules, so-called secondary molecular messengers with role in cellular signaling [8, 37].

A particular kind of intercellular communication between adjacent telopodes is performed by plasma membrane recombination process, the place where affronted two plasmalemmas appear to undergo dissolution, so that an open cell–cell communication is visible (Figures 8 and 13). Plasma membranes recombination/fusion is frequently described in case of adjacent tumor cells [38] but was also reported in case of telocytes located inside of tumor stroma [10].

The ability of TCs to perform intercellular communications and consequently to make a virtual 3D (three-dimensional) network is related to their functional role inside of the tissue where they are located and also, in a larger context of maintaining the homeostasis of the whole body. Any abnormalities concerning the quantity and location of TC inside of the stromal tissue may be related to some diseases, including cancer [10].

Heterocellular junctions

Besides the homocellular junctions a telocyte may establish also heterocellular synapses with different other types as stem cells, nerve cells, fibroblasts/fibrocytes, endothelial cells (EC), pericytes (PC), macrophage, mast cell as well as collagen and elastic fibers (Figures 5 and 6). Is remarkable the strategic position of TCs adjacent to capillary in almost tissues: skin [10], mammary gland [34], adipose tissue (present study), *dura mater* layer of meninges [33].

Telopodes may exhibit two times dichotomous branching aspect as is depicted in Figure 6, upper part. Coated pit and coated caveole (Figure 6, insets a and b), cytoskeleton and short patches of basement membrane (Figure 6, inset c), can be seen. Usually, telocytes are devoid of basement membrane. Sometimes, short profiles of basement membrane may accompany a telopode (Figure 6, inset c).

Often, many telocytes run at the periphery of the continuous blood microvessels as is depicted in Figure 7. Such distribution of TCs as sheath of telopodes enfolding the vascular endothelial cells was described in ectopic endometriosis [39].

It is worth to mention existence of the focal sub-plasmalemmal densities detectable in some telopodes (Figures 8 and 9).

Telocytes are also present inside of stromal tissue between two or more apposed adipocytes (Figures 10–12). Here, telocytes exhibit very long (sometimes convoluted) and slender telopodes and quite often, telocytes accompany capillaries from adipose tissue stroma. When pericytes are missing, as is the case of grade II of obesity, to some extent, telopode takes a pericytic position as is depicted in Figure 12.

Indirect cell–cell communication mediated by special shedding membrane microvesicles

Almost normal or malignant cells, *via* the exocytotic endomembranes after fusing with plasma membrane are able to release into their extracellular micromedium [40]. It is considered that such delivered microvesicles play a special role in the horizontal transfer of important macromolecules among neighboring cells with role in intercellular signaling [15, 41].

Mention must be made that also telopodes can be involved in so-called event of shedding membrane vesicles [10, 11].

In another published paper, we reported [10] that two telopodes become in direct contact by their plasma membranes and perform a membrane recombination process, as is also depicted in Figure 13. At this level, a multivesicular cargo is visible inside of one telopode.

TCs release microvesicles (mean diameter of 180 nm) as a single or a pool of shedding membrane vesicles; the delivered macromolecules from microvesicles are considered to play a paracrine role by sending signals to neighboring cells and eventually modifying their transcriptional activity [12].

Functional roles

Nowadays is well documented that stromal (interstitial) cells play important roles during morphogenesis and tissue/body homeostasis as well as during tumor development. Among the heterogeneous stromal (interstitial) cellular populations, telocytes seems to be of great interest concerning their ability to perform a 3D network, connecting each with other, but especially connecting to other cell types. So far, the exact function of TCs has not been fully understood, but their location in close vicinity of important cell types, even establishing different kind of synapses, as is the case of pericytes, endothelial cells, nerve endings, mastocytes suggest that TCs play important role in cell signaling. TCs are also involved in intercellular signaling *via* stromal synapses and shed microvesicle transfer.

Telocytes are considered a special cell phenotype member of the stem cell/putative stem cell niches with a presumptive role of “nurse” (supportive) cells. By their homo- and heterocellular contacts, TCs integrate the informations from nervous, vascular, stem cells and immune system. TCs are considered to play an important role in almost tissues homeostasis [8, 42, 43].

Any perturbation in their number or loss of cell contacts seems to have negative consequences associated with different diseases (see the section concerning TCs implications in human pathology).

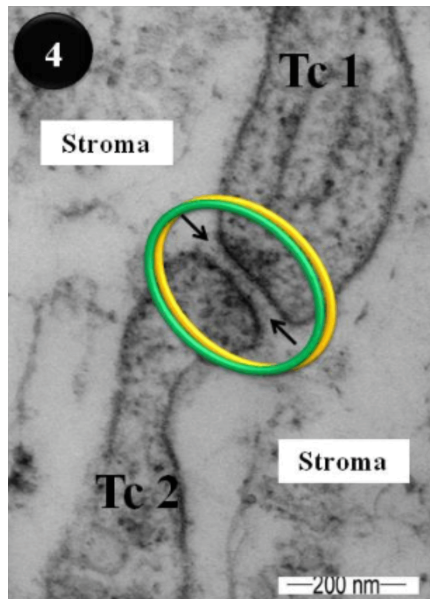


Figure 4 – Homocellular junction (yellow and green ellipsoidal areas) between two telocytes (TC1 and TC2). An electron dense material can be detected between the end of TC1 and TC2 (black opposite arrows). (Mammary carcinoma).

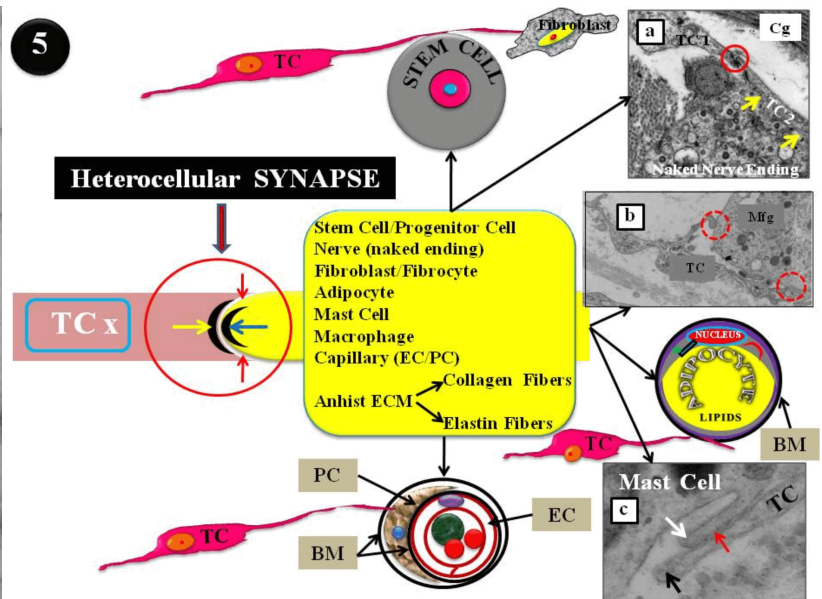


Figure 5 – Diagrammatic representation of homocellular and heterocellular junctions. Besides the homocellular junctions as is visible in inset (a) between TC1 and TC2 (red encircled area), a telocyte (TC x) establish also heterocellular synapses with different other types as stem cells, nerve cells, fibroblasts (Fbl)/fibrocytes, adipocytes, endothelial cells (EC), pericytes (PC), macrophage (Mfg) [dotted encircled areas in inset (b)], mast cell [red arrow in inset (c)] as well as collagen (Cg) and elastic fibers (Fb). BM: Basement membrane; ECM: Extracellular matrix; TC: Telocyte. (Original).

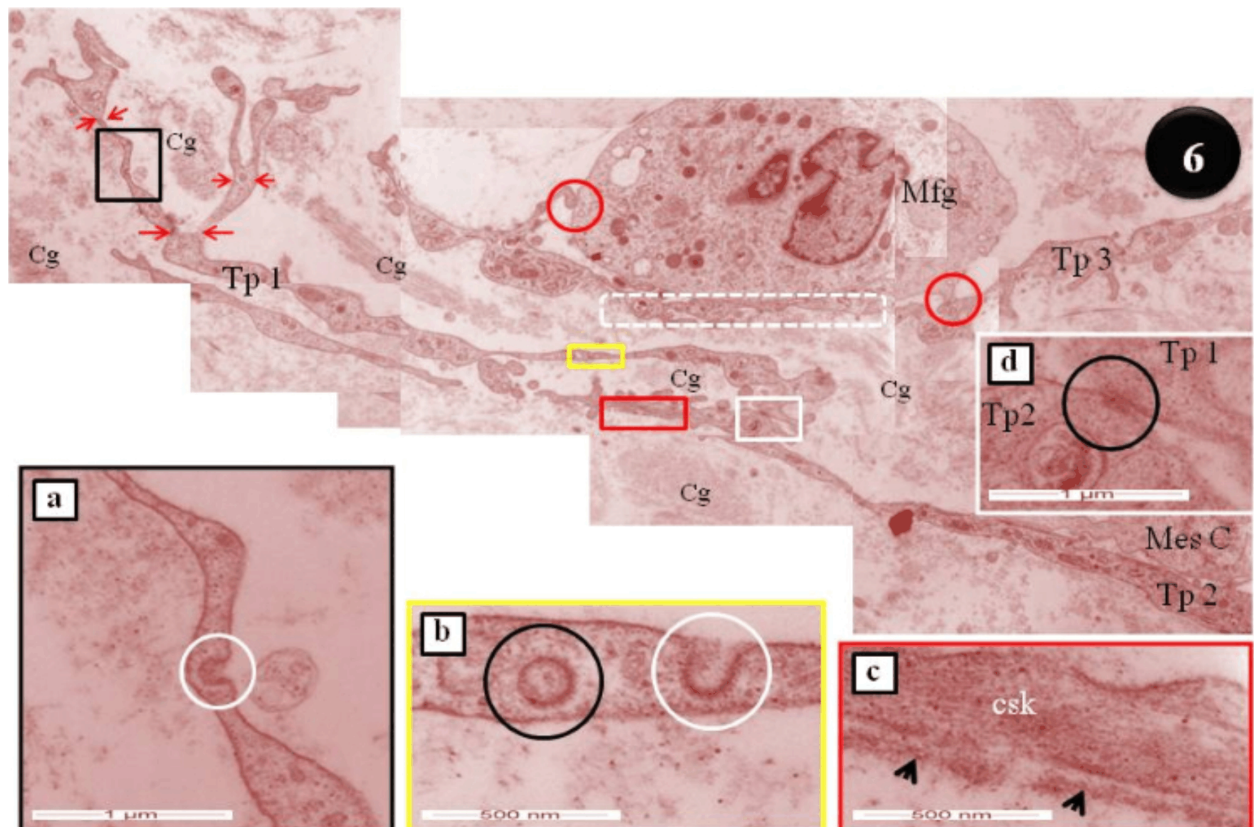


Figure 6 – Three telopodes (Tp 1–Tp 3) establish homocellular and heterocellular junctions. Tp 1 exhibits two times dichotomous branching (red arrows in left upper part of the image). In case of Tp 1, a coated pit can be seen [black framed area, detailed in inset (a), encircled area], while a coated pit and a coated caveole in yellow framed area is detailed in inset (b) (white encircled area and black encircled area, respectively). In case of Tp 2, red framed area, detailed in inset (c), depicted a telopodial segment with visible cytoskeleton (csk) and patches of basement membrane (black head arrows). In white framed area, detailed in inset (d), a homocellular junction between Tp 1 and Tp 2 is visible (black circle). Red encircled areas include two heterocellular junctions between Tp 3 and a macrophage (Mfg). Cg: Collagen; Mes C: Mesenchymal cell. (Mammary carcinoma).

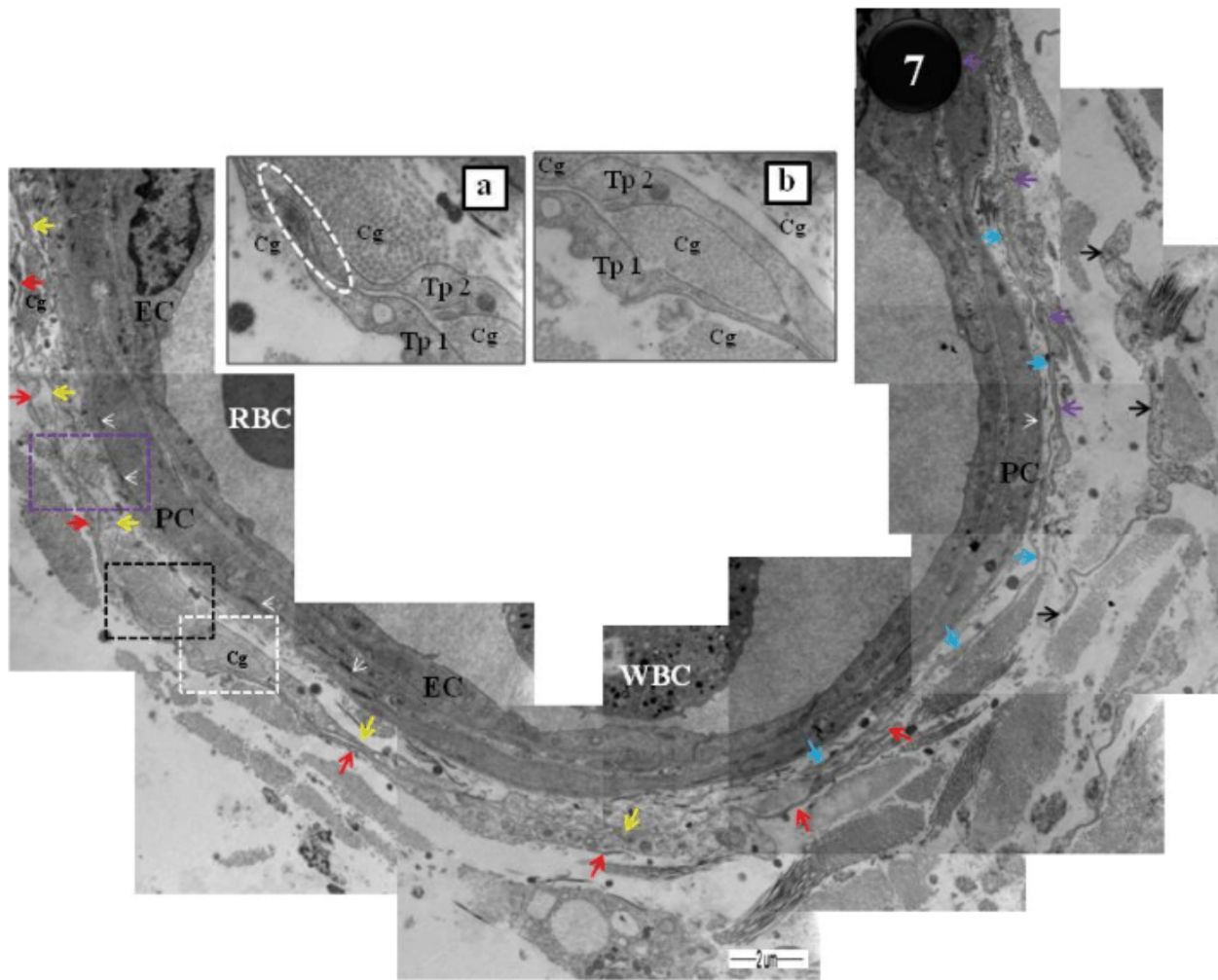


Figure 7 – A continuous endothelial wall (EC) is accompanied by pericytes (PC) with specific peripheral subplasmalemmal densities (white head arrows). Many telopodes (blue, yellow, red, pink and black arrows) run at the periphery of the blood microvessel. Inside of the blood vessel lumen, red (RBC) and white (WBC) blood cells are visible. Pink dotted framed area is detailed in Figure 8, while black and white framed areas correspond to the inset (a), respectively inset (b). In inset (a) and inset (b), collagen (Cg) fibrils can be detected both at the periphery of telopodes (Tp 1 and Tp 2) as well as in between telocytes. Elliptic area in inset (a) delimits a homocellular junction between two telopodes Tp 1 and Tp 2. (Cutaneous BCC).

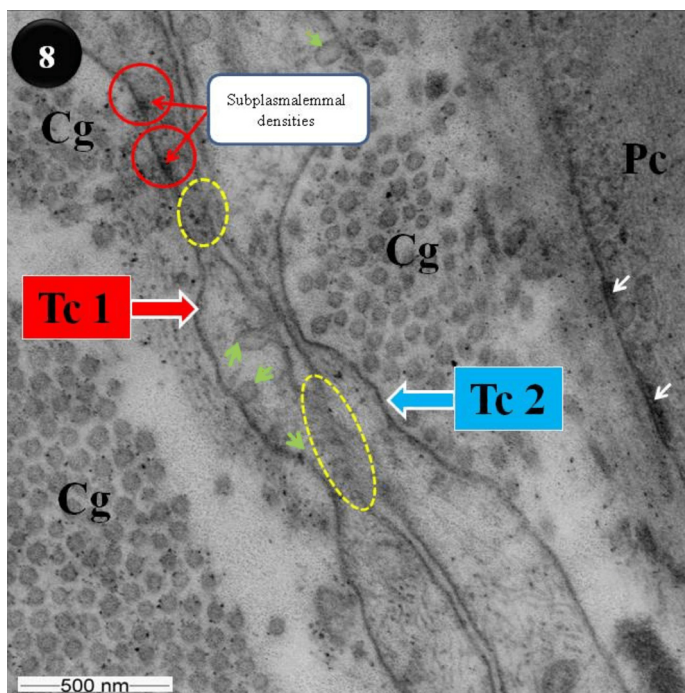


Figure 8 – Detail for pink framed area in Figure 7. Two telopodes of telocytes TC1 and TC2 become in close apposition so that, to some extent, they perform plasma membrane recombination (yellow elliptic areas). TC1 exhibits small subplasmalemmal densities (red arrows in red circles) and microvesicles (green arrows). White arrows mark subplasmalemmal densities characteristic to the pericyte (PC). Cg: Collagen. (Subcutaneous adipose tissue).

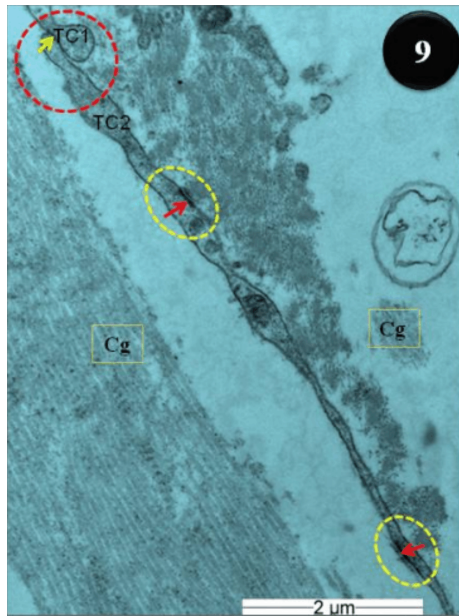


Figure 9 – Inside of the tumor stroma, in between tumor cells (not shown), two telocytes (TC1 and TC2) establish a homocellular junction (yellow arrow in red encircled area). TC2 exhibits two small subplasmalemmal densities (small red arrows) in an opposite manner each to other. Cg: Collagen. (Mammary carcinoma).

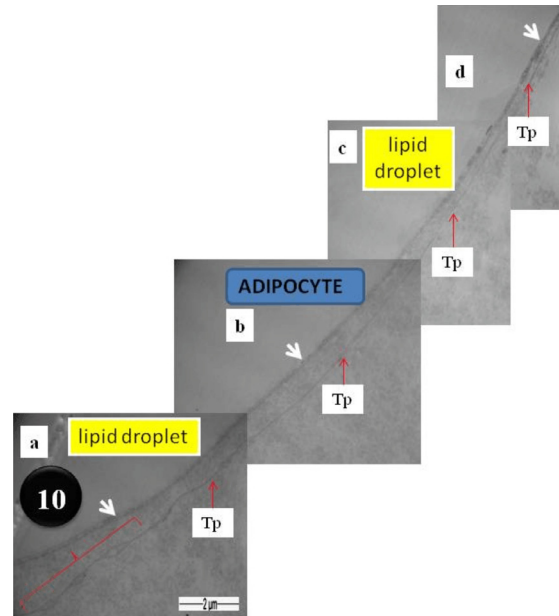


Figure 10 – A slender telopode (Tp) accompanies the periphery of an adipocyte. A rim of adipocyte cytoplasm (white head arrows) can be seen. (Human mesentery).

Figure 11 – Enlarged frame (a) from Figure 10 shows the characteristic alternation of podoms (blue head arrows) and podomers (yellow head arrows) of the telopode. (Human mesentery).

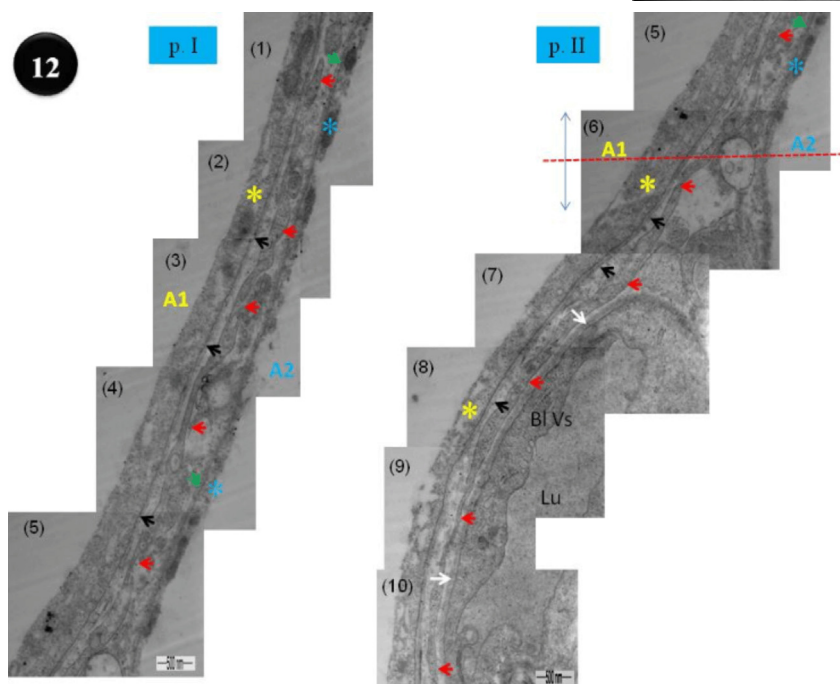
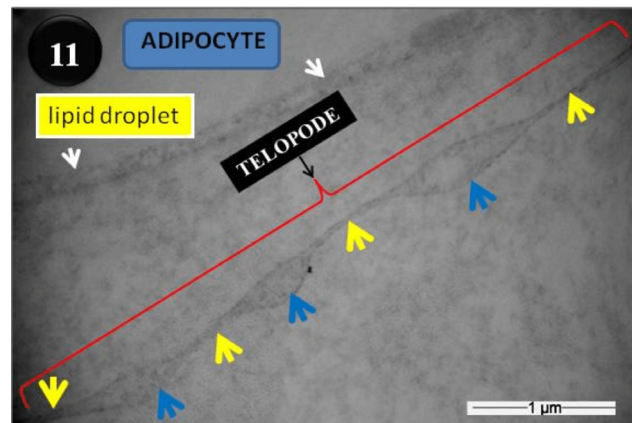


Figure 12 – A reconstruct from 10 successive pictures [(1)–(10)] shows a very long telopode (red arrows) from the adipose tissue stroma running between two adipocytes (A1 and A2). No basement membrane can be seen associated to telopode. Each adipocyte has a small rim of cytoplasm (yellow asterisks, respectively blue asterisks and a properly basement membrane at the periphery (black small arrows and green small arrows, respectively). A capillary (Bl Vs) is interposed between the telopode and adipocytes. Around the endothelial cells/wall, a basement membrane (white arrows) can be seen but pericytes are missing; to some extent, telopode is in pericytic position. Lu: Capillary lumen. (Human omentum – grade II obesity).

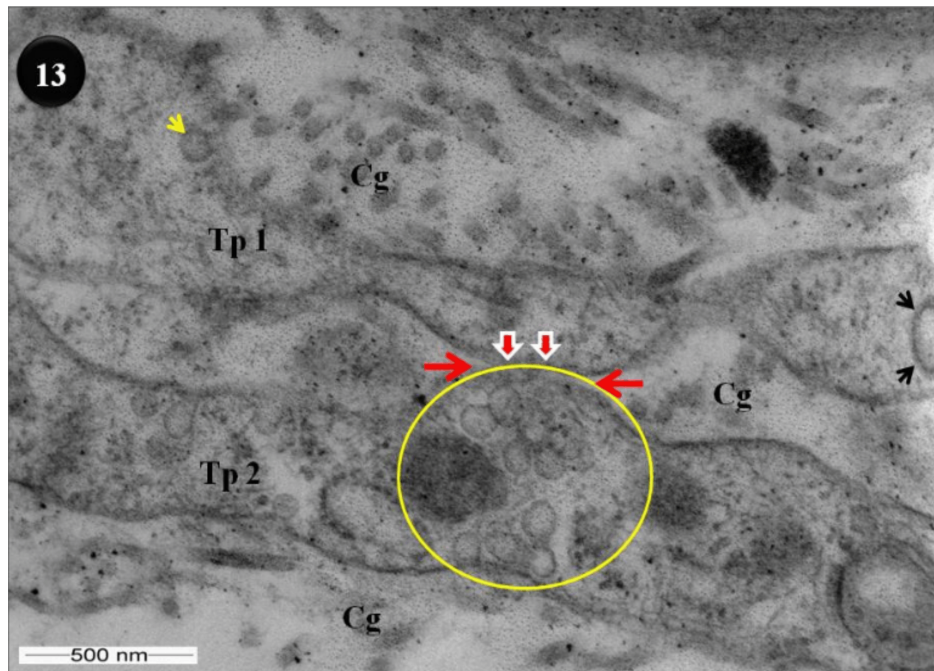


Figure 13 – Two telopodes (Tp 1 and Tp 2) become in direct contact (red arrows) by their plasma membranes and perform a membrane recombination process (large head arrows). At this level, a multivesicular cargo is visible inside of telopode Tp 2 (yellow elliptic area). Yellow head arrow marks a clathrin-coated pit while black head arrows mark a clathrin-coated vesicle inside of telopode Tp 1. Cg: Collagen. (Subcutaneous adipose tissue).

☞ To which extent endoneurial fibroblasts/dendritic cells can be assimilated to the telocytes?

The peripheral nervous system is composed of three different compartments: (1) epineurium, (2) perineurium and (3) endoneurium.

Resident and imported/transitory endoneurial cell types can be detected inside of the endoneurium. Endoneurium compartment of the peripheral nerve sheath is represented mainly by myelinated and/or unmyelinated axons and their surrounding Schwann cells, fibroblasts, capillaries (endothelial cells and their associated pericytes), collagen fibers mainly type I collagen synthesized by Schwann cells and to a lesser extent, by endoneurial fibroblasts [44–46]. Imported/transitory endoneurial cell types can be also detected, *e.g.*, macrophages [47, 48], a few mast cells [49–51].

There is a matter of debate concerning the origin and function as well as implication in different pathology of the stromal cells inside of endoneurium. Normally, when cross-sectioned a human cutaneous peripheral nerve, exhibit a perineurial epithelial cell sheath with a basement membrane on both sides, which enwrapped the endoneurium. Mainly, inside of endoneurium, embedded into a fibrillar collagen net there are myelinated or non-myelinated axons, Schwann cells surrounded by basement membrane and, a polymorphic cell population generally termed fibroblasts (Figures 14 and 15).

There are evidences that neural crest stem cells give rise to more than just Schwann cells in developing nerve. Josef *et al.* (2004) [52] identified endoneurial fibroblasts as a novel neural crest derivative whereas perineurial cells, pericytes and endothelial cells are not neural crest derived. Pericytes express α -SMA, Schwann cells are associated with axons and express glial markers as S100 β and a basal lamina, while endoneurial fibroblasts lack a basal lamina and fail to express α -SMA or S100 β . Previously,

Salonen *et al.* (1988) [53] also reported that after experimental nerve trauma S100 protein was expressed as a marker for Schwann cells while endoneurial fibroblast-like cells were S100-negative. Endoneurial fibroblasts are CD34 positive [18].

Comparative analysis of so far published papers leads to the conclusion that inside of the peripheral nerve sheath there are few cellular subpopulations of endoneurial fibroblasts.

In fact, is still a matter of debate concerning the differences between genuine fibroblasts from many other fibroblast-like cells [4].

Röyttä *et al.* (1987) [54] termed endoneurial fibroblasts as endoneurial fibroblast-like cells. They reported that during Wallerian degeneration and subsequent regeneration, endoneurial fibroblast-like cells showed marked phagocytotic activity and also fragments of basement membrane on their surface. Indeed, it seems that endoneurial dendritic cells may function as phagocytes under certain condition (assimilated to the endoneurial macrophages) [50, 55, 56].

There are few reports concerning identification of so-called endoneurial dendritic cells, distinct from the Schwann cells and conventional fibroblasts, able to express CD34 [50, 56–58]. Concerning the basement membrane presence or absence around the endoneurial fibroblast-like cells, there are conflictual data. Salonen *et al.* (1988) [53] reported that in normal peripheral nerves, ultra-structurally always Schwann cells are surrounded by a basement membrane but is absent around endoneurial fibroblasts.

Richard *et al.* (2014) [51] demonstrated that endoneurial fibroblast-like cells express CD34, neural/glial antigen 2 (NG2) and prolyl-4-hydroxylase- β . Moreover, half of the endoneurial fibroblast-like cells are able to express platelet-derived growth factor receptor- β and some also express the intermediate filament nestin *in vivo* (at a lower level than Schwann cells, which express high level of nestin [51].

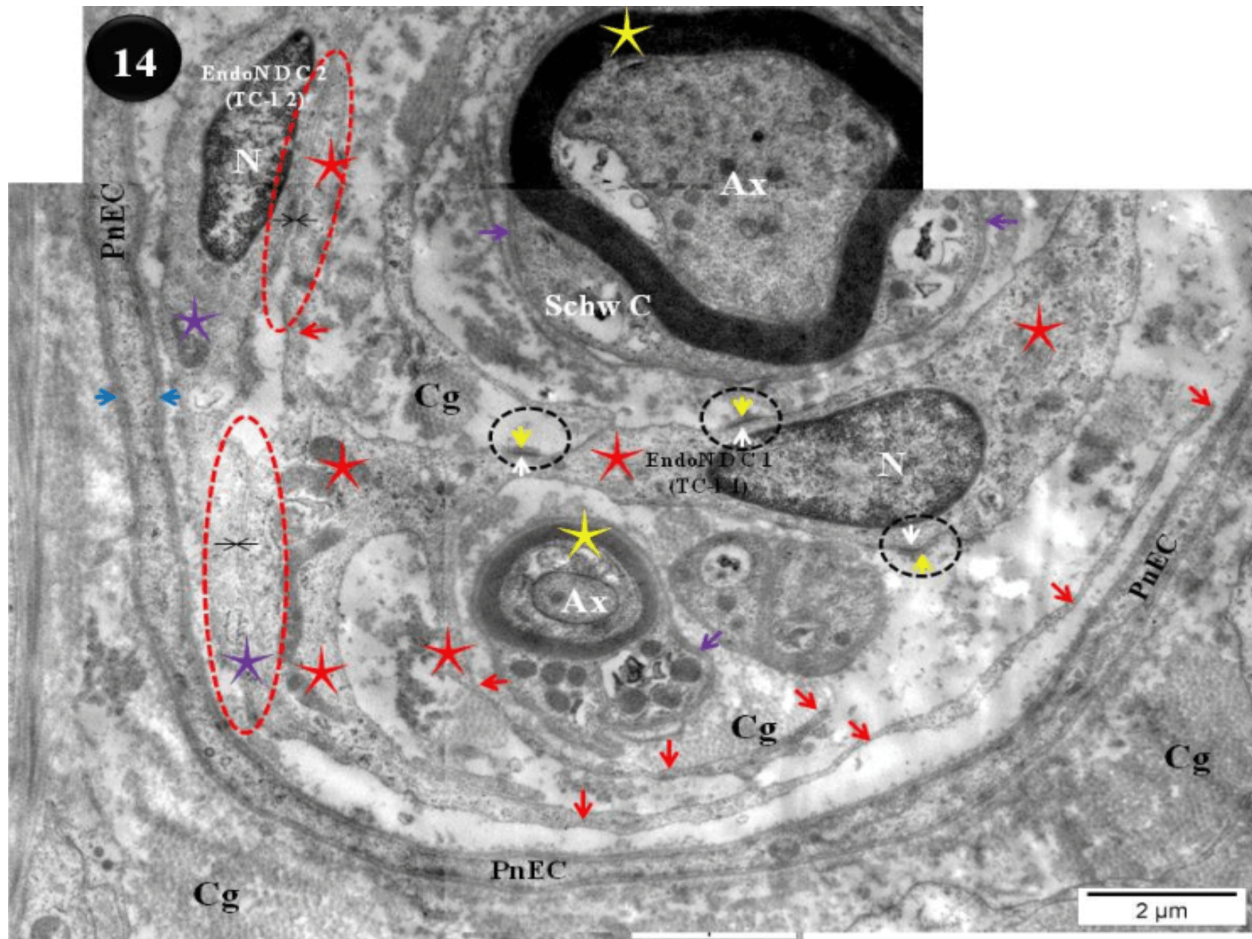


Figure 14 – Cross-sectioned human cutaneous peripheral nerve. A perineurial epithelial cell (PnEC) with basement membrane on both sides (blue arrows) wrapped a peripheral nerve. Inside of the endoneurium, two myelinated axons (Ax) and two nucleated (N) endoneurial dendritic telocyte-like cells [Endo N D C (TC-I 1) and Endo N D C (TC-I 2)] can be seen. Both endoneurial dendritic telocyte-like cells exhibit telopodial-like cell extensions (red and pink stars) which, to some extent become in close synaptic contacts (affronted black arrows). Small patches of subplasmalemmal densities (white arrows in black dotted elliptic areas) can be detected. Moreover, short profile of basement membrane affronted to each density can be seen (yellow arrows). Each Schwann cell (Schw C) has a basement membrane (pink arrows). Yellow stars mark myelin sheaths. Cg: Collagen. (Cutaneous BCC).

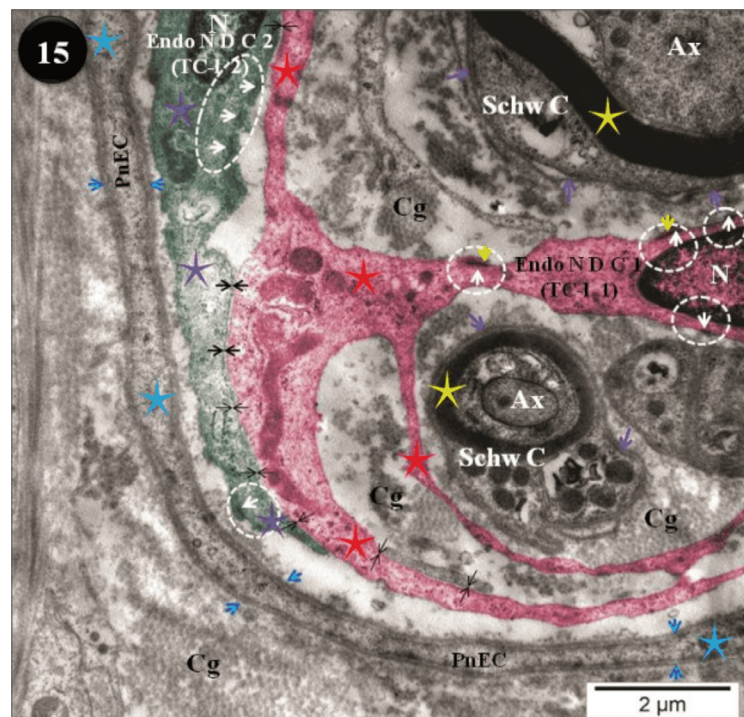


Figure 15 – Detail for Figure 14. For better identification of telopode-like profile, original/crude TEM image was digitally colored: in red for TC-I 1 and in green-blue for TC-I 2. PnEC: Perineurial epithelial cell; Ax: Axon; Nucleated (N) endoneurial dendritic telocyte-like cells [Endo N D C (TC-I 1) and Endo N D C (TC-I 2)]; Schw C: Schwann cell; Cg: Collagen. (Cutaneous BCC).

The endoneurial fibroblasts also assimilated with so-called endoneurial dendritic cells have a special morphology (Figures 14 and 15). Endoneurial dendritic cells appear as spindle or stellate in the shape. Their cellular body accommodates an ovoidal and euchromatic nucleus. Two–three slender cell extensions emerge somehow abruptly from the cell body. Moreover, sometimes, these very long cell extensions exhibit a moniliform aspect with more or less regular alternation of dilated and very thin segments remembering the telopodes (podoms alternate with podomers) characteristic to the telocytes (Figures 16 and 17). That might be the main reason to term this endoneurial cells as telocyte-like cells. Similar to telopodes of telocytes, also endoneurial telocyte-like cells exhibit telopodial-like cell extensions which, to some extent become in close synaptic contacts (homocellular junctions) but also heterocellular junctions with perineurial cells are detected (not shown here). Just to mention, Gherghiceanu & Popescu [19] described telocytes–Schwann cells junction in human heart. Small patches of subplasmalemmal densities can be detected. Moreover, short profile of basement membrane affronted to one of such densities can be seen in case of Figure 14; better visible in Figure 15.

In a recently published paper, Díaz-Flores *et al.* [59] review the morpho-functional characteristics of CD34+ stromal fibroblasts/fibrocytes/telocytes. When refer to the fibroblastic endoneurial cells, they identified and termed their prolongations with the term telopodes.

Because so far, there is no report about a reliable immune labeling specific to TCs, still is very hard to discriminate canonical TCs better identified by infrastructural aspects from other stromal cell mimicking the telocytic phenotype. In these circumstances, in a recently published paper [10] we appreciated that endoneurial dendritic cells of peripheral nerves in the skin, which also exhibit few long cell extensions, to some extent, mimicking telopodes and having somatic synapses with other endoneurial dendritic cells as well as with perineurial epithelial cells and Schwann cells, cannot be assimilated to TCs. Now, we performed additionally investigations, including an immune electron microscopic

(IEM) study, for different molecules of interest (type IV collagen, $\alpha 6 \beta 4$ integrins, etc.) applied to normal human skin. Following the IEM protocol published elsewhere [60–62], we investigated by immune electron microscopy especially type IV collagen distribution inside of the normal human peripheral/cutaneous nerve.

Our immune electron microscopy applied to the terminal nerve in normal human skin showed an accurately detection for type IV collagen corresponding to the continuous basement membrane around perineurial epithelial cells as well as accompanying Schwann cells inside of the endoneurium (Figures 16 and 17). Moreover, basement membranes of endothelial cells and pericytes of the blood microvasculature are positive for type IV collagen (Figure 18). This is in contrast with the almost absence immune signal for type IV collagen around the dendritic endoneurial cells. Our TEM examination and immune electron microscopic investigations demonstrate that very occasionally some endoneurial dendritic cells exhibiting telopodes express only patches of basement membrane (Figures 14 and 15) coincident with/corresponding to short profile of immunopositive detection for type IV collagen (not shown). This aspect is similar to that observed by TEM for human dermal telocytes or telocytes located inside of human mammary gland (Figure 6c) or adipose tissue stroma (not shown).

Moreover, a very interesting infrastructure we described for the first time in the literature is that telocytes located in dermal skin in BCC exhibit small subplasmalemmal densities (Figure 8). Their size runs from 250 to 500 nm in length and 10–20 nm wide. Such kind of infrastructures we identified as small subplasmalemmal densities are also detectable in TCs from the human mammary gland (Figure 9) or adipose tissue stroma. It is worthy to note that small subplasmalemmal densities detectable in TCs are similar/remember those expressed by pericytes (Figure 8). In case of pericytes, subplasmalemmal densities are all the time oriented to the abluminal face of capillary while, mention must be made that these densities can be located opposite each other as is the case of those TC located inside of the human mammary gland (Figure 9).

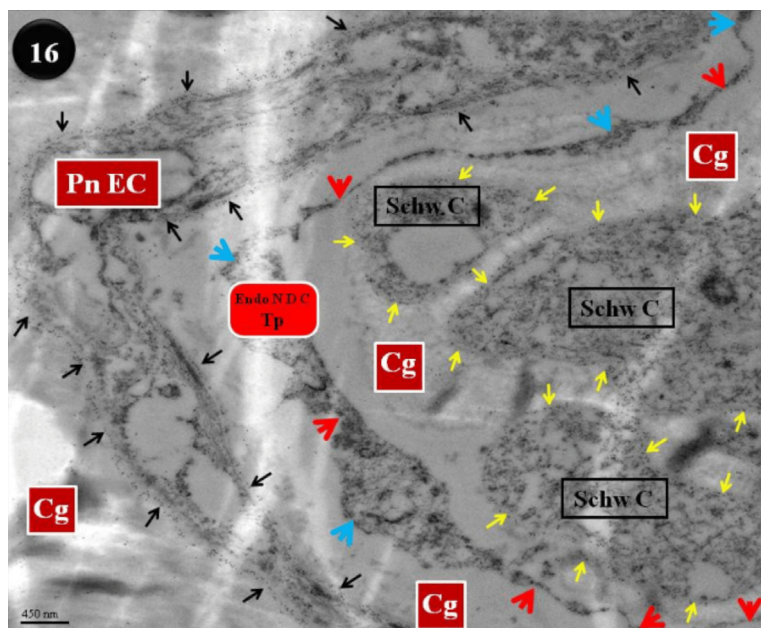


Figure 16 – An overview of cross-sectioned normal human cutaneous peripheral nerve. By IEM, immune reaction for type IV collagen is positive, corresponding to the basement membrane of perineurial epithelial cell (PnEC) (black arrows) as well as of Schwann cells (Schw C) (yellow arrows). Note the very long and slender cell extension (Tp) of the endoneurial dendritic cell (Endo N D C) with moniliform phenotype similar to the telopodes: podoms (blue head arrows) alternate with podomers (red head arrows). Moreover, no immunoreaction for type IV collagen can be detected in association with endoneurial dendritic telocyte-like can be seen. Cg: Collagen (Normal human skin).

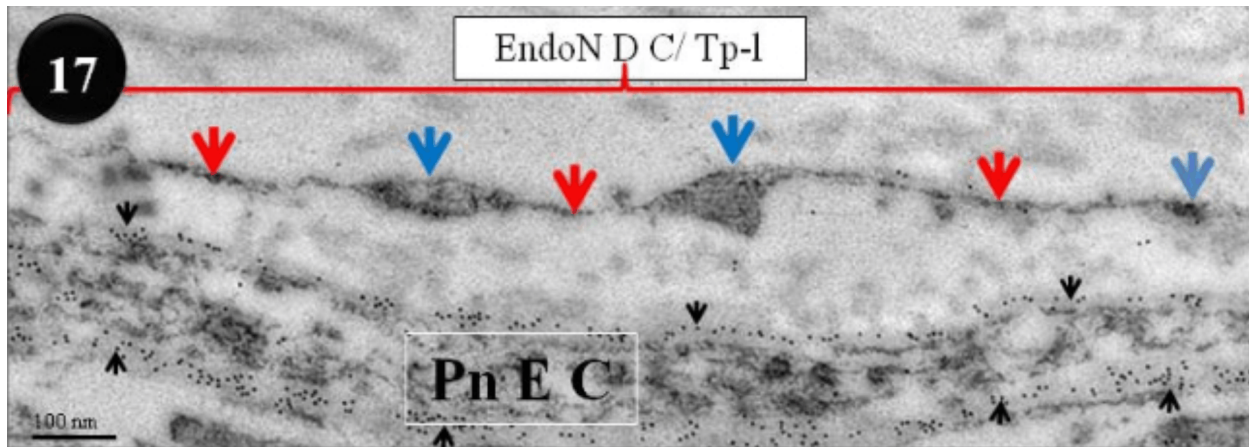


Figure 17 – Near the perineurial epithelial cell (Pn E C), a long and slender endoneurial dendritic cell with telocyte-like extension (telopode-like) exhibit a moniliform pattern: podoms (blue head arrows) alternate with podomers (red head arrows). Corresponding to the basement membranes of perineurial cell (PN) immune labeling with gold conjugated antibody identified the type IV collagen (black head arrows), while immunolabeling is missing in case of telopode. (Normal human skin).

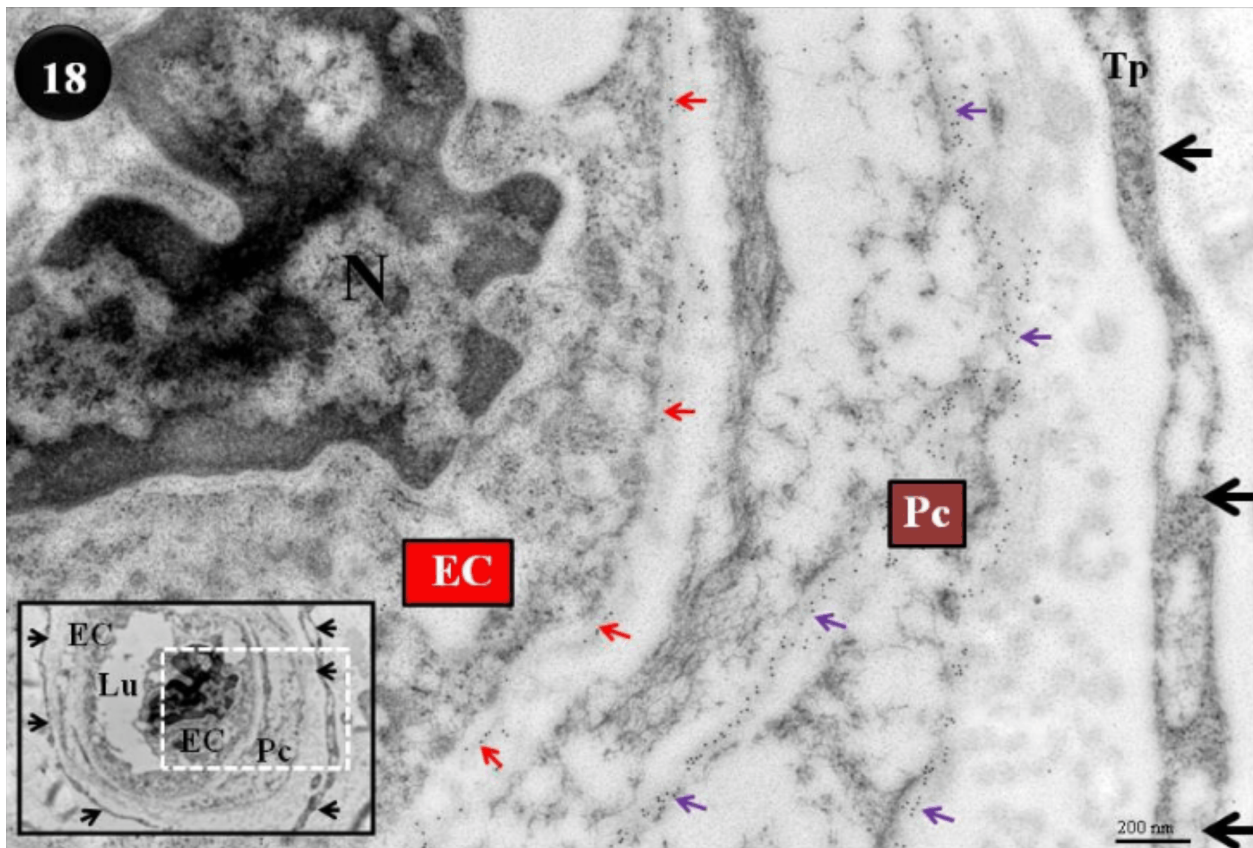


Figure 18 – Sector of a dermal capillary (see the white dotted frame in insert). By IEM, immunoreaction for type IV collagen is positive, corresponding to the basement membrane (red arrows) around the endothelial cells (EC) as well as associated pericytes (Pc; pink arrows). The telopodia (Tp) of the telocyte (black arrows) is devoid of basement membrane and, consequently also negative for type IV collagen. In inset: an overview for a dermal capillary represented by endothelial cells (EC) and associated pericytes (Pc). Telocytic processes can be seen (small black arrows) around blood vessel. Lu: Lumen; N: Nucleus. (Normal human skin).

Our data obtained by correlated TEM and IEM investigations concerning the endoneurial dendritic fibroblasts inside of the human skin nerve and other human tissues (human mammary gland and adipose tissue) emphasize that there are few common infrastructural aspects, which suggest that, to some extent, endoneurial dendritic cells may be assimilated to telocytes or, at least, to be considered a particular cell-phenotype, namely telocyte-like

cell. In conclusion, just to identify common infrastructural aspects for TCs vs. endoneurial dendritic fibroblasts, we emphasize: cell body accommodate an ovoidal nucleus, cell extensions are long, slender and, sometimes even showing a moniliform aspect, exhibit small subplasmalemmal densities, basement membrane is almost missing (except, for small patches of basement membrane).

Why to consider endoneurial fibroblast dendritic cells as TCs-like?

There is a consensus that there exist several TC sub-populations [8]. Moreover, endoneurial fibroblasts also represent a polymorphic cell population in normal or pathologic diseases involving peripheral nerves. In this context, infrastructural aspects of the endoneurial dendritic fibroblasts mimicking in many respects telocytes are as we summarize:

1. Telopodia-like slender cell processes exhibit more or less moniliform aspect;
2. Homocellular contacts between telopodia-like suggest a network organization inside of the endoneurium;
3. By their telopodial extensions, TC-like perform also heterocellular contacts;
4. Endoneurial TCs-like are devoid of basement membrane but similar to TCs from other tissues/organs, short patches of basement membrane can be seen as is also documented by IEM when very scanty immune signal for type IV collagen is detected;
5. Small subplasmalemmal densities are expressed, sometimes affronted by dense extracellular matrix material (a kind of focal contacts), an infrastructural aspect also observed in case of TC located in other tissue/organ types.

Moreover, to all the above infrastructural aspects of the endoneurial fibroblasts mentioned we add that endoneurial dendritic fibroblasts are CD34 positive [18, 56, 59], and CD34 remains the most reliable TC marker [8].

In conclusion, there is a body of evidence sustaining that some endoneurial dendritic fibroblasts of the human peripheral nerves represent a particular cell phenotype, in many respects mimicking telocytes, so that we propose to be considered telocytes or at least, telocytes-like.

TCs implications in human pathology

From so far published papers, it seems that TCs are involved in many diseases. For example, Bosco *et al.* [63] suggested that TCs have a putative role in placental barrier impairment during preeclampsia (PE). They found that different from the normal placenta, in PE TCs are embedded in very high amount of fibrillar collagen.

Richter & Kostin [64] reported that during failing human heart telocytes decreased in number as result of apoptosis and altered extracellular matrix composition (in zones of heart with replacement fibrosis or in zones with tightly packed fibrillar collagens), the TCs are significantly reduced or even absent.

TCs from BCC and SCC are reduced as number and mostly located inside of very fibrotic tumor stroma and, have a restraint number of heterocellular junctions. This limitation of TCs heterocellular contacts suggests a possible alteration of cell–cell communication into the peritumoral stroma as well as into the whole tumor mass. Alterations of cellular signaling and, consequently, a limitation in cell–cell cooperation is a general hallmark of tumor cells, a prerequisite for invasive behavior and migration through blood and lymphatic vessels and nerve sheaths to disseminate and proliferate in ectopic and distant places to form other tumors [10].

In normal skin, TCs usually surround blood vessels [25], while in the papillary dermis of psoriatic skin small

blood vessels are not surrounded by TCs [65]. Interestingly, a recovery of dermal TCs redistribution is reported after local corticoid therapy [6, 66].

Manetti *et al.* [67] reported severe ultrastructural alterations of dermal TCs followed by a significant reduction/loss of dermal telocytes in systemic sclerosis (SSc). Severe reduction in number or even totally absence of TCs in SSc is not restricted to the skin, but it is recorded also in many visceral organs (gastric wall, myocardium, lung) affected by SSc [68].

Telocytes are reduced in fibrotic liver [69] but after partial hepatectomy it seems that TCs role in hepatic regeneration emphasized [70].

In acute salpingitis, exposure to acute inflammatory induces ultrastructural alterations of TCs, loss of their specific homo- and heterocellular connections, excessive amount of collagen fibers (interstitial fibrosis) and consequently small vasculature impairment, all leading to oviduct dysfunction [71]. Similar TCs alterations were reported by Yang *et al.* [39] in affected oviduct by endometriosis.

In an elegant study, concerning variations of chromosome 2 and 3 gene expression profiles among pulmonary TCs and other resident or infiltrative cells in the lung, Zheng *et al.* [72] concluded that TCs might be involved in anti-inflammatory response, prevention of lung cancer and may be associated with protective effects on pulmonary fibrosis or acute and chronic interstitial lung diseases.

Aging the skin, mainly due to telomere shortening [73], defective mechanisms of DNA repair, oxidative stress by reactive oxygen species damage and, cumulative genetic and/epigenetic alterations, all together affecting not only the keratinocytes but also epidermal unipotent progenitor cells including interstitial TCs, which, by their strategic relationships with putative stem cells and endothelial wall, play a special role in skin homeostasis and regeneration [25, 42].

Mention must be made that TCs as ubiquitous component of the interstitial cell population play important role in maintaining normal tissue/organ function. Any alteration in TCs number, infrastructure, and cells relationships is associated with imbalance in tissue regenerations and tissue/organ function. So far, published paper concerning interstitial cells analysis documented the involvement of TCs in almost investigated diseases. This is related mainly to their homo- and heterocellular junctions, so that any alterations of TCs immediately affects in principally capillary stability. In an experimental acute myocardial infarction model, Manole *et al.* [74] appreciated that TCs contribute to neo-angiogenesis *via* direct contact with endothelial cells and/or pericytes as well as *via* paracrine secretion (VEGF or NOS2). Moreover, TCs contain angiogenic miRNAs.

Perspectives: TCs involvement in Tissue Engineering and Regenerative Medicine

In order to repair/regenerate damaged or lost tissue/organ, many experimental models were elaborated. Worldwide laboratories obtained and characterized reconstructed tissue acquiring normal function from isolated cells, including stem cells, placed in an adequate cocktail of molecules and electrolytes to support not only cell pro-

liferation but especially cell differentiation and specific extracellular components expression in a temporally manner mimicking *in vivo* situation, finally leading to normal histogenesis. In this line, remarkable efforts were done in the recent years, more successfully being the human skin equivalent reconstruction as organotypic coculture, including a model with intrinsic vascularization [75–77].

Taken in consideration TCs' arrangement as a 3D network, their ability to perform homo- and/or heterocellular junctions plus membrane vesicles delivery into microenvironment, all together important players in cell signaling, presence of TCs in association with stem cell niches in different tissues [13, 22], one may conclude that TCs have a potential role in tissue regeneration and regenerative medicine [41, 78]. So far is still difficult to culture and propagate TCs but one may anticipate that an appropriate scaffold model as support for co-culture incorporating stem cells and TCs will offer the opportunity for tissue/organ reconstruction (tissue engineering) and regenerative medicine. Isolated and cultured human lung telocytes produce growth factors as VEGF and EGF *in vitro*, so that TCs might play an important role in angiogenesis [72].

In vivo, TCs may play a role in skin regeneration [42].

TCs may be involved in cardiac regeneration and repair by neo-angiogenesis after acute myocardial infarction [74, 79, 80].

Injection of TCs *via* caudal rat vein after renal ischemia-perfusion injury leads to attenuation of renal dysfunction [81].

Inside of the skeletal muscle tissue, there are some interstitial cells with characteristic morphology of TCs also positive for c-Kit/CD117 and VEGF. Bojin *et al.* [17] reported that such interstitial cells resembling TCs in co-culture with heterogeneous muscle stem cells (MuSCs) in adequate media *in vitro* systems enhance the capacity of MuSCs for mesodermal trilineages differentiation (adipocytes, osteoblasts and chondrocytes).

Currently is well documented that adult neurogenesis, namely the ability of neural stem/progenitor cells (NPCs) mostly located in the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus to differentiate to neurons and to migrate to the olfactory bulb and hippocampus, respectively is a real phenomenon. NPCs are also located in the meninges, neocortex and amigdala, brain stem and choroid plexus [80, 82–84]. Popescu *et al.* [83] detected TCs in meninges and choroid plexus, both structures able to modulate brain function during embryogenesis and adult life. Modulation of neurogenesis appears as a main therapy to correct stroke and neurodegenerative diseases [85, 86]. Taken in consideration that both meninges and choroid plexus contain putative stem cells in contact with TCs, Popescu *et al.* [83] consider that TCs might play a role in neuroregeneration during postnatal brain development.

Many reports documented the ability of TCs to release extracellular vesicles [5, 11, 14, 87]. In a recently published paper, Cismasiu & Popescu [87] demonstrated that in various tissues (including myocardium) telocytes deliver miRNAs to stem cells by extracellular vesicles suggesting that TCs have a role in cardiac tissue regeneration.

For many reasons, well emphasized in the above-mentioned publications, at least to some extent, telocytes by their cell contacts seem to play the role of a primitive nervous system [88].

Many laboratories worldwide devoted much attention to this very special cell phenotype termed telocyte and consequently, taking advantages from so many interesting results, especially concerning telocytes' roles, we should think for clinical applications.

☞ Conclusions

Telocyte represents a particular interstitial cell phenotype so far, better identified and characterized at the ultrastructural level. Their strategic tissue location (around stem cell niche, near or in contact with peripheral nerves and capillaries) correlated with their ability to establish homo- and heterocellular contacts (a 3D network) plus extracellular deliverance of microvesicles suggests a special role in cell signaling. To some extent, endoneurial dendritic cells may be assimilated to telocytes or, at least, to be considered a particular cell-phenotype, namely telocyte-like cell. An attractive field of research and useful opportunities for clinic applications of TCs in tissue engineering and regenerative medicine are already open.

Note

The illustrative support used for this review is in totality original and was performed and belongs to the author.

Conflict of interests

The author declares no conflict of interests.

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Corresponding author

Nicolae Mirancea, Professor, PhD, Department of Plant and Animal Cytobiology, Institute of Biology Bucharest of Romanian Academy, 296 Independenței Avenue, P.O. Box 56–53, 060031 Bucharest, Romania; Phone +4021–221 92 02, Fax +4021–221 90 71, e-mail: nick_mirancea@yahoo.com

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