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Telocytes revisited

Abstract: Telocytes (TCs) are a novel interstitial (stromal) cell type described in many tissues and organs (www.telocytes.com). A TC is characterized by a small cell body (9–15 μm) and a variable number (one to five) of extremely long and thin telopodes (Tps), with alternating regions of podomers (~80 nm) and podoms (250–300 nm). Tps are interconnected by homo- and heterocellular junctions and form three-dimensional networks. Moreover, Tps release three types of extracellular vesicles: exosomes, ectosomes, and multivesicular cargos, which are involved in paracrine signaling. Different techniques have been used to characterize TCs, from classical methods (light microscopy, electron microscopy) to modern 'omics'. It is considered that electron microscopy is essential for their identification, and CD34/PDGFRα double immunohistochemistry can orientate the diagnosis. Functional evidence is accumulating that TCs may be intimately involved in the maintenance of tissue homeostasis and renewal by short- and long-distance intercellular communication. This review focuses on the most recent findings regarding TC features and locations and the principal hypotheses about their functions in normal and diseased organs. TC involvement in regenerative medicine is also considered.

Keywords: exosomes/ectosomes; intercellular signaling; regenerative medicine; telocytes; telopodes.

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Introduction: identification and phenotypic expression of TCs

Telocytes (TCs) are identified as a new cell type among 'classical' interstitial cells. The key feature that distinguishes TCs from any other cell is their extremely long and thin prolongations named telopodes (Tps) (1). Therefore, TCs are shortly defined as 'cells with telopodes' (2) (Figure 1). Discovered by serendipity in 2010, TCs were previously (between 2005 and 2009) described by our team using the acronym ICLC (interstitial Cajal-like cells) (1). However, TCs are not Cajal-like cells. They are different from the well-known Cajal cells of the intestine and considered to be completely distinct in ultrastructure, immunophenotype, electrophysiology, gene profile, and proteomics (2–6). The TCs are widely distributed in vertebrate (fish, reptiles, birds, mammals, including humans) organs, as well as in serous membranes as detailed in Table 1.

Ultrastructural portrait

TCs are a rather unique cell type with a particular morphology, if it is examined by electron microscopy. TCs are defined by specific very long and thin, dichotomously branched, cytoplasmic processes called Tps, considered to be the 'ultrastructural hallmark' (1). The cell body, measuring between 9 and 15 μm, has a variable morphology: fusiform/pyriform/triangular depending on the number of Tps (21, 60). The Tps measure up to 1000 μm in length and between 0.05 and 0.2 μm in thickness, and have a moniliform aspect with many dilations – a 'bead on a string' appearance (1, 44) (Figures 2 and 3). The thin, fibrillar segments are called podomers (average diameter, ~75–80 nm) and the dilated, cistern-like regions are called podoms (average caliber, 250–300 nm) (42, 61). Podoms accommodate functional units consisting of caveolae, mitochondria, and endoplasmic reticulum, possibly involved in calcium uptake/release (5, 10) (Figure 4). Cytoplasmic organelles are scarce, located mainly in the cell body and in the podoms (mitochondria 5%, endoplasmic reticulum 1–2% of cell volume, caveolae 2–3%) (42, 61).

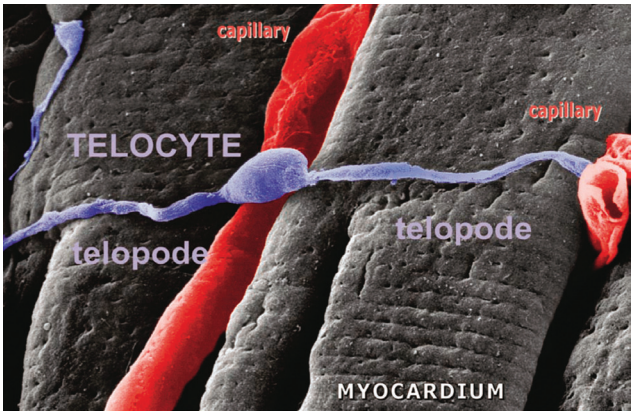

Figure 1 Representative scanning electron micrograph. Monkey left ventricular myocardium. The image shows a typical telocyte located across the cardiomyocytes. Another (possible) telocyte appears located near the cardiomyocytes (upper left). The 3D view reveals close interconnections of TCs with cardiomyocytes and capillaries. Note the cardiomyocyte striations and the openings of T tubules. Reproduced with permission from ref. (8).

TCs and their Tps are usually evidenced by transmission and scanning electron microscopy, electron tomography, and focused ion beam scanning electron microscopy (FIB-SEM) (Figures 5–7).

TCs have tortuous, overlapping Tps that interconnect to form a three-dimensional (3D) network by homocellular interactions (13, 40). Tps' homocellular contacts are established at distances between 10 and 30 nm, and generally can be classified as close contacts and nanocontacts; 'classical' cell–cell junctions such as gap junctions (42), and atypical homocellular junctions such as puncta adhaerentia minima, processus adhaerens, and manubria adhaerentia (13). Recessus adhaerentes junctions can also be formed between Tps and the cellular body of TCs or between Tps of different cells (13).

TCs occupy a strategic position in relation to stem cell niches (3, 32, 57, 62), blood capillaries (15, 45, 48, 63), and/or nerve bundles (21). Tps also establish contacts with other cells such as mast cells, basophils, lymphocytes, eosinophils, plasma cells, or macrophages (64), and non-cellular elements, e.g., collagen and elastic fibers.

Recently, evidence has come to light about the fact that TCs are able to release extracellular vesicles (12, 25, 27, 42, 65, 66). These vesicles might function as intercellular shuttles for biological signals. There are at least three types of extracellular vesicles: exosomes (released from endosomes, 45±8 nm), ectosomes (budding directly from the plasma membrane, 128±28 nm), and multivesicular cargos (MVCs, 1±0.4 μm).

Table 1 Telocyte distribution in various organs.

Heart	
Epicardium	(3, 7)
Myocardium	(4, 8–14)
Endocardium	(15)
Myocardial sleeves	(16)
Heart valves	(17)
Digestive tract and annex glands	
Esophagus	(18, 19)
Duodenum	(20)
Jejunum	(21)
Liver	(22)
Gallbladder	(23, 24)
Salivary gland	(87)
Exocrine pancreas	(26–29)
Respiratory system	
Trachea	(30, 31)
Lungs	(30, 32)
Urinary system	
Kidney	(33, 34)
Renal pelvis	(35)
Ureters	(34, 35)
Bladder	(34, 36)
Urethra	(35)
Female reproductive system	
Fallopian tube	(37, 38)
Uterus	(39–42)
Placenta	(43, 44)
Mammary gland	(45–47)
Vasculature	
Blood vessels	(48, 49)
Thoracic duct	(50)
Serous membranes	
Mesentery	(51)
Pleura	(52)
Other organs	
Meninges and choroid plexus	(53)
Skeletal muscle	(54, 55)
Neuromuscular spindles	(56)
Skin	(25, 60)
Eye	(57)
Prostate	(58)
Bone marrow	(59)

There is a net distinction between TCs and fibroblasts both from an ultrastructural point of view (Figure 8 and Table 2) and concerning gene expression profile. More than 2000 genes were found to be upregulated and >4000 downregulated in TCs compared with mesenchymal stem cells and fibroblasts (Figure 9). Functionally, fibroblasts are mainly involved in the synthesis of collagen and other matrix components, while TCs are oriented to intercellular signaling, either by direct contact (junctions) with surrounding elements or at long distance by release of extracellular vesicles (66).

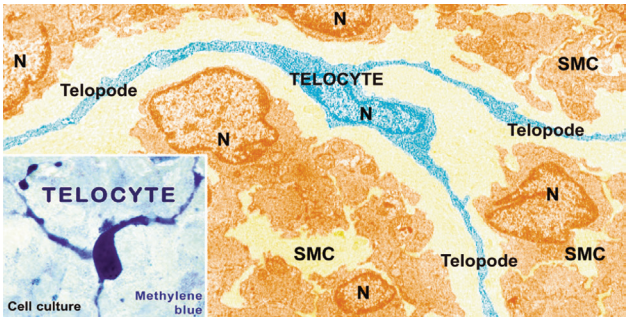

Figure 2 Digitally colored electron microscope image of a telocyte in rat myometrium.
Blue, TC; sienna-brown, smooth muscle cells; N, nuclei. Note the three long, moniliform processes that encircle bundles of cross-cut smooth muscle cells. Original magnification, ×6800. Inset, human pregnant myometrium. Primary confluent culture (day 8) showing a telocyte with at least three prolongations with several 'beads' along telopodes. Reproduced with permission from ref. (1).

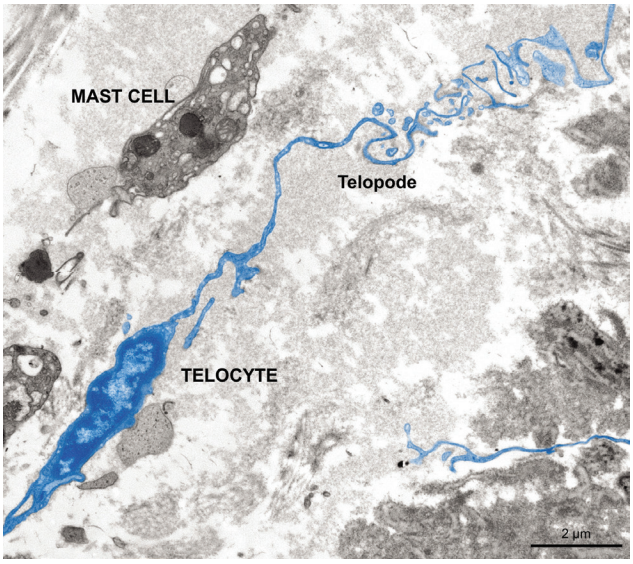

Figure 3 Transmission electron microscopy on skin.
TC with typical cellular prolongation named telopodes. Courtesy of Dr. M. Gherghiceanu, Department of Ultrastructural Pathology, Victor Babeş National Institute of Pathology, Bucharest, Romania.

Phase-contrast microscopy, supra(vital) staining, immunophenotype

In vitro, after 72 h in cell culture, TCs take on particular morphological characteristics: a small cell body and extremely long Tps with uneven caliber due to the alternation of podoms and podomers (Figures 10 and 11). Early studies demonstrated by phase-contrast microscopy that Tps are interconnected in a network-like pattern.

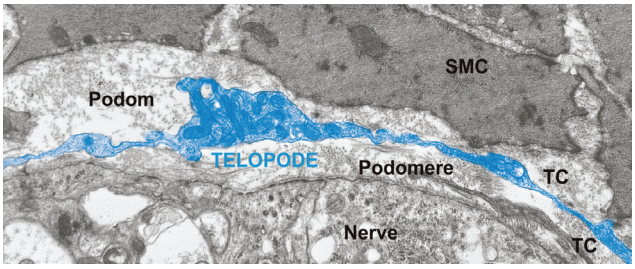

Figure 4 Rat jejunum.
A typical Tp (blue) located between smooth muscle cells (SMC) and nerve endings. Note a large podom and the corresponding podomeres. TC body is not captured in the image. Courtesy of Dr. D. Cretoiu, Division of Cell Biology and Histology, University of Medicine, Bucharest, Romania.

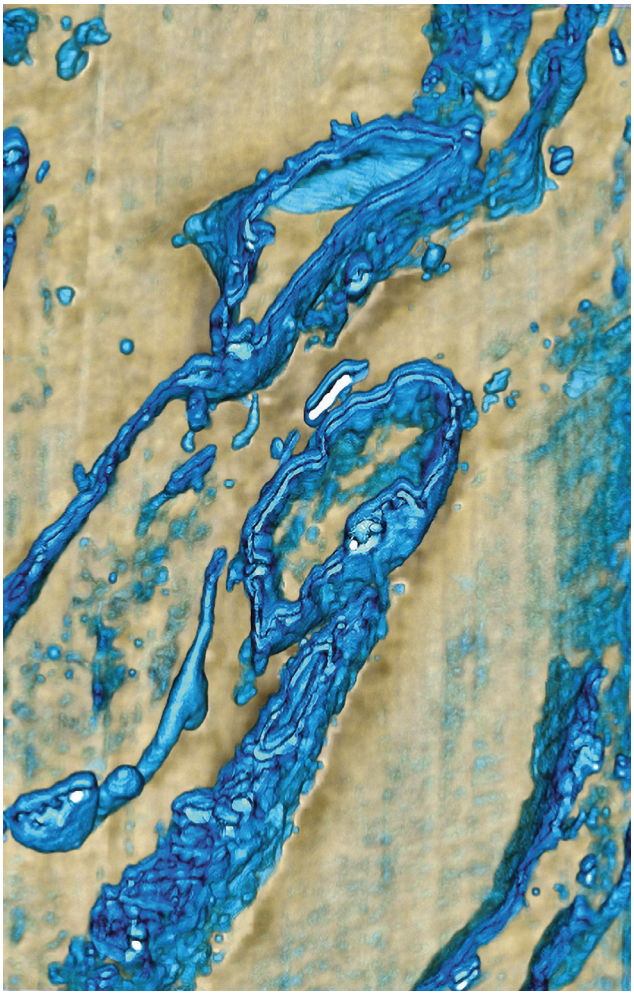

Figure 5 Three-dimensional reconstruction of TCs in myocardium using FIB-SEM serial images.
Courtesy of Dr. D. Cretoiu, Division of Cell Biology and Histology, University of Medicine, Bucharest, Romania and Carl Zeiss Microscopy GmbH, Munich, Germany.

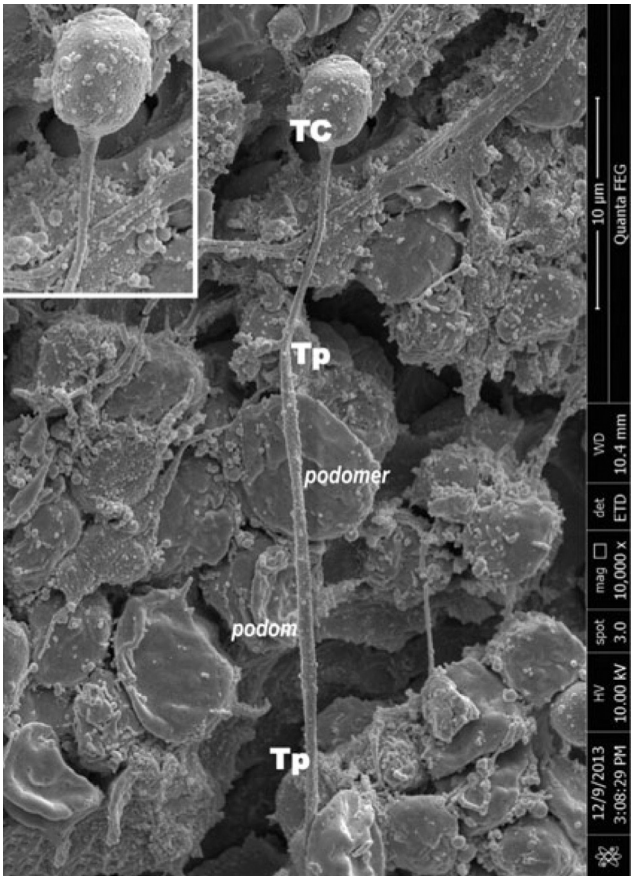

Figure 6 Scanning electron microscope images of mice bone marrow. A telocyte (TC) with one visible telopode (Tp) is shown. The cellular body of TC is round (inset), having measured sizes of 3.55/4.5 µm. Tps have a measured length of 66.5 µm, with the distal end partially covered. The inset shows the abrupt emerging on the Tp from the cellular body of TC; bar, 30 µm. Reproduced with permission from ref. (59).

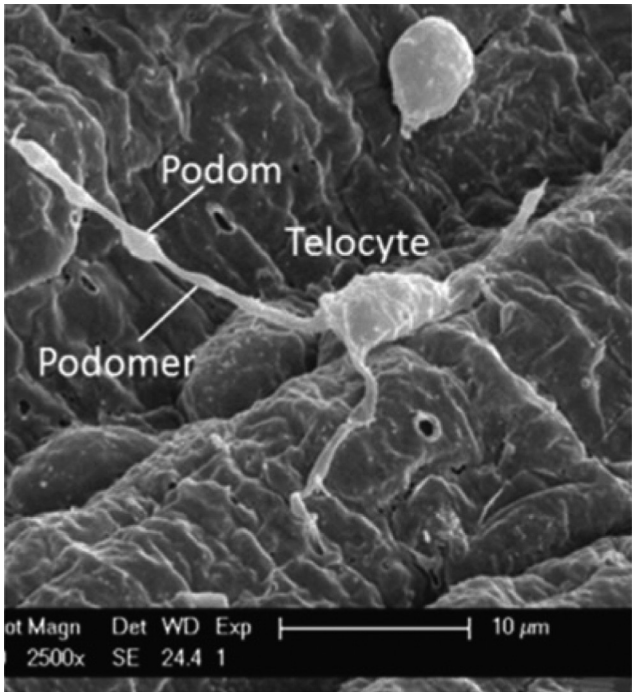

Figure 7 Scanning electron microscope image of a medium-sized artery in pig.
A TC with three Tps and typical podomer and podom. Reproduced with permission from ref. (49).

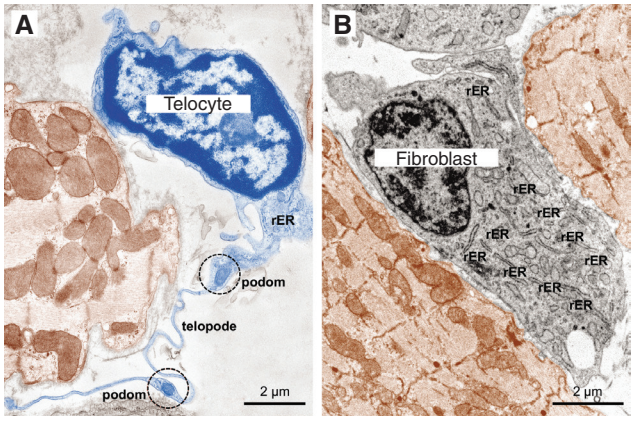

Figure 8 (A) Digitally colored electron micrograph of rat ventricular myocardium: a typical TC (blue) with a long tortuous Tp and with uneven caliber (moniliform) in between two cardiomyocytes.
The circle indicates a podom. Reproduced with permission from ref. (8). (B) A typical fibroblast with abundant rough endoplasmic reticulum (rER).

Moreover, it has been shown that TCs have affinity for supravital dyes, such as methylene blue and crystal violet, which do not induce immediately evident degenerative changes (45, 63). MitoTracker Green FM and Janus Green B were also used to demonstrate the presence of mitochondria in the cell body of TCs and in Tps (5, 30, 42). *In vitro*, TCs' dynamic behavior can be analyzed by time-lapse videomicroscopy and reveals that Tps are responsible for a cellular-driven guidance for neighboring cells and are able to detach from the cell body and to release signaling (macro)molecules (42), possibly contained in exosomes or ectosomes (66).

Although TCs have no definite immunophenotypic characteristics, several reports claim that they have the ability to bind different antibodies. However, we can consider that the double-positive immunostaining with CD34/PDGFRα and CD34/vimentin (for Tps) is appropriate when we refer to these cells (36, 67–70). It is believed that TCs suffer temporal changes in immunophenotype, explaining why sometimes the results vary between laboratories (71). Moreover, TCs inconstantly express stem cell markers such as c-kit, Sca-1, and Oct 4 (44, 72, 73), suggesting their ability to be active players in the regenerative process (73).

Table 2 Comparison of the characteristics of telocytes and fibroblasts. Modified with permission from ref. (6).

Feature	Telocytes	Fibroblasts
Cell body	Small; piriform/spindle/triangular/stellate shaped	Pleomorphic (phenotypic heterogeneity)
Cytoplasm	Small amount	Large amount
Nucleus	One, oval/rod-shaped	One, oval
Chromatin	Heterochromatin dominates	Typically euchromatic
Nucleolus	Rarely visible	1–2 nucleoli
Organelles		
Golgi complex	Small	Prominent
Mitochondria	2–5% of cell cytoplasm; present in podoms (not in podomers)	~5%
Endoplasmic reticulum (ER)	~2% of cell volume; either smooth or rough; located in podoms	Smooth ER virtually absent, but rough ER prominent (8–12% of cell volume), located mainly in cell body but also in processes
Membrane		
Caveolae	Many; more on the cell processes vs. cell body	Hardly any, *in situ*[a]
Junctions	Homo- and heterocellular junctions	No junctions (or difficult to assess) with other cells[b]
Number of prolongations	2–5 telopodes	Usually 2
Branching	Dichotomic pattern, forming 3D convoluted network(s)	Randomly (?)
Conformation	Overall moniliform aspect (alternating podoms and podomers)	Usually cone shaped
Emergence from the cell body	Thin	Thick, followed by gradual thinning
Length	Very long[c] (tens, up to hundreds, of micrometers)	Usually several micrometers
Podomers	Very thin (mostly <0.2 μm, below the resolving power of light microscopy); their caliber does not allow the presence of any membrane-bound organelles inside	No
Podoms	Dilated portions ('knobs') of telopodes, with an average width of about 0.5 μm; they accommodate caveolae, mitochondria, and ER	No
Gene expression profile	Upregulated genes in TCs vs. fibroblasts: *Ctgf*, *Mmp10*, *Mmp3*, and *Myh14*	
Proteomic analysis	Upregulated proteins in TCs vs. fibroblasts: myosin-14, periplakin, mitochondrial thioredoxin-dependent peroxide reductase, protein disulfide-isomerase A3, myosin-10, filamin-B, sodium/potassium-transporting ATPase subunit-1	

[a]Fibroblasts *in situ* have few caveolae. Many caveolae could be found in human/mammalian cultured fibroblasts; phenotypic modification.
[b]Finding connexin 43 by immunofluorescence does not necessarily imply the existence of stable 'gap junctions'. Electron microscope detailed studies failed to find the existence of gap junctions between fibroblasts and other cell types.
[c]Only some nerve cell processes (axons) appear longer than telopodes in the human/mammalian body.

In skeletal muscle interstitium, TCs were found to express VEGF and PDGFR-β both *in situ* and *in vitro*, proposing a role in angiogenesis and vascular stability during tissue repair (54, 55). Also, expression of estrogen receptor (ER) and progesterone receptor (PR) have been identified in TCs from fallopian tubes (74), myometrium (75), and in the upper lamina propria of the renal pelvis, ureter, bladder, and urethra (35).

Also, we must not overlook a recent attempt to clarify TCs phenotype(s) in the human urinary bladder by transmission electron microscopy and immunohistochemistry. Vannucchi et al. describe three types of TCs in human bladder according to their ultrastructure and two types of different TCs on the basis of their immunolabelling characteristics (36). Several antibodies were used: CD34, PDGFRα, αSMA, c-Kit and calreticulin. It was revealed that PDGFRα/calret-positive, CD34/c-Kit-negative TCs are present in the sub- urothelium while PDGFRα/αSMA/c-Kit-negative, CD34/calret-positive TCs are located in the submucosa and detrusor (36). These observations point out possible region-specific roles played by TCs subtypes which seem to adapt their morphology and phenotype to the organ activity.

MicroRNA imprint, gene profile, and proteomic analysis

MicroRNAs are important for development and cell- and tissue-specific gene expression. In the heart, TCs express significant amounts of miR-21, miR-22, miR-29, and miR-199a but lack the expression of cardiomyocyte-specific

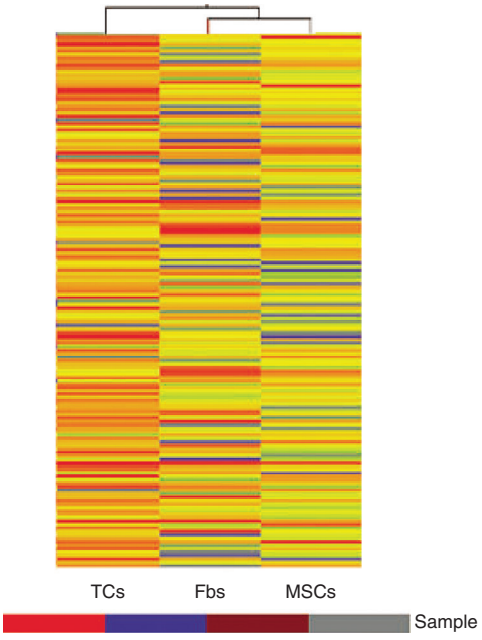

Figure 9 Hierarchical cluster analysis of the differentially expressed genes among TCs, mesenchymal stem cells (MSCs), and fibroblasts (Fbs).
Reproduced with permission from ref. (77).

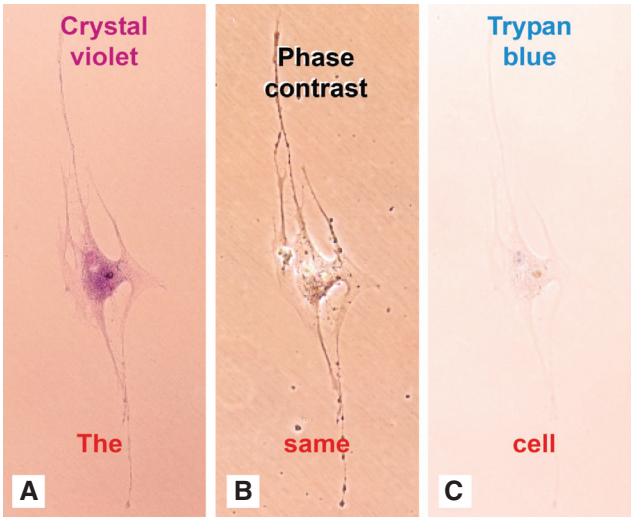

Figure 10 Fallopian tube TCs in primary culture.
Original magnification, ×40. (A) Crystal violet vital staining makes the TC visible, using conventional light microscopy. (B) The same cell after the dye was washed out (30 min with DMEM); the TC was visible only in phase contrast. (C) The same cell after trypan blue staining (this viability test shows that the cell is still alive, as the dye was excluded). 'Invisible' prolongations may be only presumed using conventional light microscopy. Reproduced with permission from ref. (37).

miRs (miR-1 and miR-133a or miR-208a), and do not express miR-193, which supports the view that TCs are of mesenchymal origin (76). Transcriptomic analysis also revealed

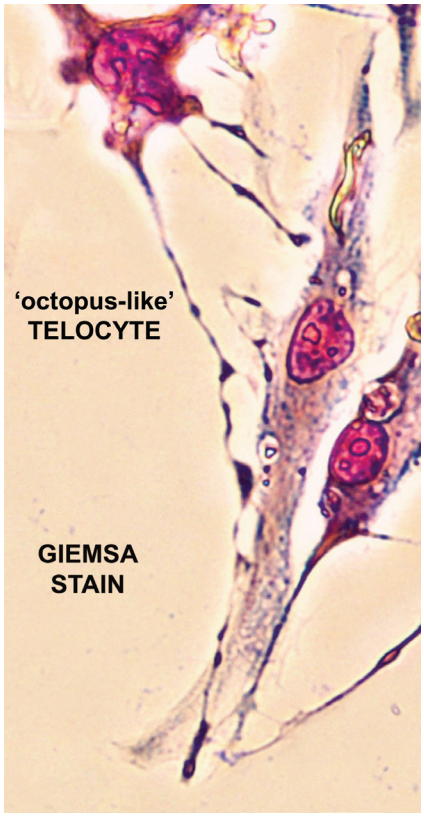

Figure 11 Human fallopian tube, preconfluent primary cell cultures. A TC with 'octopus' morphology can be recognized. Observe the very long, moniliform telopodes. Giemsa staining; original magnification, ×100; oil immersion. Reproduced with permission from ref. (37).

that TCs express many of the pro-angiogenic microRNAs (e.g., miR-126, miR-130, let-7e, miR-21, miR-27b, miR143, miR-503, and miR-100) (12).

The murine lung TC gene expression profile was established by comparing them with both fibroblasts and mesenchymal stem cells. Several genes were found to be highly upregulated in TCs as compared with mesenchymal stem cells: connective tissue growth factor (*Ctgf*), transgelin (*Tagln*), nidogen 1 (*Nid1*), tissue inhibitor of metalloproteinase 3 (*Timp3*), collagen type IV, matrix metallopeptidase 3 (*Mmp3*), and matrix metallopeptidase 10 (*Mmp10*), with regulatory effects in tissue remodeling/repair. Approximately the same genes were found to be upregulated also in TCs when compared with fibroblasts: *Ctgf*, *Mmp10*, *Mmp3*, and *Myh14* (myosin, heavy chain 14) (77). Moreover, the network of main genes and the potential functional correlations were investigated and differences in the expression of chromosomes 1, 2, and 3 genes, between TCs and mesenchymal stem cells, fibroblasts, alveolar type II cells, airway epithelial cells, and lymphocytes were analyzed (Figure 12) (78, 79).

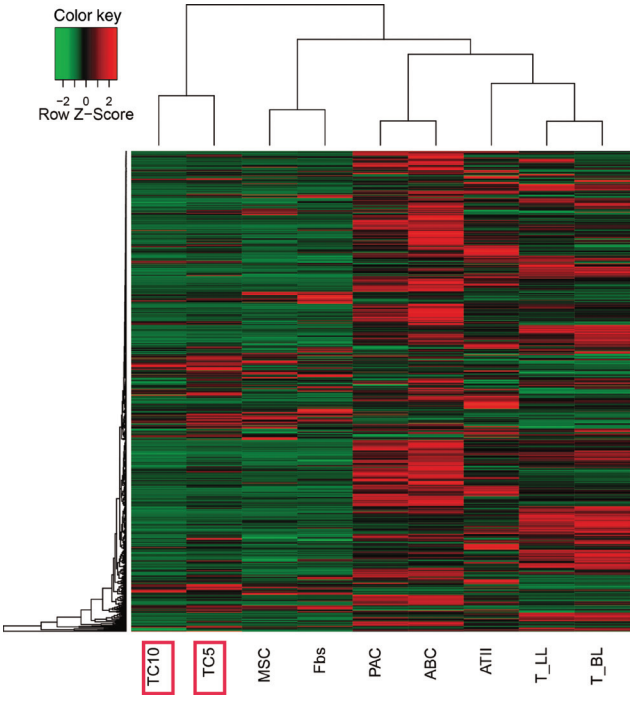

Figure 12 Hierarchical cluster analysis of the differentially expressed genes among TCs, MSCs, Fbs, proximal airway cells (PACs), airway basal cells (ABCs), alveolar type II cells (ATII), and lymphocytes from lungs (T-LL) and bronchial lymph nodes (T-BL). TC5 – telocytes in cell culture, 5th day. TC10 – telocytes in cell culture, 10th day. Reproduced with permission from ref. (78).

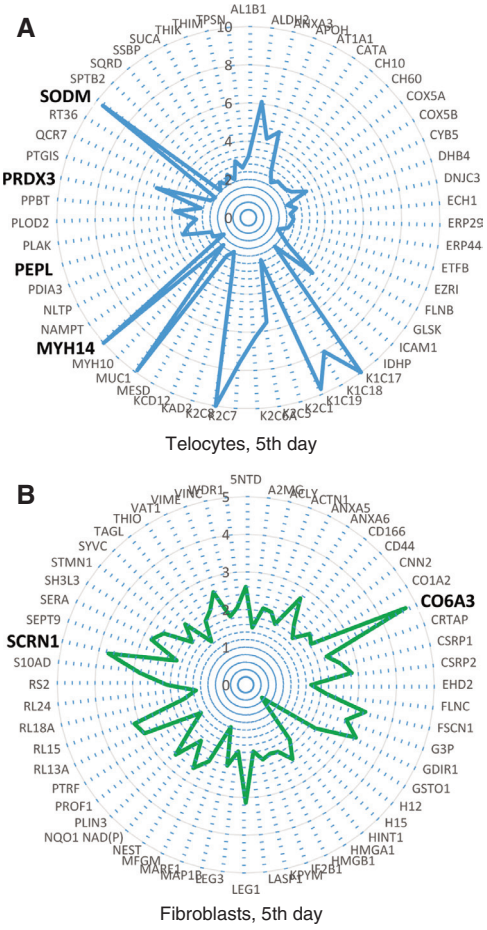

Figure 13 Radars of differential protein expression on the 5th day in cell culture for top proteins of TCs (A) and Fbs (B).
For display purposes, high values of fold change were limited to 10 in (A) and to 5 in (B), respectively. For proteins with fold change >2, the corresponding fold change value was taken into account, even if <2. Reproduced with permission from ref. (80).

Lately, proteomic analysis of TCs showed that they are, indeed, completely different from fibroblasts (Figure 13) and endothelial cells (Figure 14) (80, 81). According to the proteomic analysis, the following proteins were found to be upregulated in TCs as compared with fibroblasts: myosin-14, periplakin, and several proteins with oxidoreductase activity, mostly located within mitochondria. Their presence was considered suggestive for a role in mechanical sensing, mechanochemical conversion, tissue homoeostasis, and remodeling/renewal (80). Some of the upregulated proteins, such as mitochondrial thioredoxin-dependent peroxide reductase, protein disulfide-isomerase A3, myosin-14, myosin-10, filamin-B, sodium/potassium-transporting ATPase subunit-1, and keratin, type II cytoskeletal, were found to be common with extracellular vesicle proteome (82), and therefore a role in intercellular signaling and stem cell niche modulation has been suggested for lung TCs (80). Moreover, when TCs were compared with microvascular endothelial cells, their proteome revealed the upregulated presence of superoxide dismutase 2, acid ceramidase, and envoplakin, suggesting that TCs might play specific roles in intercellular communication, oxidative stress, and cellular aging, and might have pro-proliferative effects through the inhibition of apoptosis (81).

Electrophysiology

Ion channels, present in the membranes of all cells, are also of significance in understanding the function of TCs. Several ion channels have been identified in the TCs from non-pregnant and pregnant human myometrium. SK3 channels have been found in CD34-positive TCs in human non-pregnant myometrium using immunohistochemistry and SK3 mRNA determined by qRT-PCR. The same CD34-positive TCs lacked SK3 channel expression in pregnant myometrium, which indicated that SK3 channel

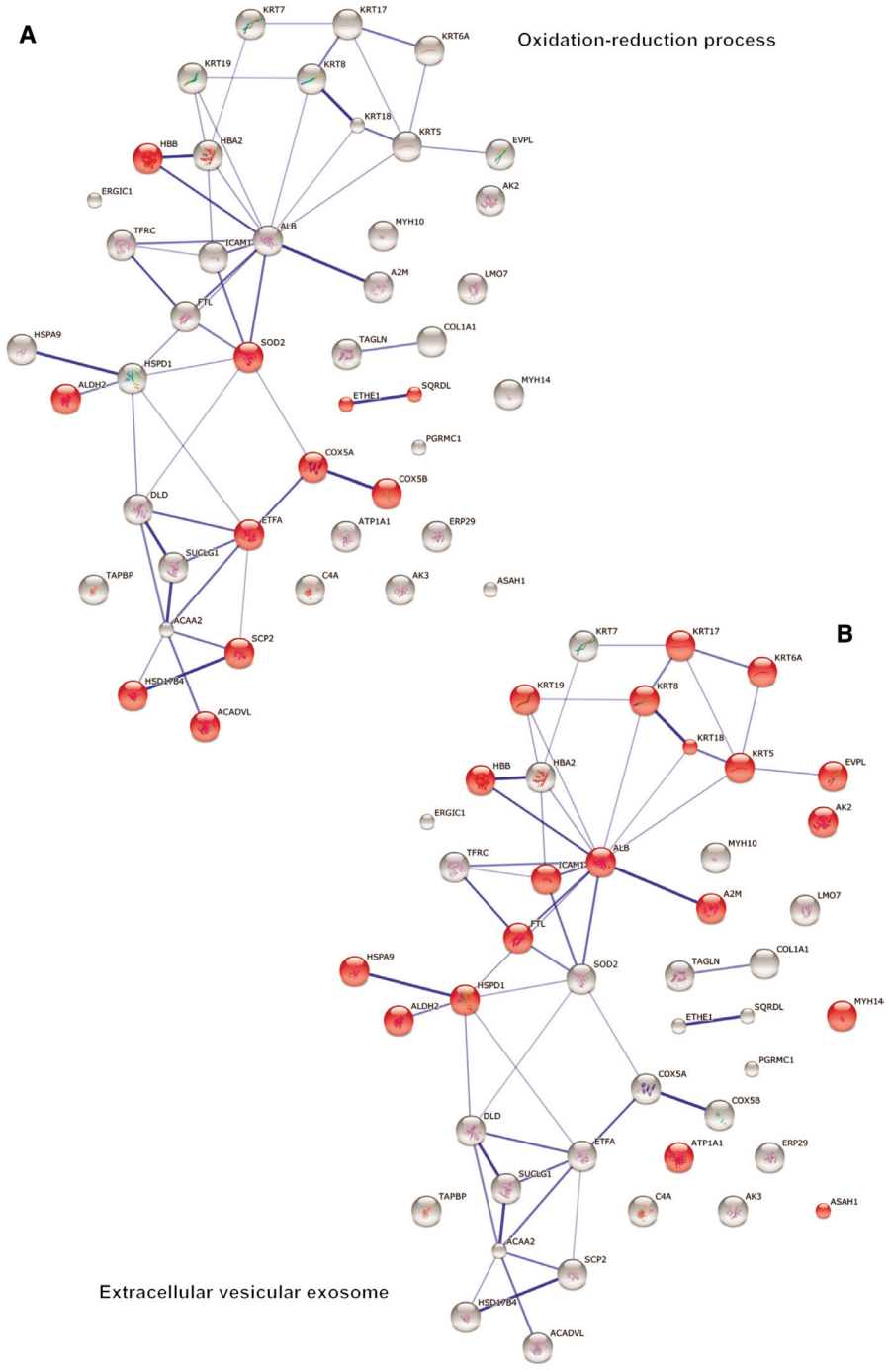

Figure 14 iTRAQ quantitative proteomics of TCs compared with endothelial cells.
Protein interaction network generated with STRING showing, for TCs at day 5 in cell culture, the major clusters of interacting proteins including those involved in oxidation-reduction process (A) and extracellular vesicular exosome (B). Red nodes represent upregulated proteins involved in these processes. Reproduced with permission from ref. (81).

modulation may be involved in myometrial contractility during pregnancy through the TC influence (83). In addition, TCs also express T-type (transient) calcium channels ($Ca_V3.1$ and $Ca_V3.2$), as demonstrated by immunofluorescence analysis and confirmed by the application of brief ramp depolarization protocols (84).

Because of the paucity of electrophysiological data regarding TCs and regardless of the absence of regular slow waves of depolarization in TCs (42, 85), new strategies for understanding uterine bioelectrical signaling mechanisms must be developed. In the human heart, the electrophysiological properties of TCs were explored

by whole-cell patch clamp and it was demonstrated that TCs expressed large conductance Ca^{2+}-activated K^+ current (BK(Ca)) and inwardly rectifying K^+ current (IK(ir)), but not transient outward K^+ current (I(to)) and ATP-sensitive potassium current (K(ATP)) (86).

There is strong evidence that TCs have the ability to form homo- and heterocellular interactions and therefore the formation, elongation, deviation, and ramification of Tps may importantly modulate the morphology and the function of TCs. Stimulation by near-infrared laser of the Tps have been used to test their ability to grow. Low-level laser stimulation (LLLS) induces a higher growth rate of telopodal lateral extension (TLE) in pregnant myometrium. Therefore, the modulatory effects of LLLS on TLE growth can be regarded as future therapeutic strategy in uterine regenerative medicine (69).

The roles of TCs

The importance of TCs is reflected by the exponential growth of publications in the field, and many (un)proven roles were attributed to TCs. One of the first hypothesized role of TCs was in juxta- and/or paracrine signaling (26). Nowadays, it has become evident that, indeed, TCs are able to perform such a role, as it was proved that TCs establish homo- and heterocellular junctions (42, 61) and are able to release extracellular vesicles (Figure 15) (27, 42, 65, 66, 87).

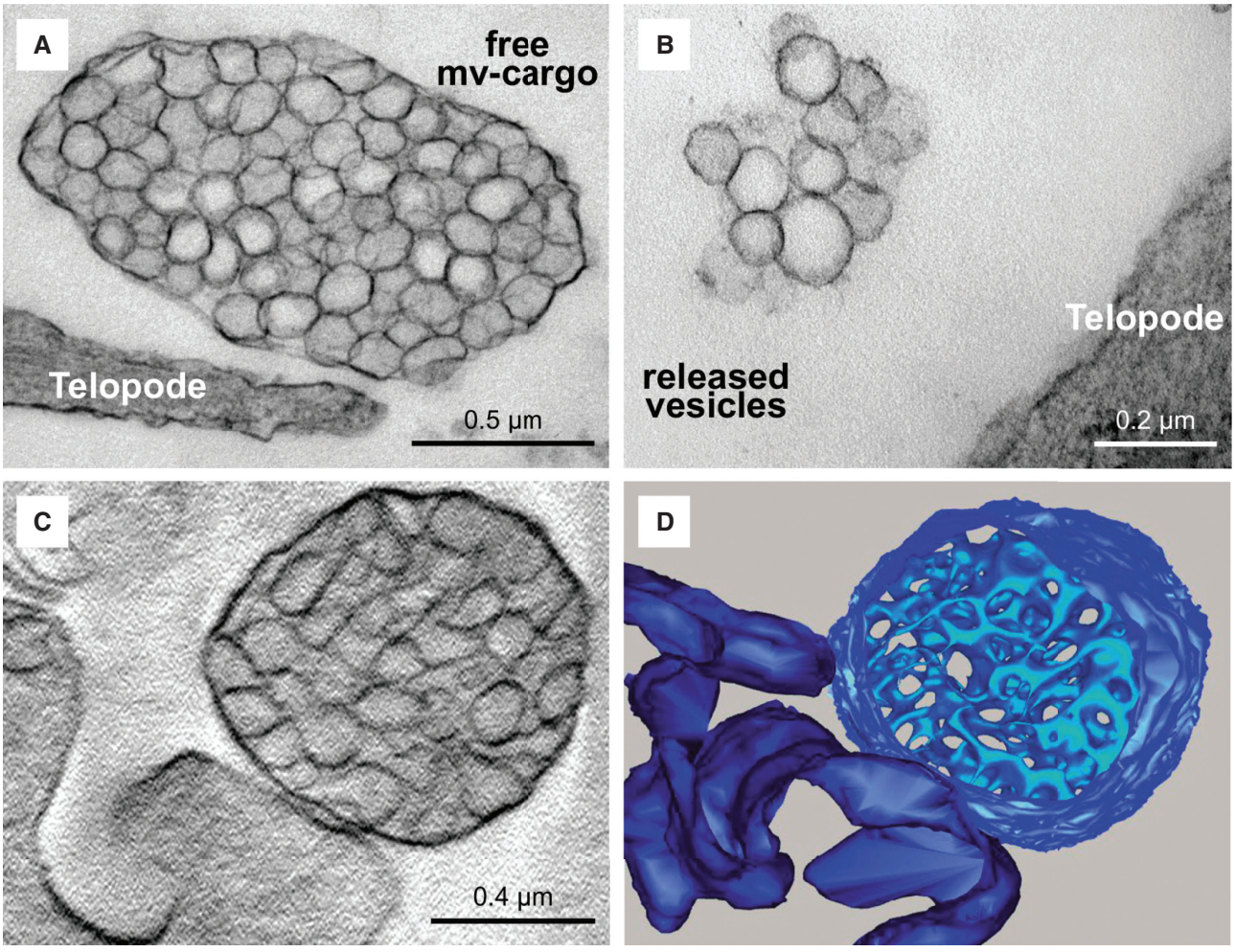

Figure 15 Electron microscopy of TCs in culture releasing MVC.
(A) Gathered endomembrane-bound vesicles released into the extracellular space as a cargo shielded by plasma membrane. (B) Dissolution of external membrane of MVC release individual or grouped endomembrane vesicles into the extracellular space. Electron tomography of MVCs: (C) Central tomogram section of an MVC, in direct contact with the cell membrane, revealing clustered vesicles enclosed by a membrane. (D) 3D model of section shown in (C) with isosurface representation of contained vesicles, revealing dense packaging. Cell membrane shown in dark blue. Scale bar represents 400 nm. Reproduced with permission from ref. (66).

TCs could function as mechanical support, resistant and deformable owing to the 3D network properties, possibly controlling the blood vessel closure or rheology in rat mesentery (51). It was also suggested that TCs located in the neuromuscular spindles can participate in the control of muscle tone and motor activity (56).

TCs might act as guiding devices for the surrounding cells (e.g., mesenchymal cells, myocardial precursors, neural stem cells) (3, 53, 62) and might even be able to control and regulate their activity of participating in tissue remodeling/renewal. TCs were described to be in close contact with cardiac stem cells and cardiomyocyte progenitors (Figure 16), and also with blood capillaries, nerve endings (Figure 17), and other cells found in the interstitial space, e.g., immune cells (Figures 18 and 19) (3, 88, 89). Consequently, TCs might be essential for the proliferation, differentiation, and maturation of myocardial precursors into new cardiomyocytes in normal and/or injured heart (90) and also as potential stimulators of angiogenesis (12). Skin is regarded as the body's largest and fastest-growing organ, known for its extraordinary regenerative capacity and is frequently chosen as a model for studying interactions between stem cells and their microenvironments (91). Skin TCs were reported in close vicinity of collagen and elastic fibers, as well as with mast cells, fibroblasts, adipocytes, blood vessels, nerves, and around the cluster of stem cells in the hair follicle bulge (25, 60). Very recent bioinformatics analysis of lung TCs has also demonstrated the potential involvement of TCs in processes such as stem cell niche modulation, tissue homeostasis, inhibition of oxidative stress, and prevention of cellular aging (80, 81).

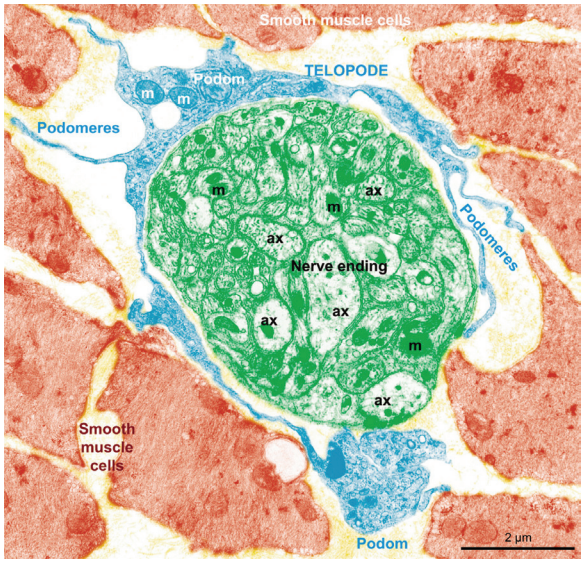

Figure 17 Rat jejunum muscularis mucosae.
The photo is a color-enhanced digital micrograph of a black-and-white transmission electron microscopy image. A blue Tp of 14.2 µm in the section plane is illustrated around a nerve bundle (green) between SMCs (brown). ax, axon; m, mitochondria. Scale bar, 2 µm. Reproduced with permission from ref. (21).

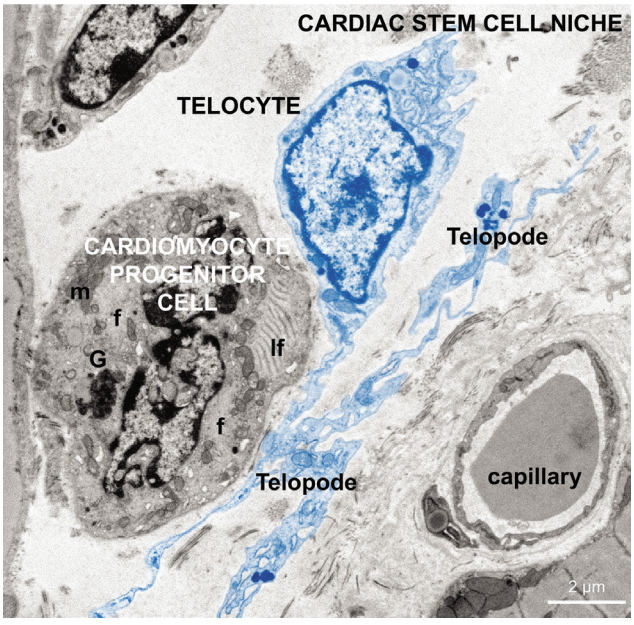

Figure 16 Electron microscopy images from epicardial stem cell niche showing more differentiated cardiomyocyte progenitors (CMP) with characteristic leptofibrils.
TC chaperone a low differentiated CMP with distinctive leptofibrils (lf), unorganized myofibrils (f), Golgi apparatus, and clusters of mitochondria (m). Reproduced with permission from ref. (3).

Strange as it may seem, we must not neglect the possibility that TCs are capable of neurotransmission in the gut, where 'smooth muscle cells are electrically coupled to interstitial cells of Cajal (ICC) and PDGFRα cells, forming an integrated unit called the SIP syncytium' (92). Pieri et al. (93) also considered the role of TCs in spreading the slow waves generated by the ICC.

TCs might be considered as active players in immunomodulation and immunosurveillance (64), acting like 'local data suppliers' for the immune response (78). We must not exclude that in the human reproductive tract, TCs could function as 'hormonal sensors' as they express estrogen and progesterone receptors (94, 95). In general, being under hormonal control, TCs may support the structure of the stratum functionalis of the endometrium (41) or could influence the timing of the contractile activity of smooth muscle cells (42), and even contribute to cell migration and proliferation of myometrial tissue (84). Last, but not least, recent work suggests that TCs might act as a primitive

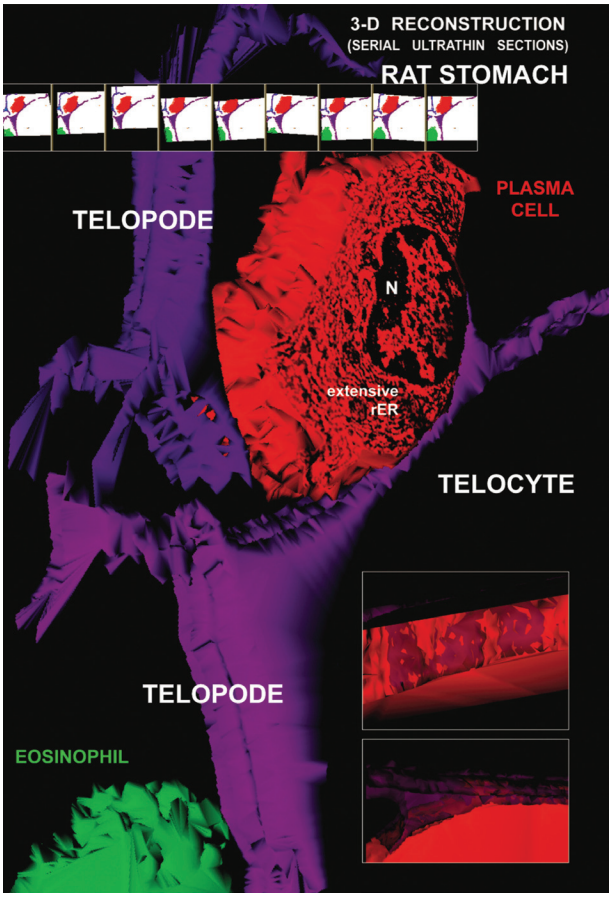

Figure 18 Rat stomach, multicontact stromal synapses between two TC, a plasma cell, and an eosinophil, respectively. Three-dimensional image computer-aided reconstruction from nine serial ultrathin sections; original magnification, ×1500. The upper inset shows contact points where the distance between both cell membranes (Tp membrane and plasma-cell membrane) is ≤15 nm (in violet), seen from the plasma cell cytoplasm. In the lower inset, Tp were rendered transparent in order to depict the same synapse. Reproduced with permission from ref. (64).

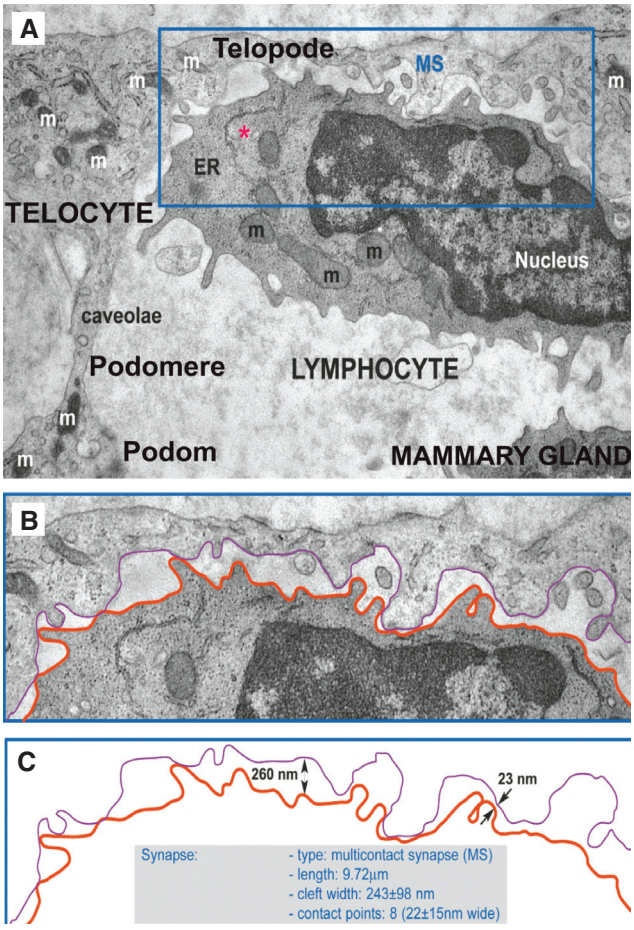

Figure 19 Human mammary gland stroma. Transmission electron microscopy; original magnification, ×9100. (A) Lymphocyte establishing a multicontact synapse (MS) with a TC. The blue rectangle shows the synaptic 'kiss and run' region. The synaptic membranes appear traced in (B) (violet, TC; orange, lymphocyte). The distances between membranes are shown in (C). Note (asterisk) a peculiar conformation of ER connecting mitochondria with the cell surface, suggestive for a possible role in synaptic Ca^{2+} homeostasis. Reproduced with permission from ref. (64).

nervous system for the cells found in close relations with TCs and even for those found at a distance, and might be influenced by means of extracellular vesicles (96). The same authors (97) also claim that TCs are well-equipped cells (as concerns different types of junctions, extracellular vesicle release, and the expressed ion channels), able to play at least a part of the role needed in a bioelectric 'information pathway' described by Levin (98).

TCs in pathology

In the heart, experimental studies showed that the number of TCs decrease during myocardial infarction (99). TC injection in the infarcted area reduces the infarction size and improved myocardial function (100). TCs have also been proposed to be associated with amyloid deposit formation in patients with long-standing atrial fibrillation. In this process, Tps play an important role, surrounding the amyloid deposits, perhaps with the intention to limit their spreading in the surrounding areas (101).

In lung pathology, TCs are proposed to stimulate and induce cell proliferation through the inhibition of apoptosis (81), which may be one of the mechanisms for the development of interstitial fibrosis. Also, it was hypothesized that TCs may be damaged in chronic obstructive pulmonary disease; therefore, the integrity of the lung tissue could not be reinstituted and emphysema develops (102, 103).

TCs were reported in mouse liver, located in the Disse space, with similar density in the four hepatic lobes and close spatial relations with hepatic putative stem (progenitor) cells (22). Their importance in liver regeneration was emphasized using a murine model of partial hepatectomy, concluding that TCs might influence proliferation of hepatocytes and/or the activation of stem/progenitor cells (68).

TCs with severe ultrastructural damages, reduced in number and even lost, were recently reported in scleroderma (104). In addition, the 3D network of TCs is affected (discontinuous or even completely absent) in the myocardium, lung, and gastric wall of patients with systemic sclerosis (105). Consequently, TCs might be key players in the regulation of skin (and not only) homeostasis, repair, and regeneration and a new target for the treatment of this disease. Last but not least, TCs from stroma of the basal and squamous cell skin carcinomas were analyzed, being shown to have a very restrained number of heterocellular junctions and remains to be explained (106).

TCs were identified in the human uterus and fallopian tube (107, 108), organs with reproductive significance that can be disrupted by various pathological states. TCs were morphometrically analyzed in rat uteri and found to be significantly lower in number in immature and pregnant uteri and significantly higher in postpartum uteri (109). Regarding the involvement of TCs in pathological conditions, it has been reported that a gastrointestinal stromal tumor of the uterus may be derived from TCs present in the myometrium (110). This hypothesis is supported by data claiming that TCs share the expression of several markers with gastrointestinal stromal tumors and perivascular epithelioid cell tumors (PEComas) (111). Another study suggested that such cells might have a role in preventing premature uterine contractility and found no increased number of such cells in the myometrium of women affected by uterine endometriosis (112). The most recent evidence showed that TCs suffer a significant decrease or may be even lost in endometriosis-affected rat oviduct, participating in the deregulation of intercellular signaling, including immune surveillance/regulation (113).

Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are severe disorders that sometimes are complicated by the development of fibrosis (114, 115). Recent studies have demonstrated that, during fibrotic remodeling of the intestinal wall in patients affected either by Crohn's disease or ulcerative colitis, the number of TCs is reduced leading to bowel architectural derangement and dysmotility (116, 117).

Several studies reported the presence of TCs in the urinary system, in the kidneys (33), and especially in the lamina propria of drainage system and in the storage reservoir (34–36), claiming that these are 'peculiar TC able to adapt their morphology to the organ activity' (36). After renal ischemia-reperfusion injury in rats, it has been shown that that injection of renal TCs can attenuate renal histological damage and dysfunction, although the underlying mechanism remains unclear, being probably dependent on growth factors (118).

The gallbladder activity seems to be also dependent on the integrity of the TC network, as it was reported that TCs are significantly decreased in the gallbladder wall in patients with gallstone disease (119, 120). It seems that bile composition may influence the TC network integrity: the supersaturated bile can decrease the number of TCs, while glycocholic and taurocholic acids have protective effects on TCs (24).

TC involvement was also considered in the maintenance of epithelium-stroma balance in the mammary gland. TCs were detected and found to be connected with other stromal cells in reconstituted breast cancer tissue and are considered to participate in self-assembly of cells and inhibition of apoptosis, thus facilitating the growth of cancer cells (47).

TCs and regenerative medicine

In the adult life of humans, the regenerative potential is limited except in liver regeneration. Therefore, stem cell-based therapy remains a hope for regeneration in the future. Researchers have tried different types of methods and cells (embryonic stem cells; induced pluripotent stem cells; bone marrow-derived hematopoietic stem cells; multipotent mesenchymal stromal cells derived from blood, bone marrow, umbilical cord, and adipose tissue, etc.), none of them with spectacular results in humans. We are becoming increasingly confident that TCs and stem cells make a tandem (2, 6). TCs seem to play a crucial role challenging the power of regeneration (121, 122), and have been regarded as important interstitial cells to guide or nurse putative stem and progenitor cells in stem cell niches in a spectrum of tissues and organs; thus, TCs might importantly contribute to tissue repair and regeneration (123). Important lessons in regenerative medicine came from the heart as stated by Bani and Nistri (124), which underline the importance of TCs in morphogenesis based on previous observations that TCs, during mouse heart development, act as mediators for heart compaction from embryonic myocardial trabeculae (10). Anyway, in vitro studies showed that there is a high dynamics of Tps extensions and ramification depending on the type of extracellular matrix proteins (125).

Perspectives

Given the rapidly expanding data concerning TCs (>1500 citations in 4 years) and their possible physiological/pathological functions, one may expect that some of the following questions will soon be answered:

- Are TCs only a specific form of the wider concept of mesenchymal/progenitor stem cells?
- How important is the role of TCs in tandem with stem cells?
- Are TCs involved in mechanotransduction, intercellular signaling, or in modifying the transcriptional activity of cells in their proximity?
- Which are the consequences of mistiming or errors in TCs biogenesis (number, marker expression, etc.)?

Answering these (and some still not formulated) questions may open new avenues for exploring TC functions.

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