**TELOCYTES – A Novel Type of Interstitial Cells**

LAWRENCE M. POPESCU  
Department of Cellular and Molecular Medicine  
‘Carol Davila’ University of Medicine and Pharmacy, Bucharest, Romania  
‘Victor Babes’ National Institute of Pathology, Bucharest, Romania  
99-101 Splaiul Independenței, 050096 Bucharest  
ROMANIA

lpopescu@jcmm.org  
www.telocytes.com

**Abstract:** We have recently described a novel type of interstitial (stromal) cells – Telocytes (TC) – in several cavitory and non-cavitory organs from humans and other mammals. TC have a small cell body, but specific (unique) prolongations that we named Telopodes (Tp). Therefore, the simplest definition for TC is: cells with Tp. Tp are characterized by: a) number (1-5/cell, frequently 2 or 3); b) length (tens up to hundreds of µm); c) moniliform aspect – an alternation of thin segments, podomeres (with caliber under 200 nm, below the resolving power of light microscopy) and dilated segments, podoms, which accommodate mitochondria, (rough) endoplasmic reticulum and caveolae, the so-called “Ca²⁺ uptake/release units”; d) dichotomous branching pattern forming a 3D network, a labyrinthine system with complex homo- and heterocellular junctions, revealed only by electron tomography. Significantly, TC (especially Tp) release shed vesicles and exosomes, sending macromolecular signals to neighbor cells, thus modifying their transcriptional activity, eventually. The length and ramifications of Tp together with the intercellular junctions and the releasing of shed vesicles or exosomes suggest an essential role of TC in intercellular signaling and coordination. Noteworthy, at least in some organs (e.g. heart and lungs) TC and stem cells (SC) are located in tandem within the so called stem cell niches, where Tp surround stem cells (SC). TC heterocellular contacts, as well as the impulse of shed vesicles assure TC - SC sinergy. Presumably, TC “nurse” SC in stem cell niches.

**Key-Words:** Telocytes, Telopodes, Interstitial cells, Stem cells, Stem-cell niches, Intercellular signalling, Stromal synapse, Shed vesicles / Exosomes, Cell junctions, Electron tomography

**1 Rationale for the term “telocyte”**  
During the last 5 years we described a new type of cell which became known as “interstitial Cajal-like cells” (acronym - ICLC). We named these cells ICLC because they (apparently) seemed similar, at first glance, with the canonical gastrointestinal interstitial cells of Cajal (ICC). However, little by little, it became clear that the ultrastructure of ICLC was (completely) different from that of ICC, and that the difference between these cells was not only semantic, as they have different ultrastructure and immunophenotype, and therefore should be functionally distinct [1]. Hence, we coined the terms Telocyte (TC) - for these cells, and Telopodes (Tp) [1] for their extremely long but thin prolongations [1-7] in order to prevent further confusion with other interstitial (stromal) cells (e.g., fibroblast, fibroblast-like cells, myofibroblast, mesenchymal cells) (see Figs. 1-7). The concept of TC was promptly adopted by othe Laboratories [8-14].

**2 Telocytes and/or fibroblasts?**  
The interstitium (stroma) is in most of the cases seen as a connecting “device” for the specific structures of an organ. Usually, people are perceiving interstitial cells as being mainly (or even, only) fibroblasts. However, fibroblasts have the function of generating connective tissue matrix, specifically, collagen. The distinction between TC and fibroblasts is obvious since they have different ultrastructure and phenotype. Therefore, their functions should be mostly different: TC - intercellular signalling (connections), but fibroblasts - collagen synthesis. In other words, TC are “more” functionally oriented, and fibroblasts are “more” structurally oriented, responsible for fibrosis.

There are some clear ultrastructural features that differentiate telocytes from fibroblasts. For instance, the general aspect of TC is of a small oval(piriform/spindle/triangular/stellate)-shaped cellular body, containing a nucleus surrounded by a small amount of cytoplasm. Anyway, the shape of the cell body depends on the number of Tp. Fibroblast cell body is pleiomorphic (phenotype heterogeneity ?). TC cellular body average dimensions are, as measured on EM images, 9.3 µm ± 3.2 µm (min. 6.3µm; max. 16.4 µm). Fibroblast nucleus is tipycally euchromatic, but TC nucleus is mostly heterochromatic. Mitochondria represent only 2% of cell body volume and the Golgi complex is small in TC. Fibroblasts Golgi complex is prominent and the rough endoplasmic reticulum is very well developd (usually 5-12%) of cell volume.

Since we are thinking that telopodes are distinctive for telocytes, we would like to emphasize at least...
the following characteristics:

(1) **Number**: 1–5, frequently only 2–3 telopodes are observed on a single section, depending on site and angle of section, since their 3D convolutions prevent them to be observed at their full length in a 2D very thin section;

(2) **Length**: tens – up to hundreds of μm, as measured on EM images (e.g. Figs. 2-10). However, under favourable conditions in cell cultures, their entire length can be captured in several successive images (Fig. 1);

(3) **Thickness**: uneven calibre, mostly below 0.2 μm (below the resolving power of light microscopy), visible under electron microscopy; moniliform aspect: podoms and podomerces; average caliber of podomerces: 0.1 μm ± 0.05μm, min. = 0.003 μm; max. = 0.24 μm;

(4) **Podoms accommodate**: mitochondria, (rough) endoplasmic reticulum, caveolae, a trio called ‘Ca²⁺-uptake/release units’.

(5) **Branching**, with a dichotomous pattern;

(6) **Organization in a labyrinthine system forming a 3D network** anchored by hetero- and homocellular junctions.

Figure 1. Human non-pregnant myometrium in cell culture; day 3; the first passage. Giemsa staining. One TC establishing contacts with a myocyte by a Tp of about 65 μm long. Photographic composition of 4 serial phase contrast images; original magnification 40x. In red rectangles, a higher magnification clearly shows the moniliform aspect; at least 40 specific dilations (podoms) interconnected by thin segments (podomerces) are visible in a ‘bead-like’ fashion. Reproduced with permission from [1].

Figure 2. Digitally coloured TEM image shows TC (blue) in human subepicardium, bordering the peripheral cardiomyocytes (CM, highlighted in brown). The TC has three telopodes, illustrating: a) the distinctive dichotomous pattern of branching (arrows); b) Tp are very thin at the emergence of the cell body; c) alternating podoms and podomerces. Note that some portions of podomerces have the same thickness as collagen fibrills, which make them impossible to be observed under light microscopy. E - elastin Scale bar - 2 μm
Figure 3. Human exocrine pancreas. TC (blue) form with their typical Tp a network around acini. Note the stromal synapse (red arrows) between a mast cell and the Tp of a TC.

Figure 4. Human resting mammary gland stroma. One TC hallmark, namely Tp, appears very long and convoluted. Note homocellular junctions marked by red circles, as well as shed vesicles (blue) and an exosome (violet). Reproduced with permission from [15].
Figure 5. Human term placenta. The TC (blue) has few organelles in the perinuclear area and 3 emerging Tp (red arrows); black arrowheads mark the dichotomic branching points. Note the podoms and podomerces. Black arrow points the junction between a Tp and a smooth muscle cell (SMC, colored in brown).

Figure 6. Non-pregnant myometrium. Digitally colored TC (blue) with 3 Tp that encircle bundles of cross-cut smooth muscle cells (SMC, Sienna brown); N - nuclei. Reproduced with permission from [1].

Figure 7. Rat jejunum. A typical Tp (blue) located between smooth muscle cells (SMC) and nerve endings. Note a large podom and the corresponding podomerces. TC body is not captured in the image. Courtesy of Dr. D. Crețoiu, Department of Cellular and Molecular Medicine, ‘Davila’ Medical School, Bucharest.
Figure 8. Rat stomach, multicontact stromal synapses between two TC, a plasma cell and an eosinophil, respectively. 3-D image computer-aided reconstruction from 9 serial ultrathin sections; original magnification 1,500x. The upper inset shows contact points where the distance between both cell membranes (Tp membrane and plasma-cell membrane) is 15 nm or less (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 [16].

Figure 9. Human mammary gland stroma: TEM; original magnification 9,100x. 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 Ca²⁺ homeostasis. Reproduced with permission from [16].

Figure 10. Scanning electron micrograph of monkey left ventricular myocardium. A typical TC is located across the cardiomyocytes, in close contacts with blood capillaries. Note, the cardiomyocytes striations and the openings of T tubules. Reproduced with permission from [1].
Figure 11. Digitally coloured electron micrograph of mouse ventricular endocardium (burgundy). TC (blue) make an interstitial network in the heart. Subendocardial telocytes (TC₁) sends Tp between cardiomyocytes (CM) and communicate with TC₂. Cap, blood capillary. Scale bar 5µm. Reproduced with permission from [4].

Figure 12. This electron tomography (thick section of about 300 nm) shows nanostructures connecting the TC and cardiomyocytes in adult mouse heart. The bridging structures (encircled) have 10-15 nm and suggest a molecular interaction between the Tp of one TC and the two adjacent cardiomyocytes. The dilated segment of Tp involved in the heterocellular connection (podom) - contains a mitochondrion (m).
We have presented here visual evidence (electron microscopy, electron tomography, phase-contrast microscopy) for the existence of Telocytes (TC) in many organs from human and rodents. TC and Tp and also podoms and podomeres were found in:

- **cavitary organs:**
  - heart (endo-, myo-, and pericardium);
  - stomach and intestine, with mesentery;
  - gallbladder [15];
  - uterus and Fallopian tube [16];

- **non-cavitary organs:**
  - lungs and pleura;
  - pancreas (exocrine);
  - mammary gland;
  - placenta;

Anyway, recent evidence shows the involvement of TC in pathology [19]. TC are strategically located in between blood vessels (capillaries), nerve endings and the specific resident cell population(s) of a given organ. TC establish via Tp homo- and heterocellular junctions and release shed vesicles and exosomes. Thus, TC could be “Le Violin d’Ingres” that locally orchestrate the intercellular “concerto”.

### Figure 13

High resolution light microscopy on toluidine blue stained semithin section (~1 μm thick ultramicrotome section) of Epon-embedded mouse heart (6 month old) shows the limited space where cardiomyocyte progenitors have been found by electron microscopy. Cardiac stem cell niche is located in the subepicardial area surrounding coronary artery next to the emergence from aorta (red rectangle). EM revealed a dozen of cell types, including TC as well as cardiomyocyte progenitors and precursors. Reproduced with permission from [6].

Electron micrographs illustrates the relationships of TC (blue) with cardiomyocyte progenitors (CMP, brown). The Tp run parallel with the main axis of the CMP and seem to establish their direction of development. Reproduced with permission from [4].
Figure 14. Mice lung. Terminal bronchiole. At least 4 TC with their extensive Tp are visible between the epithelium and an arteriole (SMC - smooth muscle cells). Note, the striking labyrinthine network formed by Tp. In the upper part a mitosis (prophase) is obvious (orange circle). In addition, a putative stem cell (SC, green oval) is in close contacts with telocytes prolongations, establishing a heterocellular junctions, visible at higher magnification only). The tandem TC-SC forms, presumably, a TC-SC niche. In the lower part, a macrophage (MF) makes a stromal synapse with Tp.

Figure 15. Rat striated skeletal muscle (diaphragm). A typical TC (blue) with two convoluted Tp is shown, by transmission electron microscopy. Note, two shed vesicles (sv, violet). m, mitochondria, Ly - lymphocyte. The asterisks indicate, presumably, two empty exosomes, which probably released their vesicle content. BV - small blood vessel.
4 Perspectives: Regenerative medicine

TC and SC make a tandem (due to specific intercellular junctions) within the so called SC niches, at least in heart [20] and lungs. Hence, TC could be key-players in regenerating and repair of some organs. The tandem TC-SC could be a better option for therapy rather than SC alone.

**Epilogue:**

* A man is only as good as technology

George Orwell (1903-1950)

References:


