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Resident
Stem Cells
and Regenerative Therapy

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Chapter 11

Telocytes and Stem Cells

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What Are Telocytes?

Telocytes (TC) are a newly described distinct type of interstitial cells [1-3]. Their presence was either overlooked or they were confused with other interstitial cell types, depending on the specific cellular repertoire of a given organ.

Their (most) striking ultrastructural feature is the presence of very long prolongations (several tens to hundreds of μm), called *telopodes* (Tp) [1] (see Figs. 11.1 and 11.2). Moreover, Tp conformation is ''specific'', consisting of an alternation of thin fibrillar-like segments (*podomers*) and dilated, cistern-like regions (*podoms*) [4]. Podoms accommodate mitochondria, caveolae, and elements of endoplasmic reticulum (ER) the so-called calcium accumulating/releasing units.

The term *telocyte* was coined using the Greek affix *telos*. Aristotle believed that *Telos* was an object's or individual's greatest potential [5]. The initial meaning of the word was ''burden'', and the most probable semantic development was from ''duty''/''task'' to ''execution of task'', ''completeness,'' and the most important, ''power to decide''[6].

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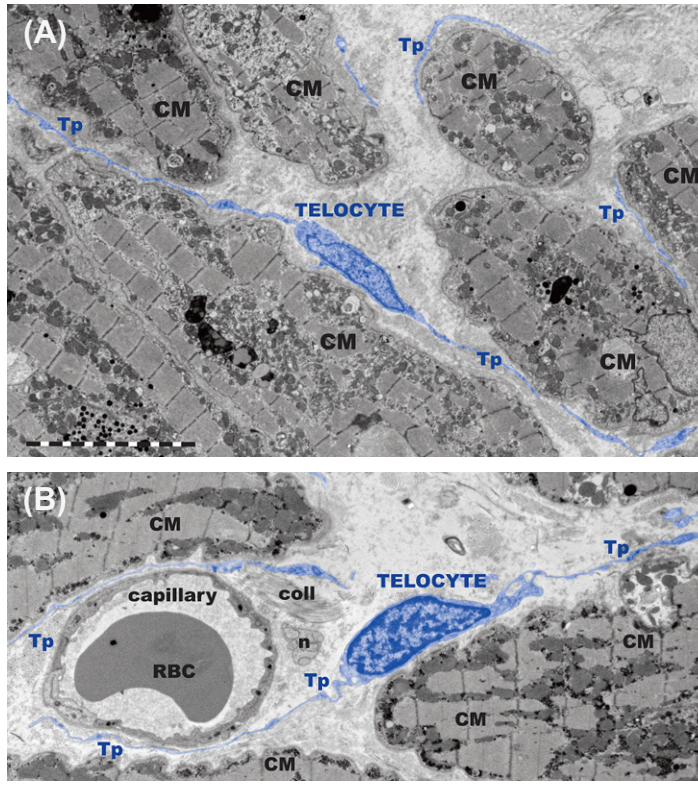

Figure 11.1 Human atrial myocardium, transmission electron microscopy. **(A)** Cardiomyocytes (CM) containing lipofuscin and atrial granules are surrounded by telopodes (Tp) of telocytes, digitally colored in blue. **(B)** Two telopodes (Tp) are bordering a myocardial capillary. RBC, red blood cell; n, nerve ending; coll, collagen. **See Plate 15**.

What Defines Telocytes as a Unique, Distinct Cell Type?

Under electron microscope (EM), the TC silhouette is distinctive, with a small, oval- or triangular-shaped body, and several (two to five) remarkably long, thin, and moniliform Tp (Figs. 11.3 to 11.5).

The identification of TC is mostly based on recognition of their Tp. Therefore, the simplest definition of telocytes is *cells with telopodes* [7]. Tp are characterized by the following:

1. **Number** (one to five, frequently two to three).
2. **Length** (several tens up to hundreds of micrometers).
3. **Moniliform aspect**: alternation of dilated segments (podoms) and thin segments (podomers–less than 200 nm thickness, below the resolving power of light

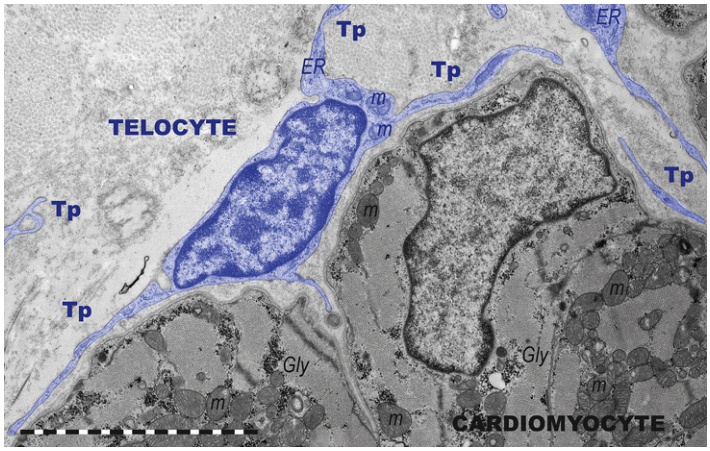

Figure 11.2 Human myocardium. Transmission electron microscopy. A telocyte (digitally colored in blue) extends several long telopodes (Tp) around and between cardiomyocytes. Gly, glycogen; m, mitochondria; ER, endoplasmic reticulum. Scale bar = 10 µm. **See Plate 16**.

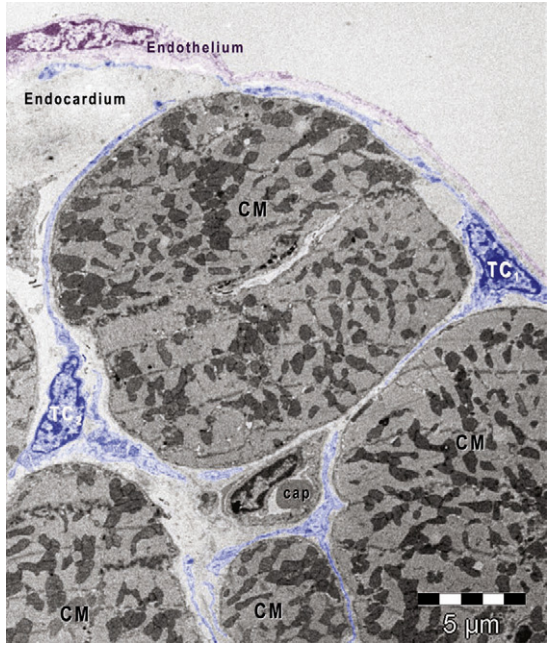

Figure 11.3 Digitally colored electron micrograph of rat ventricular endocardium (burgundy). Telocytes (blue) make an interstitial network in the heart. Subendocardial telocytes (TC_1) send telopodes among cardiomyocytes (CM) making a network with myocardial telocytes (TC_2). Tp network envelopes bundles of cardiomyocytes (CM), cross-cut here. cap, capillary. *(Reproduced with permission from [10]).* **See Plate 17**.

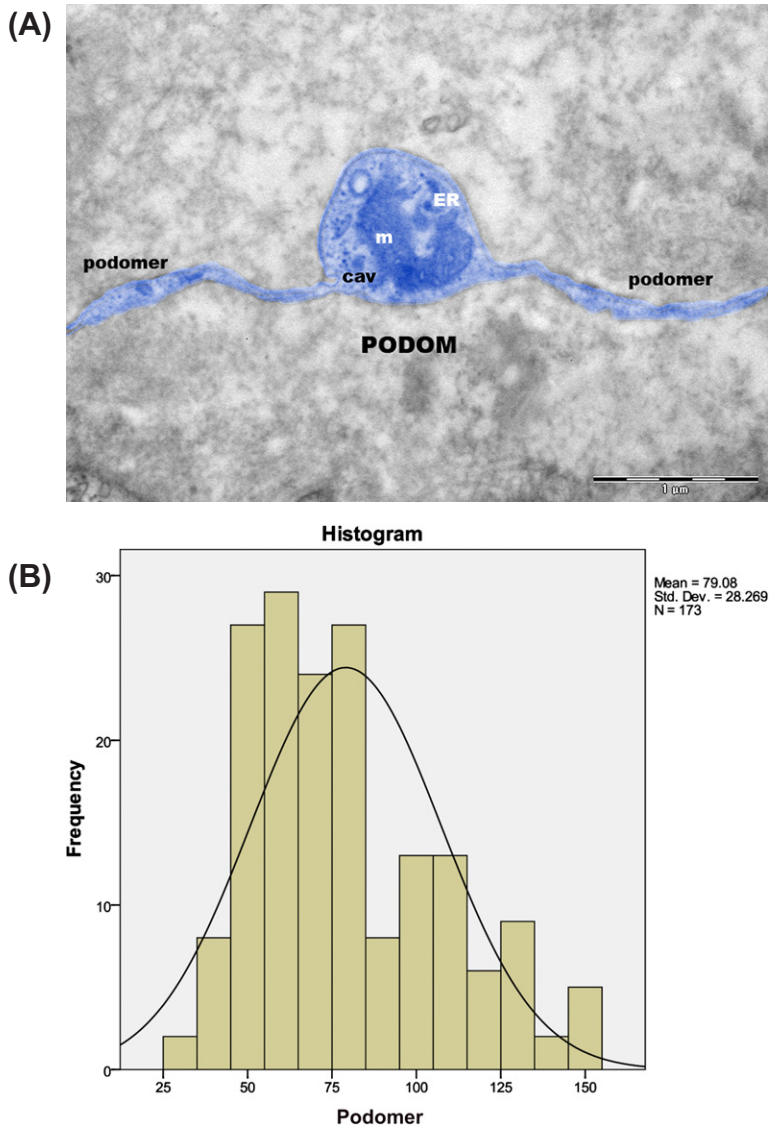

Figure 11.4 **(A)** Rat myocardium. Electron micrograph of a telopode (blue), depicting a podom between two podomers. Note that the podomer thickness is clearly below 0.2 µm, the resolving power of light microscopy. **(B)** Mean width of podomer (about 80 nm) places it under the resolving power of light microscopy. **See Plate 18**.

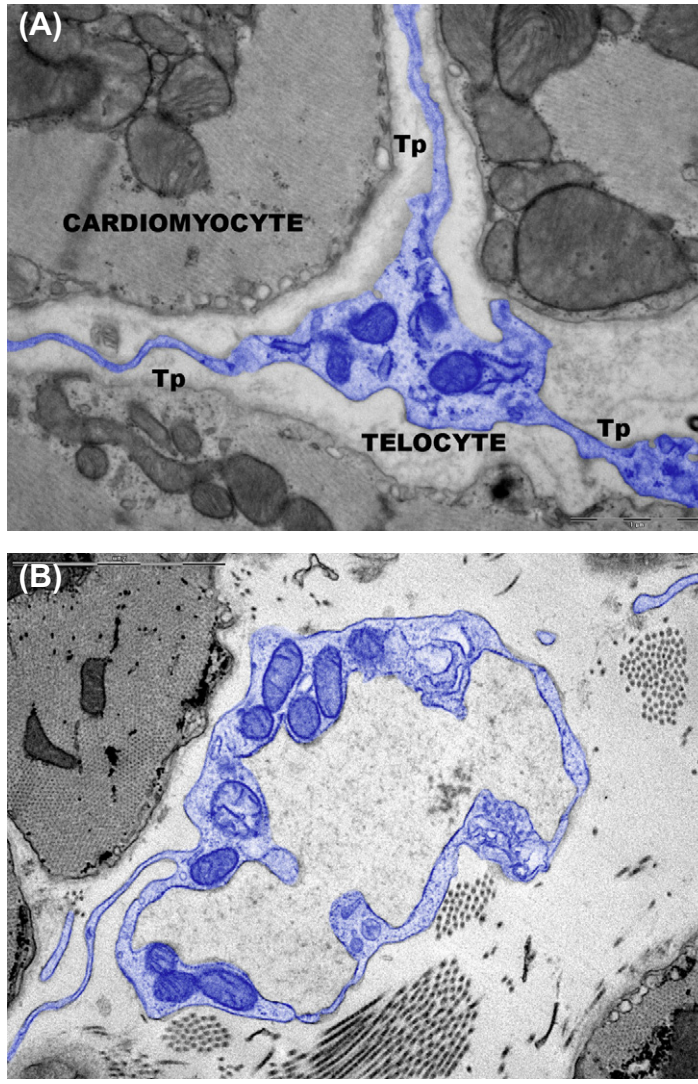

Figure 11.5 **(A)** A triangular telocyte (digitally colored in blue) with three emerging telopodes (Tp). Rat myocardium. **(B)** A particular circular appearance of a telopode, with both podoms and podomers, in rat heart interstitium. **See Plate 19**.

microscopy, explaining why TC were overlooked so far and why EM is mandatory for unequivocal TC identification).

4. **Podoms** accommodate: a) mitochondria (one or two), endoplasmic reticulum elements, either smooth or/and rough ER, and c) caveolae; the so-called Ca^{2+} uptake/release units.

5. **Dichotomous branching pattern**, making a 3D network, a labyrinthine system with particular intercellular junctions: either homocellular junctions between TC themselves or heterocellular junctions between TC and other cell types (e.g. cardiomyocytes, macrophages, stem cells etc.) [1,2,7].

To observe a Tp, one should consider its main ultrastructural features. First of all, the tortuous trajectory of a Tp requires convenient section planes, in which a larger/longer portion of a Tp is enclosed. Second, because Tp are both very long and very thin structures, both a large and detailed image is required. In other words, a higher magnification overview is needed. Several neighbor areas should be analyzed under EM and the captured images aligned and merged both horizontally and vertically. The reconstructed collage will show an area that could not have been directly captured entirely unless at lower magnification. In this way, a wider ''field of view'' may be analyzed at a higher magnification.

Comparison with Fibroblasts

A superficial likeness does not always reveal an essential likeness.

L. Mackenzie [8]

The interstitium (stroma) is in most cases seen as a connecting ''device'' for the specific structures of an organ. Usually, interstitial cells are perceived as being *mainly* (or even *only*) fibroblasts (Fig. 11.6). However, fibroblast main function is the production of collagen fibrils and some extracellular matrix proteins. Although it is obvious that TC are not fibroblasts, some are hiding behind the syntagma ''fibroblast

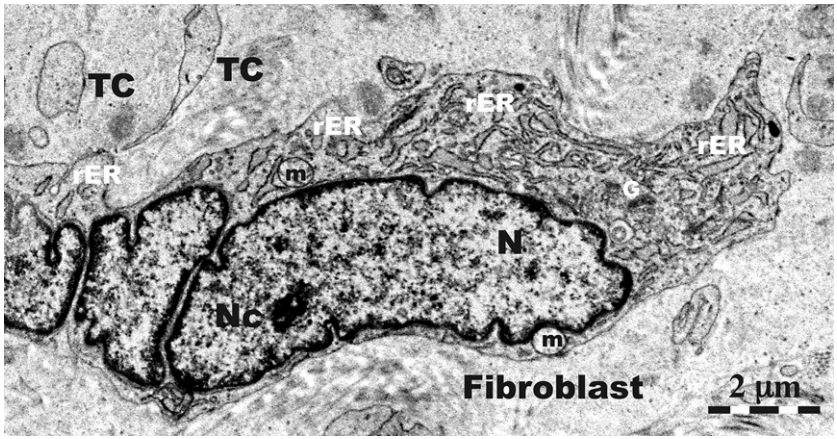

Figure 11.6 Transmission Electron Microscopy of a typical fibroblast in rat myocardium. N, nucleus; Nc, nucleolus; m, mitochondria; RER, rough endoplasmic reticulum; G, Golgi complex, TC, telocyte fragments.

like.'' Where should one draw the line(s) between the intrinsic variability of fibroblasts and their look-alikes? In fact, the so-called fibroblast-like cells were never clearly defined, the lack of specific information leading more or less to ''a transfer of ignorance''. There is a danger that a cell that is not clearly a fibroblast might be considered *a priori* fibroblast-like.

However, the distinction between TC and fibroblasts is obvious because they have different ultrastructure (Table 11.1) and phenotype. Therefore, their functions are different: fibroblasts promote collagen synthesis, while TC promote intercellular signaling either by direct contact (junctions), or remotely (via extracellular vesicles). In other words, fibroblasts are *more* structurally oriented, responsible for collagen and extracellular matrix synthesis and fibrosis, whereas TC are *more* functionally oriented, being involved in inter(trans)cellular communication via 3D network(s), and, maybe, some specific functions.

Where Are Telocytes Located?

The presence of TC has been reported in the stroma of many organs (Table 11.2). Their location is in the interstitium, where they connect with resident and nonresident cells. By branching of their long prolongations, TC are making a virtual 3D network.

Telocyte Intercellular Relationships

Extracellular Vesicles

Extracellular vesicles are: multivesicular bodies (Fig. 11.7) or shed microvesicles or exosomes. ECV might play a unique role in horizontal transfer of macromolecules between cells (e.g., proteins, various RNAs, miRs).

Intercellular Relationships

The intercellular interactions are achieved by either direct contact (intercellular junctions) or by extracelluar vesicles (ECV).

The variable Tp width might also explain the heterogeneity of the released vesicles. Thus, exosomes (with a diameter under 100 nm) could be released at the podomeric level (where average width rarely exceeds 100 nm; see Fig. 11.4B), and shed microvesicles (with a mean diameter of 180 nm) could transport macromolecular signals from podoms to neighboring cells, modifying their transcriptional activity eventually. The release of multi-vesicular bodies has been noted at both podomeric (Fig. 11.7A) and podomic (Fig 11.7B) level. The microenvironment also plays an important role in local cellular cross talk [54].

TABLE 11.1 Comparison of the Ultrastructural Characteristics of Telocytes and Fibroblasts

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	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 versus cell body	Hardly any, *in situ*[*]
Junctions	Homo- and heterocellular junctions	No junctions (or difficult to assess) with other cells[†]
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[‡] (tens, up to hundreds, of micrometers)	Usually several micrometers
Podomers	Very thin (mostly below 0.2 μm, 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

[*]Fibroblasts in situ have few caveolae. Many caveolae could be found in human/mammalian cultured fibroblasts; phenotypic modification.
[†]Finding connexin 43 by immunofluorescence does not necessarily imply the existence of stable “gap junctions.” Electron microscope detailed studies [9] failed to find the existence of gap junctions between fibroblasts and other cell types.
[‡]Only some nerve cells processes (axons) appear longer than telopodes in the human/mammalian body.

TABLE 11.2 Telocyte Presence in Various Tissues/Organs

Heart	
Endocardium	[10]
Myocardium	[9,11-15]
Epicardium	[16,17]
Skeletal Muscle	**[18-20]**
Gastrointestinal Tract and Annexes	
Duodenum	[21]
Jejunum	[22]
Salivary glands	[23]
Gallbladder	[24]
Pancreas	[25,26]
Urinary System	**[27]**
Kidney	[27]
Renal pelvis	[28]
Ureter	[28]
Bladder	[29,30]
Urethra	[28]
Respiratory System	
Lungs	[31-34]
Trachea	[35,36]
Pleura	[37]
Meninges and choroid plexus	[38]
Mammary glands	[39,40]
Uterus	[41-45]
Fallopian tube	[43,44,46]
Placenta	[47]
Skin	[48,49]
Mesentery	[50]
Vasculature	[9,51-53]

Eye: Ciliary body and iris*

*Maria-Jose Luesma Bartolome (Zaragoza, Spain) and Mihaela Gherghiceanu (Bucharest, Romania), personal communication

Intercellular Junctions

Telocytes Intercellular Junctions

TC are establishing connections, via their cell body or long Tp, located very close to neighboring structures. TC are not just bystanders stromal elements, but active participants in intercellular space.

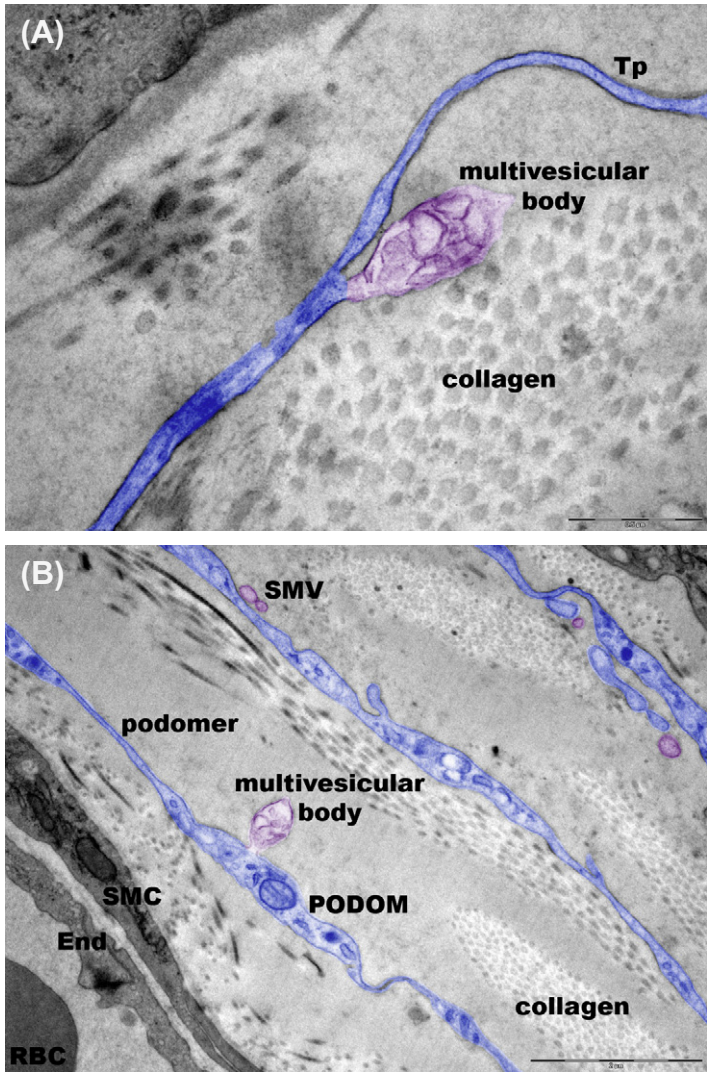

Figure 11.7 Nascent multivesicular bodies (digitally colored in violet) are budding from either podomer or podomic regions of telopodes (digitally colored in blue). Note the diameter of podomers in the range of that of collagen fibrils (cross-cut). RBC, red blood cell; End, endothelium; SMC, smooth muscle cell; SMV, shed microvesicles. *(Modified with permission from [63]).* **See Plate 20**.

Elements of the TC network are interacting with each other (**homo**-cellular connections) as well as with other cell types (**hetero**-cellular connections). The presence of homo- and hetero-tropic networks indicates the possible existence of a higher integration in a putative general interstitial system. The type of contact

depends on several aspects: the distance between the TC and the target cell(s), the specific type of the target cell(s) (e.g., immune cells, neurons), and the organ where the interaction takes place.

The TC intercellular junctions have been thoroughly described in the heart [9], but examples are reported in other organs, too (e.g. pancreas [26], salivary glands [23]).

In myocardium, **homocellular** junctions might reveal different morphologies under EM: *puncta adhaerentia minima, processus adhaerentes* or *recessus adhaerentes* [9]. The homocellular junctions (e.g., Fig. 11.8) are typical and they occur at both podomeric and podomic level, either side to side (presumably for exchanging information) or end to end (probably for relaying, passing on information).

Heterocellular junctions are encountered at myocardic level between TC and cardiomyocytes, cardiomyocytes progenitors, fibroblasts, mast cells, macrophages, pericytes, endothelial or Schwann cells [9]. TC are integrating all cardiac cellular types [9] through a complex 3D framework/lattice, formed by heterocellular junctions. These networks are providing both structural and functional support for long-distance signaling, important in cardiac renewing [55].

The connections of TC with various cell types in the adult heart might be classified depending on the intermembranar distance in nanocontacts (10 nm), point or planar contacts (10 to 30 nm), and close vicinity (under 150 nm) [9].

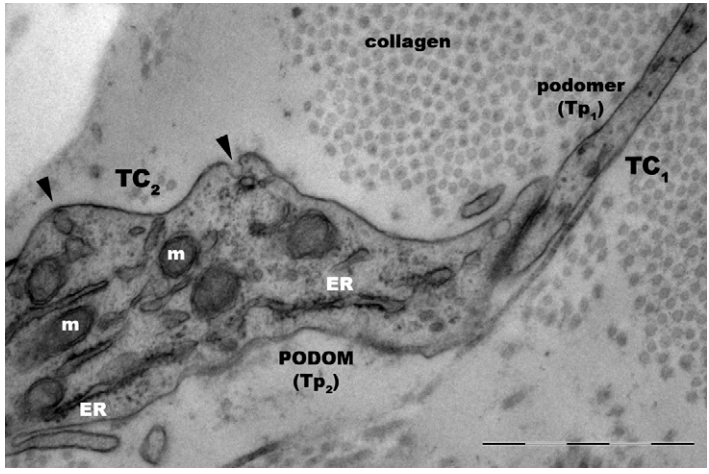

Figure 11.8 Rat myocardium. Transmission electron microscopy. Two telopodes (Tp1 and Tp2) are participating in a homocellular junction (procesus adherens, red dotted circle) between two telocytes (TC1 and TC2). The podom of Tp2 accommodates mitochondria (m), endoplasmic reticulum (ER), and caveolae *(arrowheads).* Scale bar = 1μm.

The heterocellular junctions are formed between TC and the following type of cells:

1. Specific cells from that tissue (e.g., cardiomyocytes [56]; Fig. 11.9).
2. Stem cells (SC) [17,19,57].
3. Immune reactive cells (mast cells – Fig. 11.10, basophils, eosinophils [58]). The connection with macrophages may indicate a certain role in local tissue remodeling. This particular connection type was labeled *stromal synapse* [58].

Frequently, Tp are observed in a close relation to nerve endings.

The junctions between TC and cardiomyocytes do not belong to any specific category but consist mostly in clusters of direct nanocontacts, free of any basal lamina interference. This would also depend, certainly, on the TC density in several heart areas (as reported in [59], TC concentration is higher in atria than ventricles—about 20 versus 9 cells/mm^2—and significantly higher in subepicardium than in endocardium—18 versus 7 cells/mm^2).

Phenotype "Portrait"

Immunocytochemical Phenotype of Telocytes

Several markers have been identified (with a variable expression) on TC, either by immunohistochemistry (IHC) or by confocal imaging. The immunophenotype of TC includes mainly CD34, CD117/c-Kit, and vimentin, but also caveolin-1, CD44,

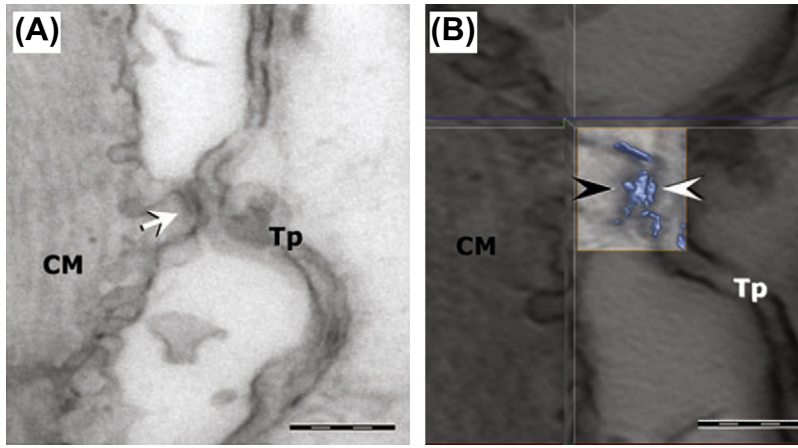

Figure 11.9 EM Tomography. **(A)** Digital section from tomographic volume shows a junction between the Tp and a discrete projection of the CM. **(B)** Top view of the 3D isosurface reconstruction of the junction shows a macromolecular complex connecting Tp and CM *(arrowheads). (Reproduced with permission from [56]).*

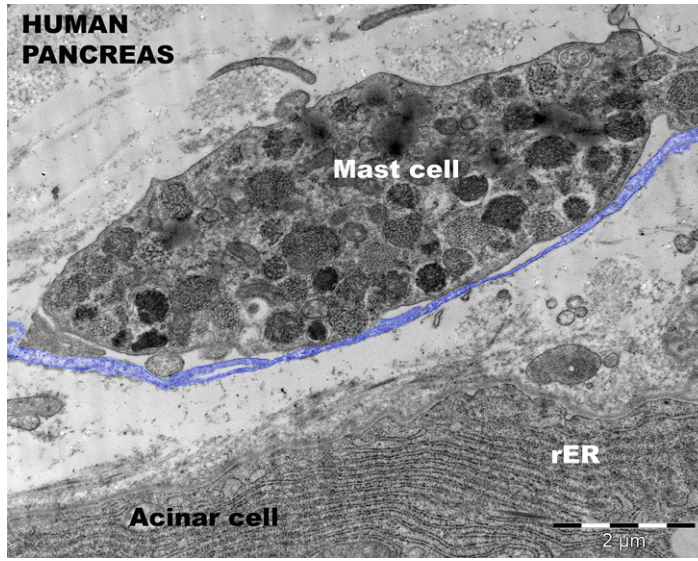

Figure 11.10 Human exocrine pancreas. A telopode (blue) establishes multiple junctions with a mast cell. RER, rough endoplasmic reticulum. **See Plate 21**.

NOS-2, desmin, cadherin-11, and PDGF-R beta [16,20,47,60]. Although for the time being, EM remains the method of choice to precisely identify TC, the double positive immunostaining with CD34/c-Kit (mainly for cell body) or CD34/vimentin (mainly for Tp) also represents a useful marker for TC. It is noteworthy that TC are immunohistochemically negative for procollagen 1 (data not published) and CD90/Thy-1, respectively [47].

Protein Secretory Profile of Telocytes

The secretory capacity of TC has been analyzed by surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS) and xMAP technology—Luminex 200 for cytokine/growth factor release. Several differentially expressed peptide and protein peaks were identified in telocyte-enriched myocardial cell culture supernatants (TEMC), compared to simple culture medium (no cells) or 3T3 ''standard'' fibroblast cultures. Using SELDI-TOF-MS (Fig. 11.11A), we were able to detect in TEMC supernatants significantly different protein peaks with estimated molecular weights of 4083, 11682, and 22596 Da, as well as several peptide peaks in the 500 to 1000 Da range (in preparation).

Using antibody-based xMAP technology (Fig. 11.11B), we detected specific secreted molecules in TEMC supernatants from both serum-free and serum-supplemented media. Detected levels of IL-6 and VEGF increased with passage number. In all experimental systems, TEMC supernatants showed a four- to five-fold

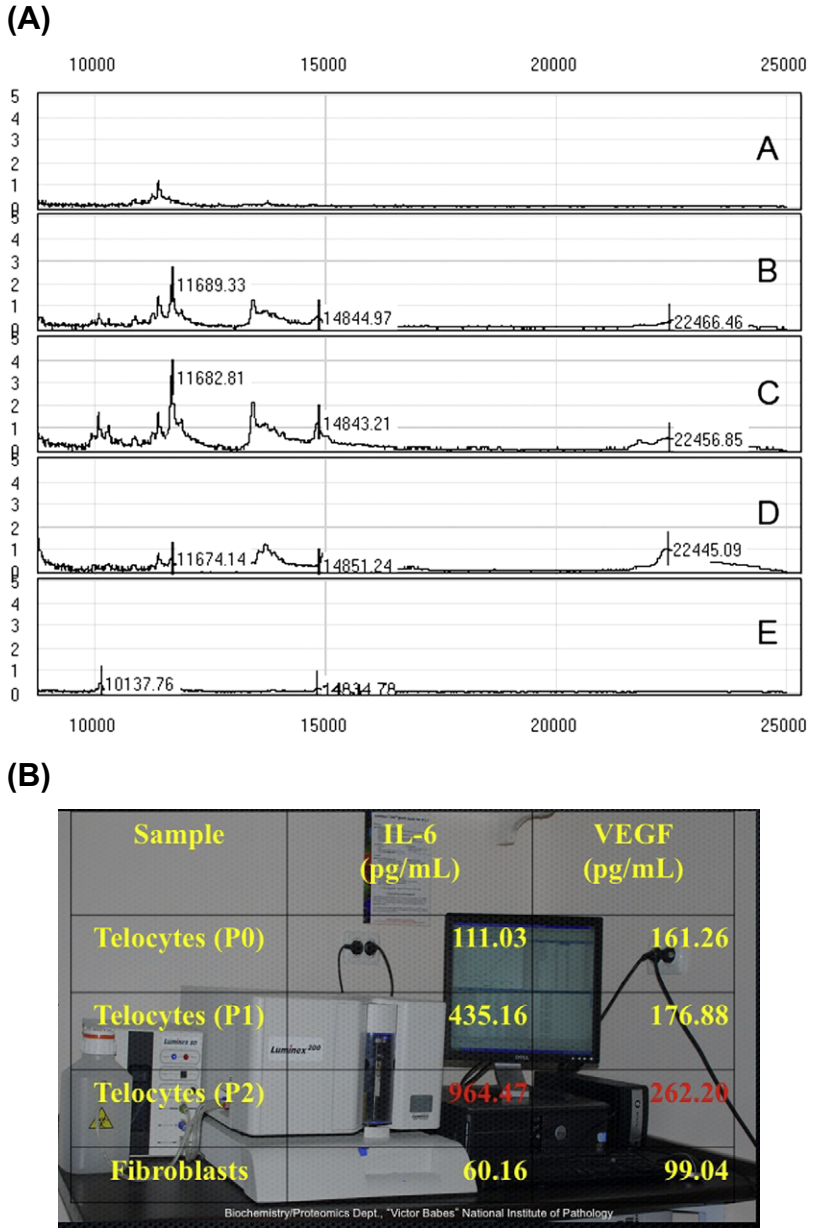

Figure 11.11 **(A)** SELDI-TOF-MS protein spectra. M/Z range: 0 to 25,000 Da, CM10 chips, SPA matrix. Characteristic proteins of TEMC at M/Z values of 4.09, 11.6 and 22.5 KDa. A: Cell culture medium, B: TEMC Passage 0, C: TEMC Passage 1, D: TEMC Passage 2, E: 3T3 Fibroblasts. **(B)** Cell culture supernatants analyzed on xMAP technology (Luminex 200) using Mouse Cytokine/Chemokine Panel.

increase of the secreted IL-6 compared to controls. The VEGF level in TEMC supernatant was also increased, but not at the same magnitude as IL-6. The secretory levels of the two cytokines suggest the potential regulatory role of TC on other cell types, including resident SC, with implications in controlling cell growth/myocyte differentiation or angiogenesis.

MicroRNA Signature of Telocytes

Seeking to identify miRs specifically expressed by TC, we have combined the laser capture microdissection method (for cell isolation) with the quantitative PCR-based microRNA assay (for miR profiling). Limited amounts of RNA (in the range of nanograms) represent a major constraint to quantify miRs by standard procedures: northern blotting, cloning, microarrays, and deep sequencing. Compared with these methods, real-time quantitative PCR (RT-qPCR) gives the highest sensitivity of miRNA quantification while producing fewer false positives and reduced bias [61]. We have found that TC express significant amounts of miR-21, 22, 29, and 199a but lack the expression of cardiomyocyte-specific miRs (miR-1 and 133a or 208a), which supports the view that TC are of mesenchymal origin. We also have shown that apart from other cardiac interstitial cells, TCs do not express miR-193 [62]. In addition, we have found recently that TC express many of the pro-angiogenic microRNAs (i.e., miR-126, miR-130, let-7e, miR-21, miR-27b, miR143, miR-503, and miR-100) [63].

The Tandem Telocytes & Stem Cells

Epicardial Stem Cell Niche

Telocytes have been spotted in the vicinity of several types of cardiac progenitors in various stages of differentiation (Fig. 11.12). Their interstitial network of telopodes builds a dynamic scaffold, a guiding framework essential for the development of new cardiomyocytes. TC, with their Tp, surround cardiac progenitors or precursors to guide them to form the coherent 3D myocardial architecture. Apparently, Tp provide ‘‘tracks’’ for the sliding of cardiomyocyte precursors in their development and integration as working cardiomyocytes.

TC are cells with a certain degree of mobility. This was demonstrated in cell cultures [4], but the moniliform aspect of Tp could indicate this also occurs in situ (a podom could represent either a fulcrum or an elongation reservoir).

The role of TC in nursing cardiomyocytes has also been studied in pathology. Thus, after an experimental myocardial infarction, the TC population is at first disorganized, but gradually regroups following a preestablished pattern and

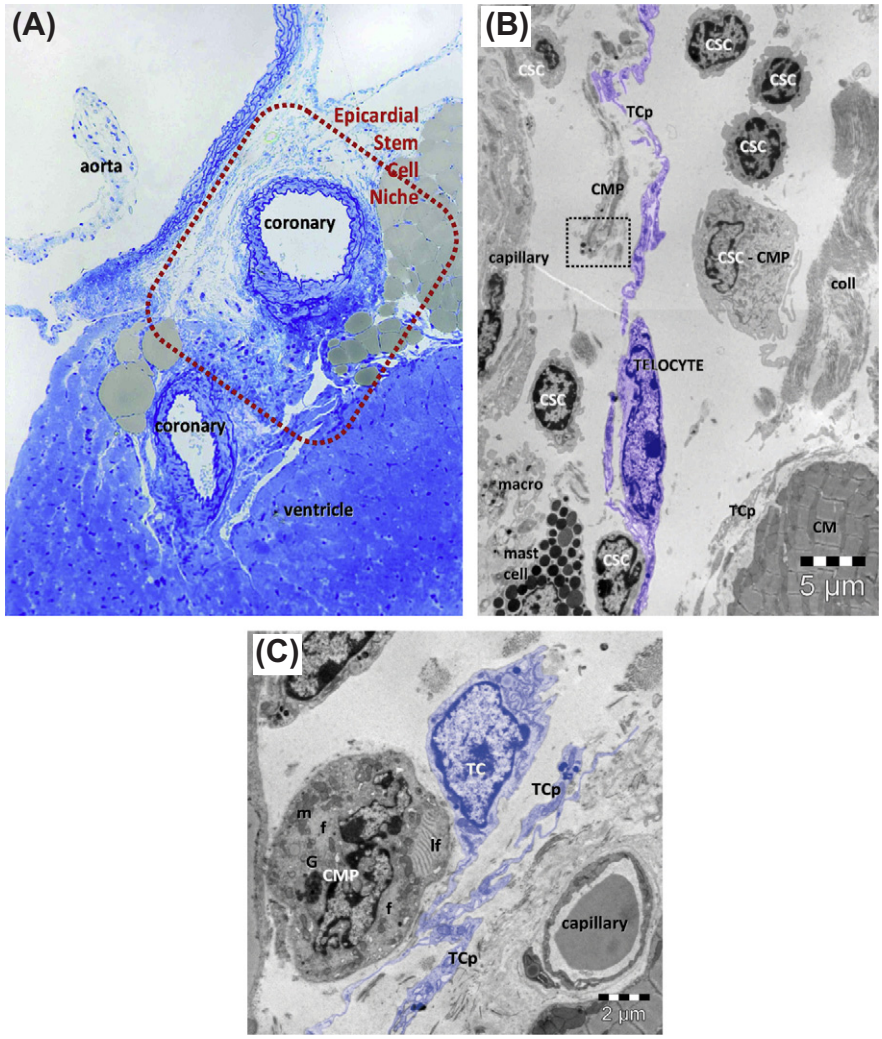

Figure 11.12 **(A)** High-resolution light microscopy on toluidine blue–stained semithin section (~1 µm thick ultramicrotome section) of Epon-embedded mouse heart (6 months old) shows the limited space where cardiomyocyte progenitors have been found by electron microscopy. The cardiac stem cell niche is located in the subepicardial area surrounding the coronary artery next to the emergence from the aorta (rectangle red mark). **(B)** Electron microscopy of the niche depicted in (A) shows the presence of putative cardiac stem cells (CSC), isolated or in small groups, cardiomyocyte progenitors (CMP), and cells with intermediate features (CSC-CMP). All of these cells are placed in a loose extracellular matrix TCp, telopodes. **(C)** A telocyte (TC) chaperone a low differentiated CMP with distinctive leptofibrils (lf), unorganized myofibrils (f), Golgi apparatus (G), and clusters of mitochondria (m). *(Reproduced with permission from [17]).* **See Plate 22**.

contributes in tandem with resident SC to an increase in the regeneration rate of the cells bordering the infarcted area and surroundings [63].

Subepithelial Lung Stem Cell Niche

The tandem arrangement of TC-SC has been identified in subepithelial niches of the bronchiolar tree (Fig. 11.13). Here, the synergy of TCs and SCs may be based on nanocontacts and shed vesicles [31].

Skeletal Muscle Stem Cell Niche

In recent studies, an interstitial nonsatellite myogenic SC niche has been identified [64]. The presence of TC has been reported in both niches (Fig. 11.14) and cell cultures [18]. The migrating capacity showed by cultured TC supports their guiding

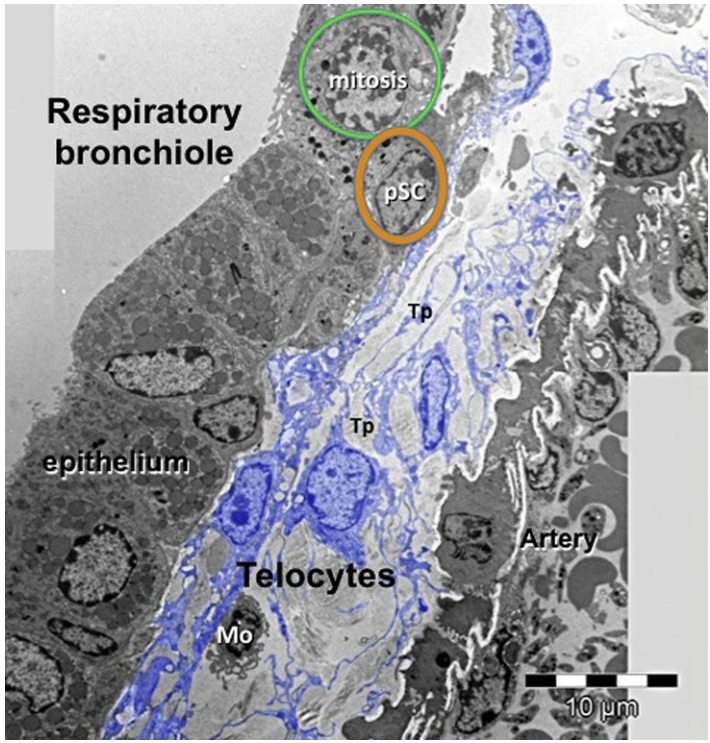

Figure 11.13 Transmission electron microscopy of mouse respiratory bronchiole. Telocytes (TC, blue) with numerous emerging telopodes (Tp). Some Tp surround a putative stem cell (pSC). Mo, macrophage. **See Plate 23**.

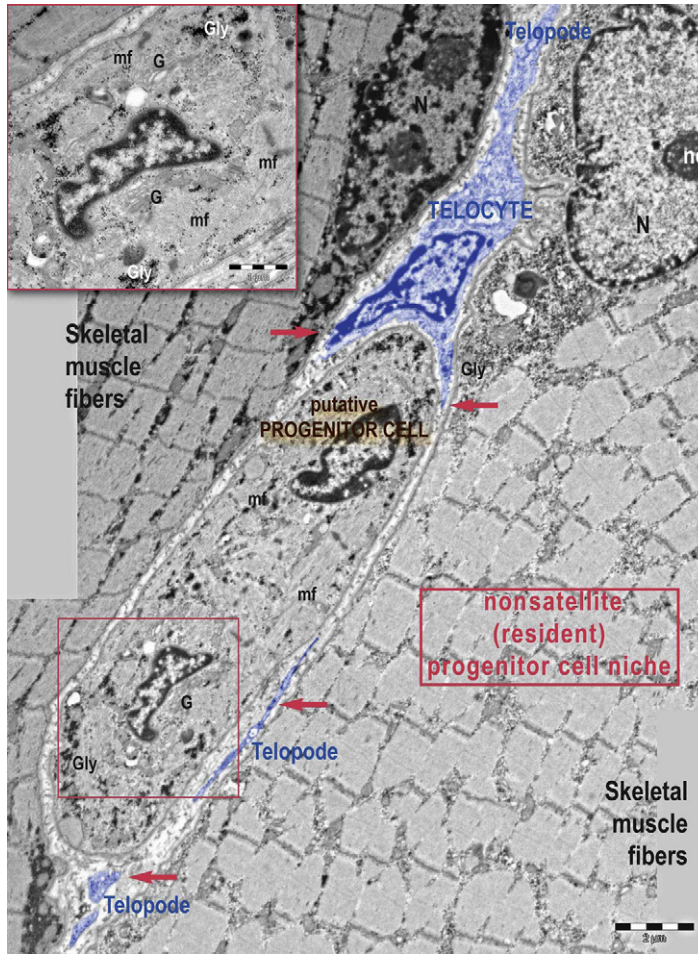

Figure 11.14 Electron micrographs of human skeletal muscle show a TC (blue colored), which extends its Tps indicated by red arrows around a striated cell, in fact, a (putative) progenitor cell. Note the tandem TC—progenitor cell making a nonsatellite (resident) progenitor stem cell niche. **(Inset)** Higher magnification of the progenitor cell shows incompletely differentiated features: unorganized myofilaments (mf), glycogen deposits (Gly), and prominent Golgi complex (G). N, nucleus; nc, nucleolus. *(Reproduced with permission from [18]).* **See Plate 24**.

features indicated by the presence of long Tp circumventing various cell types, including putative progenitor cells.

Meninges and Choroid Plexus

Telocytes establish direct intermembranar contacts with putative SC in a choroid plexus microenvironment (Fig. 11.15).

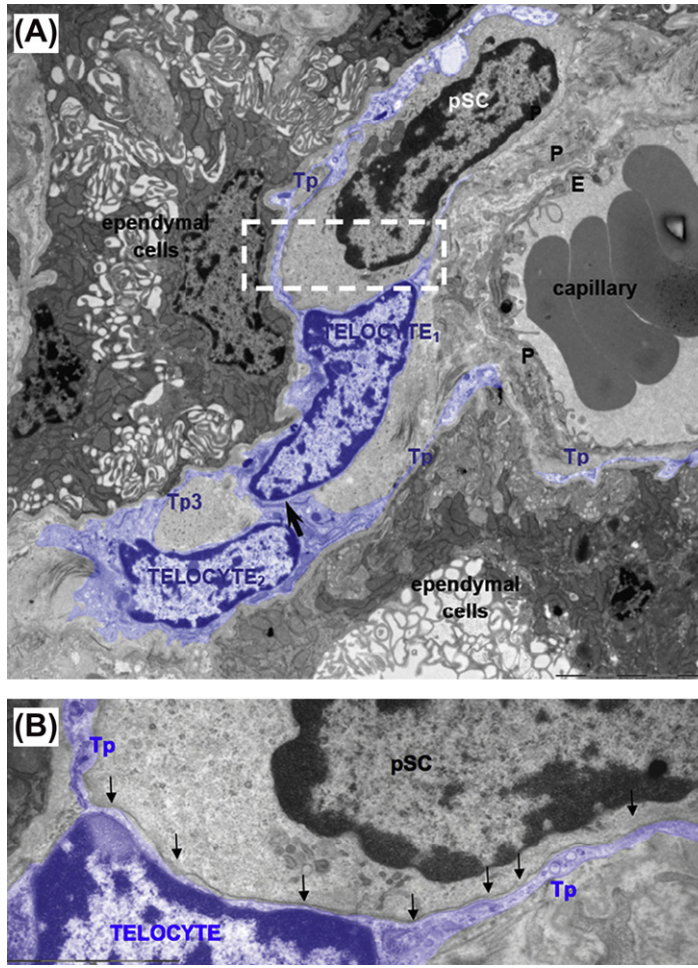

Figure 11.15 EM of adult rat choroid plexus. (A) The 3 telopodes (Tp1-Tp3) of Telocyte1 embrace a stem cell in the interstitial space between ependymal cells layer and the fenestrated capillary. Telocyte1 has a direct inter-membranar contact (arrow) with Telocyte2, whose Tp extends between capillary and ependymal cells. The telopodes width is about 100 nm. Pericytes (P) are located around the endothelial cells (E). (B) Higher magnification of a consecutive section, the rectangular area in (A). Small point contacts between TC and Tp and stem cells are indicated by arrows. The intermembranar distance is variable (mean – 28nm) on 6 µm length but direct contacts are visible (arrows). Scale bars: 5 µm (A), 2 µm (B) *Reproduced with permission from [38].* **See Plate 25**.

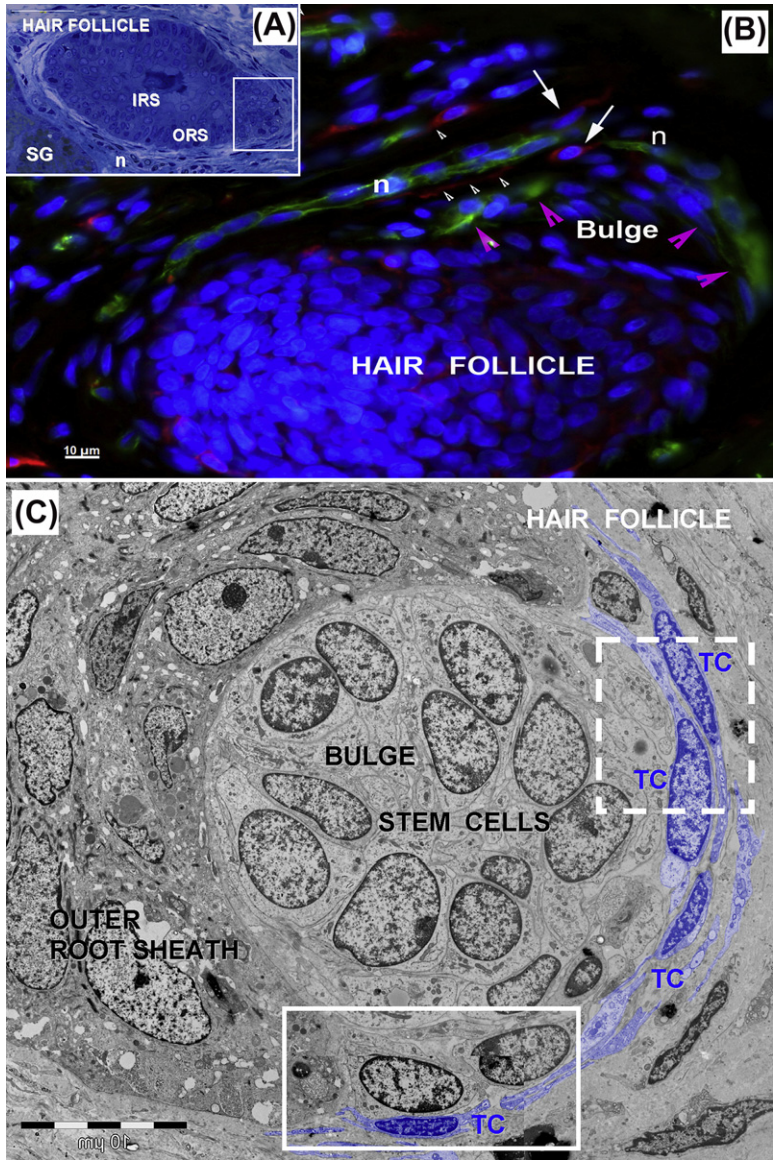

Figure 11.16 Telocytes in reticular dermis. **(A)** Light microscopy image (stained by toluidine-blue) showing a hair follicle and an adjacent sebaceous gland (SG). IRS, inner root sheath; ORS, outer root sheath; n, perifollicular nerve fibers. **(B)** Epifluorescence microscopy: double labelling revealing nestin positive cells (green), stem cells from the bulge area of hair follicle (magenta arrowheads), and perifollicular nerve fibers (N), surrounded by CD117 positive TCs (red, white arrows) with long Tps (white arrowhead). Nuclei were counterstained with DAPI (blue). Original magnification 400x. **(C)** EM of the boxed area in **(A)** shows a cluster of stem cells in the outer root sheath of a hair follicle. The stem cells are bordered by TCs with Tps, as well as other cells from the outer root sheath. *Reproduced with permission after [49].* **See Plate 26**.

Skin stem cell clusters

Telocytes presence was identified between the bulge areas of hair follicles and the adjoining nerve fibres in reticular dermis (Fig. 11.16).

A Hope for Regenerative Medicine

One debatable topic in regenerative medicine is the dedifferentiation concept. Telocytes might represent cells that are closer than others to the mesenchymal pseudo-differentiated stage and, consequently, are more likely to be the subject of dedifferentiation compared to terminally differentiated resident tissular cells.

In the adult mammalian heart, TC together with resident SC and cardiomyocyte progenitors sustain a continuous cardiac renewal process and might be key players in repairing the damaged heart. TC ''nurse'' the progenitor cells in SC niches. The tandem TC-SC could be a better option for therapy rather than SC alone. Finally, TC are directly (physically) and indirectly (chemically) involved in neoangiogenesis after myocardial infarction [63].

The substrate is also an important element in the regeneration process, even as an inducer or as a guiding mesh. The overall environment also plays a crucial role in the regeneration of various structures. The immunologic, mechanical, and bioelectric components are all-important in modeling, guiding, and influencing the regeneration. The plasticity degree of a tissue/organ is directly linked with its ability to adapt and to respond to putative injuries with a fast or slow repair/regeneration rate.

Our opinion is that TC presence and actions (by direct contact or indirect, via shed microvesicles) increase the efficiency and efficacy of resident local SC in the process of repair/regeneration.

The Functions of Telocytes in Physiology and Pathology

The implication of TC in both physiologic and pathologic situations may lead to a phenotype adjustment depending on extracellular conditions or the transmission/reception of information via microvesicles or direct contact. This would explain the inconsistency in the expression of some markers and why intermediary forms may coexist in the differentiation process with a high degree of involvement in organization/function of the organ of residence.

Because TC connections in exocrine glands include both neurovascular and exocrine elements (e.g., acini, ducts), it is attractive to think that TC

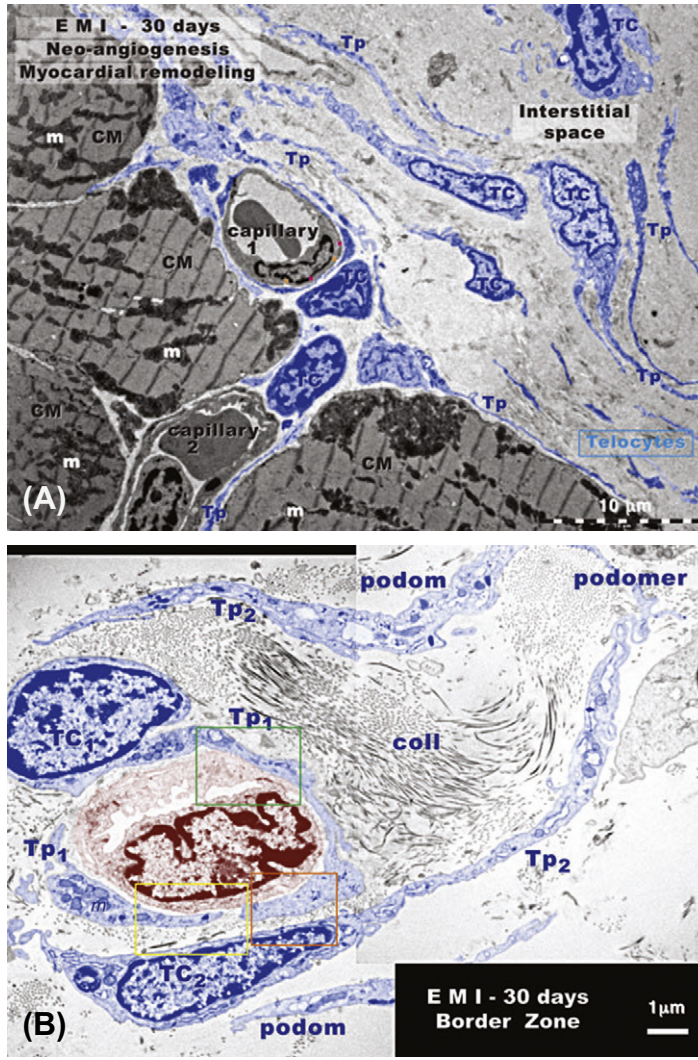

Figure 11.17 Rat experimental myocardial infarction. Border zone: 30 days old. Transmission electron microscopy. **(A)** This low-magnification view shows four cardiomyocytes (CM), two blood capillaries (1 and 2), and numerous telocytes (TC) with long and slender telopodes (Tp). Note the close spatial relationship between TC/Tp and the capillary-1 wall (endothelium). Capillary-1 is presumably a neocapillary created in the interstitial space. Capillary-2, between three cardiomyocytes (CMs), has a TC and Tps in the vicinity, but the distance between the abluminal membrane of the endothelium and the TC/Tp plasma membrane is wider. Thus, capillary-2 is probably an ''old'' capillary. **(B)** A new-formed blood capillary with an anfractuous and narrow lumen is shown (brown color) in the mass of collagen fibrils (coll) of the scar. This is surrounded by two telocytes (TC1 and TC2—blue color) and their

might be involved in modulating local homeostasis as well as in mediating and integrating neural or vascular input with the function of the organ of residence.

This would partially explain a functional link between different interstitial cells (e.g., fibroblasts to produce the collagen and TC to organize the extracellular matrix according to local/general changes).

Human Isolated Atrial Amyloidosis

Interstitial amyloid fibrillar deposits were revealed by EM upon analyzing atrial samples. Some amyloid fibrils appeared amid a honeycomb Tp framework, whereas others were simply wrapped by Tp, blood vessels, or cardiomyocytes [65].

Experimental Acute Myocardial Infarction

Immunocytochemistry, EM (Fig. 11.17), and microRNA analysis showed TC involvement in angiogenic processes in the late stage myocardial infarction, by direct contact with endothelial tubes, as well as by pro-angiogenic microRNAs and paracrine secretion (VEGF, NOS2) [61].

Mechanisms by which TC presumably influence the neoangiogenesis in the border zone of myocardial infarction are summarized in Fig. 11.18. Depending on the distance between TC and target cell(s), intercellular communication may follow a direct or indirect route. Direct physical contact (by either apposition or nanocontacts, without any basal membrane interference) may favor cellular bidirectional cooperation/information exchange. On the other hand, indirect chemical signaling relays para- or microcrine messages, presumably more one-way oriented.

Gastrointestinal and Extragastrointestinal Stromal Tumors (GISTs) and Perivascular Epithelioid Cell Tumors (PEComas)

Telocytes have been proposed as the common cells of origin for both GISTs and PEComas, an archetypal entity that is able to switch from a perivascular stromal cell to a differentiated cell type with contractile and signaling properties [66].

corresponding telopodes (Tp1 and Tp2). Typically, podoms (dilated portions) and the intercalary podomers (thin portions of Tp) can be observed. At the level of podoms there are many mitochondria (m), elements of endoplasmic reticulum, and caveolae. Note the close spatial relationships between telopodes and endothelial cells. The space between telopodes and the membrane of endothelial cell is occasionally less than 50 nm and there is no visible endothelial basal lamina. *(Reproduced with permission from [63]).* **See Plate 27**.

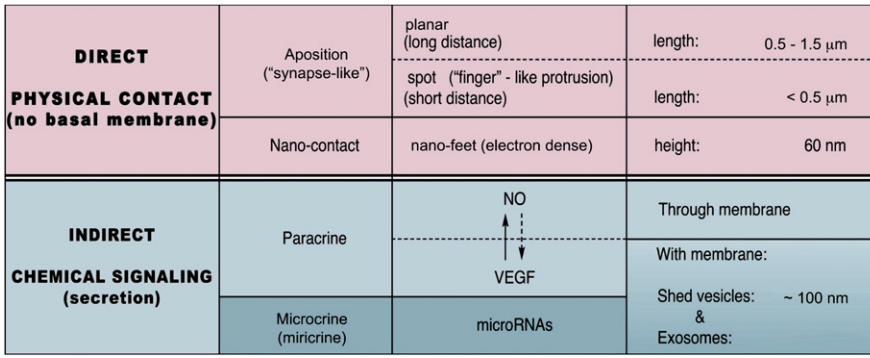

Figure 11.18 Possible mechanisms of telocyte involvement in neoangiogenesis in the border zone of myocardial infarction. *(Reproduced with permission from [63].)*

Future Research Directions

There are several directions for future telocyte research. One of them is the study of miR and cytokine repertoire released by TC. Work in progress in our laboratory using red and green fluorescent proteins suggested that TC and endothelial cells (at least in heart) have a common progenitor.

Another attractive research direction is the study of the cooperation between TC and SC in postinfarcted myocardial areas. This would further detail the mechanisms of cellular cooperation between the two cellular entities. This may be achieved experimentally by injecting either TC or SC alone, both TC and SC concomitantly, or TC followed by SC or the other way around.

Lastly, the presence/absence of telocytes in various organs in development, in different fetal stages, should give us more information regarding the existence of one or several telocyte/fibroblast/mesenchymal cell precursor(s).

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