BioMol Concepts, Vol. 2 (2011), pp. 481–489 • Copyright © by Walter de Gruyter • Berlin • Boston. DOI 10.1515/BMC.2011.039

Review

Telocytes

Maria-Simonetta Faussone Pellegrini[1,*] and Laurenţiu M. Popescu[2,3]

[1] Section of Histology, Department of Anatomy, Histology and Forensic Medicine, University of Florence, Viale G. Pieraccini 6, I-50139 Florence, Italy
[2] Department of Cellular and Molecular Medicine 'Carol Davila' University of Medicine and Pharmacy, P.O. Box 35-29, Bucharest 35, Romania
[3] Department of Advanced Studies, 'Victor Babeş' National Institute of Pathology, 99-101 Splaiul Independenţei, RO-050096 Bucharest, Romania

* Corresponding author
e-mail: s_faussone@unifi.it

Abstract

Here, we review the history, morphology, immunohistochemical phenotype, and presumptive roles of a new type of interstitial tissue cells, formerly called interstitial Cajal-like cells (ICLC) and by 2010 named 'telocytes' (TC). Many different techniques have been used to characterize TC and provide their unequivocal identification: (i) *in vitro*, cultures and isolated cells; (ii) *in situ*, fixed specimens examined by light and fluorescence microscopy, transmission (TEM) and scanning electron microscopy, and electron tomography. TEM allowed sure identification and characterization of the most peculiar feature of TC: the long, thin, and convoluted prolongations named 'telopodes'. An enormous variety of antibodies have been tested, but presently none are reliable to specifically label TC. TC have a mesenchymal origin and are resident connective tissue (stromal) cells. Possible identification with 'already identified' stromal cell types (fibroblasts, fibrocytes, fibroblast-like cells, and mesenchymal stromal cells) is discussed. We conclude that in adulthood, most of the TC have the morphology of fibrocytes. Apparently, immunocytochemistry suggests that a variety of TC populations showing different, likely organ-specific, immunophenotypes might exist. Several roles have been hypothesized for TC: mechanical roles, intercellular signaling, guiding and nursing of immature cells during organogenesis, and being themselves a pool of precursors for many of the mesenchyme-derived cells in adulthood; however, none of these roles have been proven yet. On the basis of the available data, we propose TC may be key players in organ regeneration and repair.

Keywords: fibroblasts; interstitial Cajal-like cells (ICLC); interstitial cells of Cajal (ICC); mesenchymal cells; telopodes.

Introduction: a short history

The history of telocytes (TC) is recent since these cells have been discovered only a few years ago. However, the growth of knowledge on TC has been exponential from the beginning and we already have much information. TC were discovered in 2005 when L.M. Popescu's group from Bucharest, Romania, described a new type of cell that resides in the stroma of several organs (1–7), which became known as interstitial Cajal-like cells (ICLC). This group named these cells ICLC because of their apparent similarity with the canonical gastrointestinal interstitial cells of Cajal (ICC), the gut pacemaker cells (8–11). A few years later, in 2008, M.S. Faussone-Pellegrini and her team from Florence, Italy, described ICLC in the muscle coat of the human gut and noticed they consistently differed from the ICC in both ultrastructure and immunophenotype (12). In 2010, after confirming the presence of this peculiar cell type in the stroma of many organs and characterized it by immunohistochemistry and electron microscopy, the two groups agreed they were describing a 'novel' cell type and that the name ICLC had to be changed with a more appropriate one (13). From then on, this novel cell type became known as the telocyte (13).

Rationale for the term 'telocyte'

The interstitial tissue making up the stroma of an organ is the connecting 'device' for the specific structures of the organ and the resident connective tissue cells are usually named 'stromal cells'. However, according to some authors and depending on the organ where these cells reside, they have received a variety of other names: fibroblasts, fibrocytes, fibroblast-like cells, myofibroblasts, mesenchymal cells, interstitial cells, and ICLC. Under transmission electron microscopic (TEM) examination, the cells formerly called ICLC reveal all their characteristics that are unique, unequivocal, and not yet described for any other cell type. To avoid further confusion and to give a precise identity to these cells, Bucharest's team coined for them the term 'telocyte' [=cell bearing long prolongations (13)] on the basis of their most peculiar feature: the presence of prolongations that are extremely long (tens to up to hundreds of micrometers, as measured on TEM images), thin (mostly below 0.2 μm), and with a moniliform aspect (Figures 1–5). The concept of TC was promptly adopted by this group and several other laboratories (14–24).

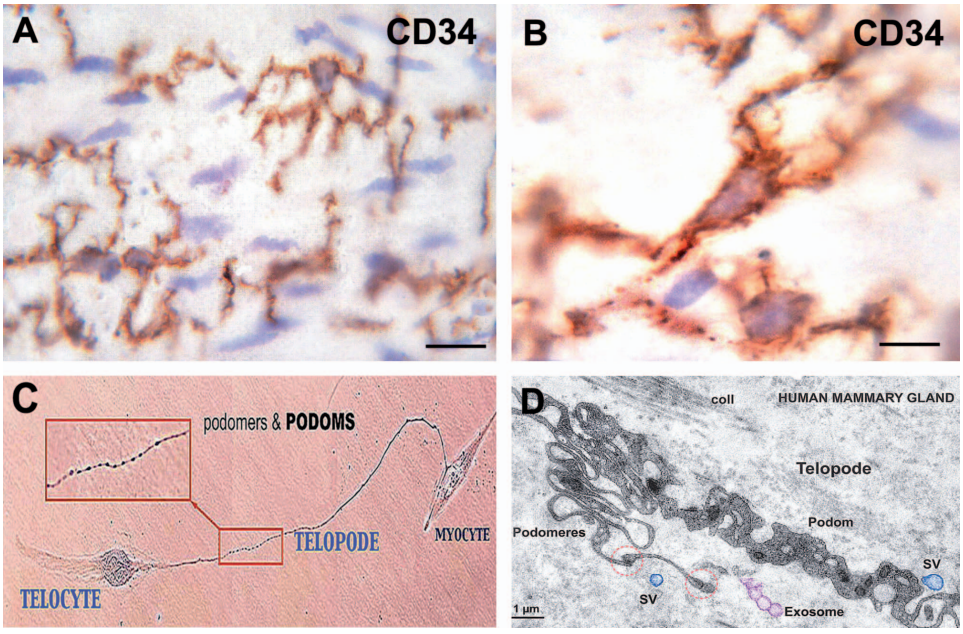

Figure 1 General features of telocytes and telopodes characteristics.
(A and B) CD34-immunoreactivity; submucosa of human stomach. (A) The CD34-positive cells (in brown) have a triangular or ovoid body and a variable number of thin and long prolongations that give a stellate shape to the whole cell. These processes have knobs along their length and a dichotomous branching. Bar, 20 µm. [With permission from (12).] (B) A detail of the body and prolongations of a CD34-positive cell. Bar, 15 µm. (C) Human nonpregnant myometrium in cell culture, day 3, first passage. Giemsa staining. One telocyte establishing contact with a smooth muscle cell (myocyte) by a cell process (telopode) of about 65 µm long. Photographic composition of four serial phase contrast images; original magnification, 40×. In the red rectangles, a higher magnification clearly shows the moniliform aspect of the telopode; at least 40 specific dilations (podoms) of the telopode, interconnected by thin segments (podomeres), are visible in a 'beadlike' fashion. Original magnification, 40× [With permission from (3).] (D) Human resting mammary gland stroma, TEM. One telopode, which appears very long and convoluted, with intercalated podomeres and podoms. Note the homocellular junctions marked by red circles, as well as shed vesicles (SV, blue) and an exosome (violet). coll, collagen. [Reproduced with permission from (1).]

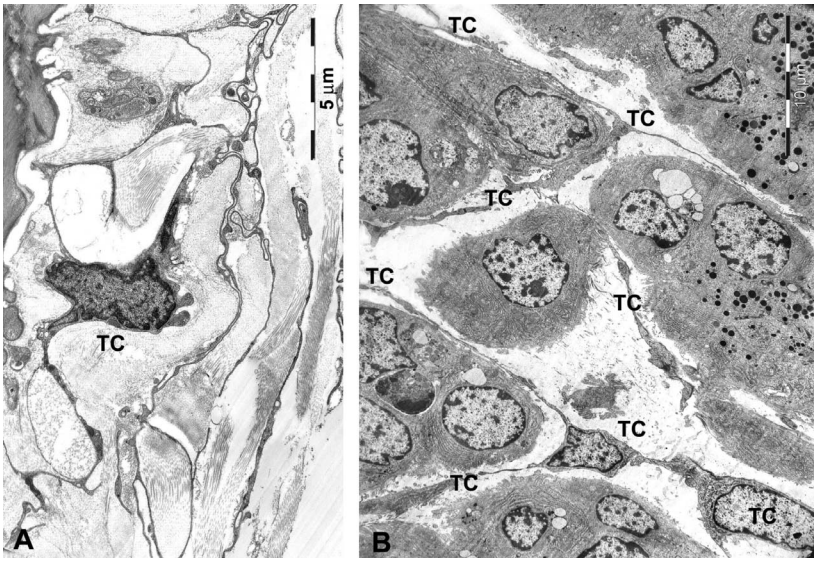

Figure 2 TEM imaging.
(A) Rat mesentery. One TC with a small nucleated body and three long telopodes, all of them having a sinuous trajectory and forming an interstitial complicated 3D network. (B) Human exocrine pancreas. The TC form with their typical long telopodes a network around the acini.

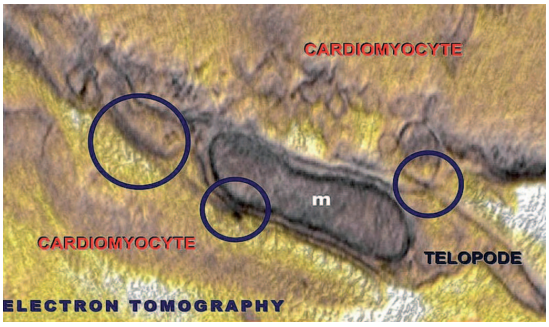

Figure 3 Electron tomography (thick section of about 300 nm) showing nanostructures connecting one telopode with two adjacent cardiomyocytes in adult mouse heart.
The bridging structures (encircled) are 10–15 nm and suggest a molecular interaction between the telopode and the cardiomyocytes. The dilated segment of this telopode contains a mitochondrion (m). [Reproduced with permission from (25).]

Morphology

To characterize these cells, many different techniques have been used: (i) *in vitro*, isolated cells in culture (Figure 1C); (ii) *in situ*, observation on fixed specimens; (iii) light (Figure 1A,B) and fluorescence microscopy (Figure 4A); (iv) transmission electron microscopy (Figures 1D, 2A,B, 4B–D and 5); (v) scanning electron microscopy; (vi) electron tomography (Figure 3).

All these techniques have shown that TC are cells with a small body and a variable number of long prolongations named telopodes (Tp). The shape of the cell body depends on the number of Tp and can be piriform/spindle/triangular/stellate (Figures 1A,B, 2A,B and 4A). The nucleus is oval, with a moderately dense chromatin, and has no obvious nucleolus. The cytoplasm surrounding the nucleus is scarce and contains a small Golgi apparatus, some mitochondria, and few cisternae of rough and smooth endoplasmic reticulum (Figure 2A,B). Average dimensions of the TC body are 9.3±3.2 μm (min. 6.3 μm; max. 16.4 μm). Mitochondria represent 2% of cell body volume. Each TC can have 1–5 Tp. However, frequently only 2–3 Tp are observed on a single section depending on site and angle of the section since their three-dimensional (3D) convolutions prevent them from being observed at their full length in a 2D thin section. Convolutions of the Tp, however, are not always present and have variable extent and complexity depending on the organ where TC are located. The Tp moniliform aspect (Figure 1C,D) is due to an alternation of thin segments, podomeres (whose caliber is below the resolving power of light microscopy, 0.1±0.05 μm; min. 0.003 μm, max. 0.24 μm) and dilated segments, podoms, which accommodate mitochondria, rough and smooth endoplasmic reticulum, and

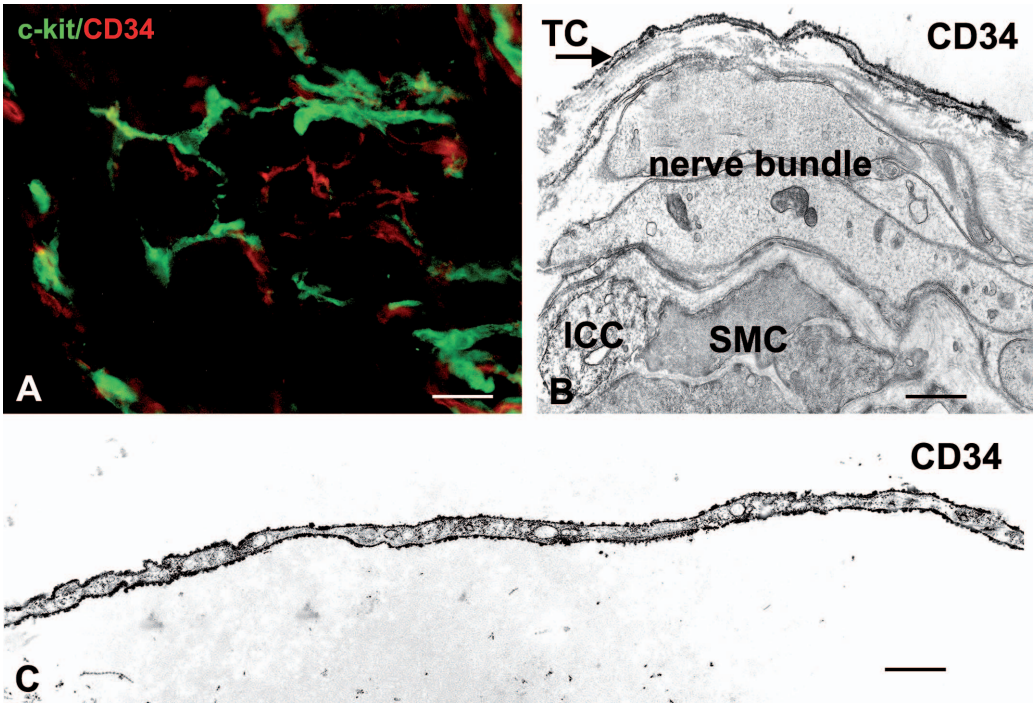

Figure 4 CD34 immunochemistry.
(A) Human stomach. Double CD34/c-kit labeling. CD34 positivity is represented in red and c-kit positivity in green. The CD34- and c-kit-positive cells are often very close to each other but none of them are double labeled. Bar, 25 μm. (B and C) CD34 immunoelectrolabeling. (B) Mouse small intestine. CD34 positivity is present along the plasma membrane of a long, thin process of a TC, while ICC, nerve fibers, and smooth muscle cells (SMC) are CD34 negative. Bar, 1 μm. (C) Mouse stomach. Detail of a CD34 immunoelectrolabeled telopode. CD34 positivity clearly appears as electron-dense spherules regularly distributed on the telopode plasma membrane. Bar, 0.4 μm.

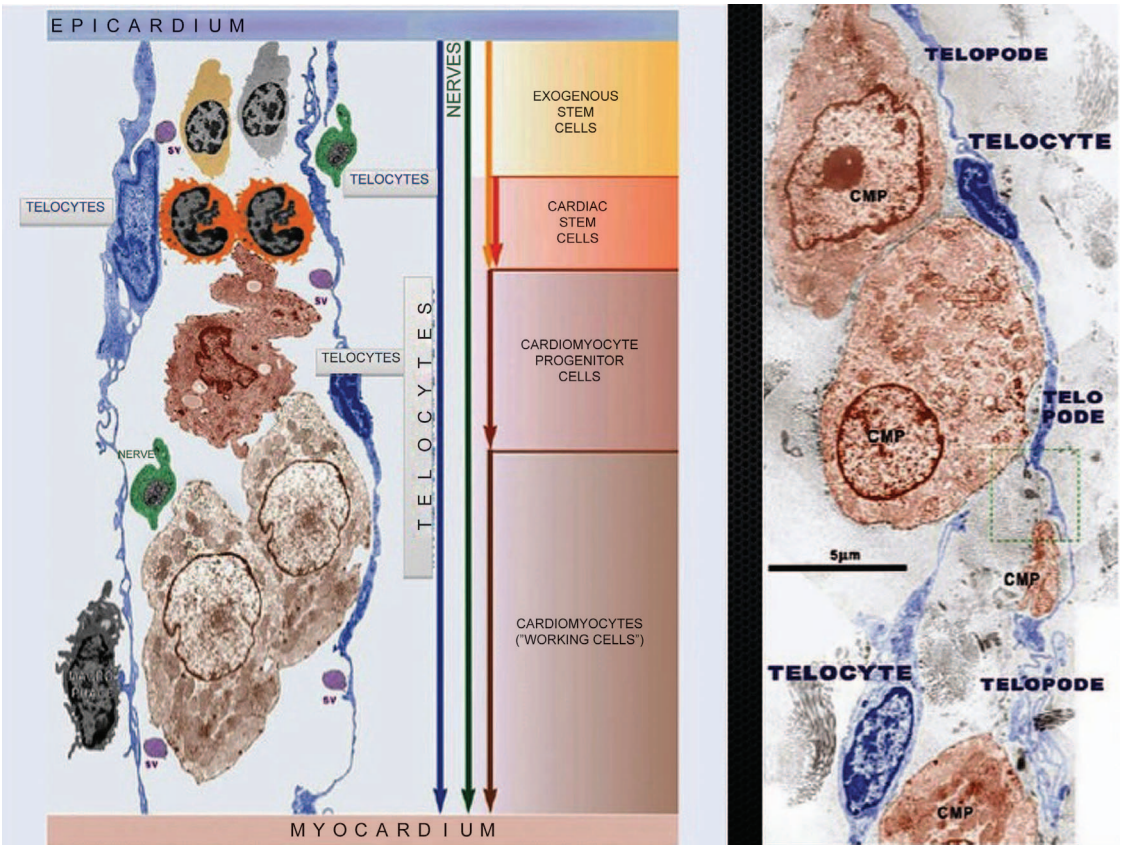

Figure 5 Schema and electron micrograph illustrating the relation of several telocytes (blue) with a column of cardiomyocyte progenitors (CMP, brown) in an epicardial stem cell niche of adult mouse.
The telopodes run parallel to the main axis of the CMP column and seem to establish the direction of development. [Reproduced with permission from (27).]

caveolae – the so-called Ca^{2+} uptake/release units. Tp establish several types of homo- and heterocellular junctions (Figure 3) (25), release shed vesicles and exosomes (Figure 1D) (26), have a dichotomous branching pattern forming a 3D labyrinthine network (Figures 1A and 2A), and might show adhesion plaques with the extracellular matrix (27).

Electron microscopy

Scanning electron microscopy provides good images of presumptive TC (13), and electron tomography provides images of cell-to-cell contacts (25). However, TEM alone allows sure identification of TC, evaluation of the cell-to-cell interrelationships, and a detailed description of the Tp.

Vital staining, cultures

In cell culture, TC shape and, in particular, Tp length can be easily evaluated since in these conditions Tp are not convoluted (Figure 1C). Moreover, MitoTracker Green FM, a lipophylic selective dye that becomes fluorescent once it accumulates in the lipid environment of mitochondria, confirms these organelles are present in the TC body and at the level of Tp dilations (5, 28). Immunohistochemistry performed on cultured or isolated TC from determined organs does not always give the same results as those obtained on the corresponding TC *in situ*.

Immunohistochemistry

To know the chemical code of TC is of fundamental importance since it allows their unequivocal identification and also helps evaluate their size, shape, number, and, eventually, movements, migration, and pathological changes. Unfortunately, although Bucharest's group made many reliable attempts in testing an enormous variety of antibodies (14, 29, 30), a single marker that can be considered specific for this cell type or, at least, specific for the TC of a given organ has not been found. Indeed, TC might show different immunohistochemical profiles among organs and even in the same organ examined. In the chorial villi (14), some TC are c-kit positive and some CD34 positive; all of the CD34-positive TC express vimentin and caveolin-1, and some of them also c-kit (14). In cultured cells from the same placental villi, some TC are double positive for c-kit and iNOS and others for c-kit and VEGF (14). Skeletal muscle TC are c-kit, caveolin-1, and CD34 positive, and have been found to secrete VEGF (18). In the mouse heart, most of the TC are

CD34 positive and a few are c-kit positive (31). Presently, only one study, performed by Florence's group on both light/fluorescence and ultrastructural detection of CD34 and c-kit in the human gut, is available (12). In this study, immunohistochemistry combined with TEM allowed to put into light that the enteric TC are CD34-positive and c-kit-negative cells, and also to exclude ICC and TC as being the same cell type (Figure 4A,B,D). Notably, the TC located in the mucosa are neither CD34 nor c-kit positive (12). Briefly, CD34 labeling does not allow an unequivocal TC identification since it does not label all TC, at least in some organs [e.g., gut, placenta, and striated muscle (12, 14, 18)] or during embryonic life [e.g., in the heart (20) and gut (Faussone-Pellegrini, personal observations)]. However, at present, CD34 labeling remains the best available choice for TC identification, possibly in combination with c-kit and vimentin labeling.

In conclusion, due to these important differences in TC immunolabeling and since none of the markers tested are 'specific', it would be desirable if more laboratories other than those in Bucharest and Florence will study this issue and perform further immunohistochemical techniques, including immunoelectron microscopy.

Distribution

TC have been found in a large variety of cavitary and noncavitary organs (Table 1). Therefore, we would reasonably conclude these cells are ubiquitous. All the cells identified as TC were located within the connective tissue and could be (i) organized in a 3D network, dispersed in the extracellular substance, and intermingled with resident (fibroblasts, mast cells, adipocytes) and nonresident (macrophages, immune cells, granulocytes) cells, or (2) at the connective border of various tissues (epithelial, muscular, and nerve tissues) lining them and around blood vessels; these TC are likely organized in a 2D network. Those located around blood vessels presumably correspond to the adventitial cells and those located around myenteric plexus ganglia and nerve strands correspond to the covering cells (12, 38).

Possible TC identification with 'already identified' stromal cell types

Usually, connective tissue cells are perceived as being mainly (or even only) fibroblasts and/or fibrocytes. Importantly, it has to be noted that across different countries and laboratories, there is great confusion between the terms fibroblast and fibrocyte. In some European countries and outside of Europe, only the term fibroblasts is used; however, two types of fibroblasts are recognized, the active and the quiescent fibroblasts. Conversely, in some other European countries (Italy, Germany, Romania, etc.) both fibroblasts and fibrocytes are recognized as distinct cell types. There is a general agreement that cells called fibroblasts correspond to the active connective tissue cells involved in synthesis and organization of extracellular components (ground substance and fibers). These cells are, therefore, obviously present during development and whenever there is a need for renewal or repair of extracellular components. The so-called fibrocytes conceivably correspond to the quiescent fibroblasts, which are typical of connective tissues during adult life. The distinction between fibrocytes and fibroblasts is based on their markedly different ultrastructural features; these differences are commonly reported in histology textbooks and can be summarized as follows.

Table 1 TC distribution.

Cavitary organs	Noncavitary organs
Heart (endo-, myo-, and pericardium) (6, 16, 19, 20, 25) (26–31)	Lung and pleura (17)
Stomach and intestine (12, 21)	Exocrine pancreas (2)
Gallbladder (32)	Mammary gland (1)
Uterus (3, 33, 34)	Placenta (14)
Fallopian tube (5, 35)	Skeletal muscle (18)
Blood vessels (36)	Mesentery (37)

The (active) fibroblast body is large and pleomorphic; the nucleus is typically euchromatic and has one to two nucleoli; the Golgi complex is prominent; and the rough endoplasmic reticulum is well developed (about 5–12% of cell volume). Cell processes are few, short, and of large caliber, thus being easily appreciable under a light microscope. These cells are markedly different from TC, but some of the cells labeled as 'fibroblasts' in the figures reported in histology textbooks and other literature show the morphology of TC and not that of active fibroblasts. Recently, some markers have been tested to differentiate cardiac TC from fibroblasts (which are c-kit negative) (39). Noteworthy, microRNA expression (e.g., miR-193) clearly differentiated TC from fibroblasts and in culture also allowed to discriminate between TC and other stromal cells (39).

The body of fibrocyte (or quiescent fibroblast) cells is small and oval; the nucleus is moderately heterochromatic and the nucleolus is difficult to locate; the Golgi complex is small; and the rough endoplasmic reticulum is scarce. Cell prolongations are few, long, and thin (usually described as tapering, slender processes). Intriguingly, the body, nucleus, and some of the ultrastructural characteristics of fibrocytes are the same as those reported for the TC, with the exception of the extension, convolution, and moniliform aspect of processes. The morphology of the cells labeled as 'fibrocytes' in figures reported in histology textbooks and other literature is very similar to that of the TC. In figure 1 of a recent review (40), the cells located in the connective tissue have the typical features of both fibrocytes and TC. These latter cells are named fibrocytes and considered to be circulating mesenchymal progenitor cells that participate in tissue responses to injury and invasion (40).

Cells having the ultrastructure of active fibroblasts have been described both in normal and pathological conditions by many laboratories, but there is a general agreement that they are not to be considered as true fibroblasts: thus, these cells were named fibroblast-like cells. No specific function has been attributed to them. These cells do not resemble TC.

According to histologists and pathologists, mesenchymal stromal cells are cells still present in adulthood that are mostly arranged along blood vessels, particularly along capillaries (41). In usual histology textbooks, these cells are never shown, but their description corresponds to that of small fibroblasts. On the contrary, embryonic mesenchymal cells are shown in many embryology textbooks and other literature. These cells have a round body filled with free ribosomes, a small Golgi complex, a nucleus with clear chromatin, and a large nucleolus. Cell processes can be absent, or when present are usually long and thin. TC morphology, therefore, does not correspond to that of mesenchymal cells, at least not those described during embryonic life.

Pre- and postnatal differentiation

Studies aimed at gaining information on pre- and postnatal TC differentiation have not been performed, and little information is currently available. Such studies would give an answer on which is the origin of TC and on whether these cells are differentiated or immature cells. The knowledge of TC morphology and immunophenotype during their maturative steps could be of great help in identifying all TC variations during development and in recognizing them at every age. Noteworthy, it is possible that, according to the organ where they reside, TC could show different degrees of differentiation. This possibility is suggestive for the presence of TC subtypes in adulthood, which differ from each other in morphology, immunophenotype, and name. Also, studies aimed at investigating whether TC can retain the capability to further differentiate, are committed to one or more specific cell lineages, and are able to differentiate spontaneously or after injury, would be welcome.

At present, Florence's team indirectly provided some evidences for TC differentiation. Results obtained by studying the developing mouse heart, as well as primary cultures of neonatal mouse cardiac cells (20, 42), showed that at earlier embryonic stages [embryonic day 14 (E14)], all the interstitial cells had typical mesenchymal ultrastructural features and none of them were CD34 positive. However, by E17, some of them acquired CD34 positivity and, at birth (P0), also fibroblast-like features. After birth (by P6), the putative TC showed their typical ultrastructural features while CD34 positivity became uncertain or limited to few of them. Of note, the acquisition of the immuno- and the ultrastructural phenotypes are not synchronized. In studies on the human small intestine from fetal life to birth and on ICC plasticity (43, 44), mesenchymal cells were seen to become ICC and smooth muscle cells passing through an intermediate cell type having fibroblast-like features. TC precursors also have fibroblast-like features; however, at variance with the ICC that were c-kit positive and already differentiated in fetuses at term (45), TC are never c-kit positive and acquire their typical CD34 positivity and ultrastructure only after birth (Faussone-Pellegrini, unpublished data). According to some recent data (46, 47), the CD34-positive cells present in these fetuses might be in fact immature ICC.

On the basis of the available information, we can reasonably conclude that TC are mesenchymal in origin, are resident connective tissue cells from their earliest developmental steps, and during their differentiation share fibroblast-like features with immature ICC, smooth muscle cells, and true fibroblasts. An obvious question arises when studying TC differentiation: does the TC correspond to fibroblast-like cells? In adulthood, most if not all of the TC have the morphology of cells called fibrocytes; however, presently we have no information on whether different TC populations exist in the various organs and on whether some of them maintain fibroblastic-like appearance also in adulthood. Moreover, it cannot be excluded that TC will acquire this feature in the presence of stimuli to tissue renewal or repair contributing to (i) new synthesis of the extracellular components, or (ii) differentiation of new cells to replace the dead ones, or (iii) spatial reorganization of the organ.

We would like to hypothesize TC are 'progenitor cells' more or less committed according to the organs and still able to further differentiate. This hypothesis opens a wide and fascinating field for future researches that will surely provide results that are surprising and of high impact.

Roles

Several roles have been suggested for TC, most of which are believable and not mutually exclusive. However, none of them have been proven yet.

TC might have a role as a mechanical support. The TC of the rat mesentery form a 3D network hypothesized to be at the same time resistant and deformable following stretches consequent to gut movements, mainly directed to avoid blood vessel closure (37). The TC located in the gut muscle coat, in particular those at the myenteric plexus level, also form a 3D network that is likely resistant to and deformable following intestinal movements (12).

TC might guide the migration of other cells to define the final organization of an organ or its repair or renewal. According to a recent study (48), TC guide the migration of mesenchymal cells into the mesothelial layer of the epicardium, thus being involved in mesothelial renewal. Cardiac TC should guide myocardial precursors to form the correct 3D tissue pattern and contribute to compaction of the embryonic myocardial trabeculae. Indeed, cardiomyoblasts and TC were seen to form stem cell (SC) niches in the subepicardial region of the adult mouse heart (Figure 5) (27, 42, 49), to migrate during development from the epicardium, from where they presumably originated, and to form an extended network of Tp closely embracing the growing cardiomyocytes (20). Results obtained in studies of co-cultures of TC and cardiomyoblasts confirmed that TC can intervene in the aggregation of cardiomyocyte clusters (20).

An immune surveillance role was suggested for the network of CD34-positive interstitial cells, further identified as TC, located in human fallopian tube (50).

Intriguingly, it has also been suggested that TC might play a role in neurotransmission in the gut, possibly contributing to spread the slow waves generated by the ICC. Indeed, the intramuscular ICC and TC seem to be part of a unique network, in which, however, only ICC are innervated (12).

TC might be involved in intercellular signaling. The cardiac TC have been hypothesized to play a nursing role (27) and those in the oviduct and myometrium to be sensors for steroid hormones (34, 35). Significantly, the Tp establish homo- and heterocellular junctions (25); release shed vesicles and exosomes (26); and show paracrine secretion of IL6, VEGF, and NO. Thus TC, by sending macromolecular signals to neighboring cells, could influence their transcriptional activity.

Finally, TC might represent a pool of cell precursors for a variety of cell types with common mesenchymal origin. Up to now, this role has been proposed for the placental (14) and enteric TC (12). The latter might be ICC precursors that renew ICC undergoing apoptosis (51), thus keeping the ICC number constant throughout life. Recently, a nonsatellite resident progenitor cell niche (presumably made by TC) was described in the striated muscle (18). In cultures of this tissue, TC (but not satellite cells) were seen to emerge from muscle explants and form cell networks, suggesting a key role in muscle regeneration and repair (18).

Pathology

Information on pathological TC would be of high interest. At present, only one published paper deals with TC involvement in heart amyloidosis in patients with atrial fibrillation (52). By TEM, amyloid deposits were located in interstitial recesses surrounded by long and slender TC processes, likely limiting the spread of deposits into the interstitium. Interstitial cells, likely TC, have been characterized in the upper lamina propria of bladders of patients with neurogenic detrusor overactivity and bladder pain syndrome. These cells were seen to shift toward a fibroblast phenotype (53).

The study of TC in mutant animals is also a tantalizing challenge. Presently, the only available information indicates the absence of caveolae in the TC from the myocardium (54) and gut muscle coat (55) of Cav-1 knockout mice. This finding remains unexplained, mostly because of the lack of physiological data.

Perspectives: regenerative medicine

It is tempting to speculate that TC, as progenitor and/or guiding and nursing cells, are a novel, possible target for therapeutic strategies (56–58). The challenge of using muscle progenitor cells for skeletal and cardiac muscle reconstruction in animal models or humans has not been solved to date, mainly due to scarce graft cell survival explained by a lack of adequate paracrine factors, tissue guidance, and blood vessel scaffold (59–64). Therefore, new attempts aimed at potentiating cardiac repair and regeneration after ischemic injury received great momentum from the hypothesis of a coexistence and cooperation of organ-specific TC and SC (20). Briefly, TC and SC can be seen as working in tandem, representing a better option for therapy rather than SC alone (65, 66). An important goal would be to ascertain whether such TC–SC cooperation requires homologous TC and SC from the same organ or whether TC from any organ source can be used for cell therapy. In the first case, TC of a given organ should be committed to differentiate or cooperate with the cells specific to this organ, likely because of their similar embryologic origin (e.g., from the epicardium, the mesothelium, or even the endoderma, ectoderma and both intra- and extraembryonic mesoderma). In the second case, TC extracted from any organ could correctly function even when grafted into organs of a different embryologic origin, with obvious advantages in terms of availability and plasticity.

For more information on telocytes, see the papers and images at http://www.telocytes.com.

References

1. Gherghiceanu M, Popescu LM. Interstitial Cajal-like cells (ICLC) in human resting mammary gland stroma. Transmission electron microscope (TEM) identification. J Cell Mol Med 2005; 9: 893–910.
2. Popescu LM, Hinescu ME, Ionescu N, Ciontea SM, Cretoiu D, Ardeleanu C. Interstitial cells of Cajal in pancreas. J Cell Mol Med 2005; 9: 169–90.
3. Ciontea SM, Radu E, Regalia T, Ceafalan L, Cretoiu D, Gherghiceanu M, Braga RI, Malincenco M, Zagrean L, Hinescu ME, Popescu LM. C-kit immunopositive interstitial cells (Cajal-type) in human myometrium. J Cell Mol Med 2005; 9: 407–20.
4. Popescu LM, Gherghiceanu M, Cretoiu D, Radu E. The connective connection: interstitial cells of Cajal (ICC) and ICC-like cells establish synapses with immunoreactive cells. Electron microscope study in situ. J Cell Mol Med 2005; 9: 714–30.
5. Popescu LM, Ciontea SM, Cretoiu D, Hinescu ME, Radu E, Ionescu N, Ceausu M, Gherghiceanu M, Braga RI, Vasilescu F, Zagrean L, Ardeleanu C. Novel type of interstitial cell (Cajal-like) in human fallopian tube. J Cell Mol Med 2005; 9: 479–523.
6. Hinescu ME, Popescu LM. Interstitial Cajal-like cells (ICLC) in human atrial myocardium. J Cell Mol Med 2005; 9: 972–5.
7. Radu E, Regalia T, Ceafalan L, Andrei F, Cretoiu D, Popescu LM. Cajal-type cells from human mammary gland stroma: phenotype characteristics in cell culture. J Cell Mol Med 2005; 9: 748–52.
8. Faussone-Pellegrini MS, Cortesini C, Romagnoli P. Sull'ultrastruttura della tunica muscolare della porzione cardiale dell'esofago e dello stomaco umano con particolare riferimento alle cosidette cellule interstiziali del Cajal. Arch It Anat Embriol 1977; 82: 157–77.
9. Thuneberg L. Interstitial cells of Cajal: intestinal pacemaker cells? Adv Anat Embryol Cell Biol 1982; 71: 1–130.
10. Faussone-Pellegrini MS. Histogenesis, structure and relationships of interstitial cells of Cajal (ICC): from morphology to functional interpretation. Eur J Morphol 1992; 30: 37–48.
11. Faussone-Pellegrini MS. Interstitial cells of Cajal: once negligible players, now blazing protagonists. Ital J Anat Embryol 2005; 110: 11–31.

12. Pieri L, Vannucchi MG, Faussone-Pellegrini MS. Histochemical and ultrastructural characteristics of an interstitial cell type different from ICC and resident in the muscle coat of human gut. J Cell Mol Med 2008; 12: 1944–55.
13. Popescu LM, Faussone-Pellegrini MS. TELOCYTES – a case of serendipity: the winding way from interstitial cells of Cajal (ICC), via interstitial Cajal-like cells (ICLC) to TELOCYTES. J Cell Mol Med 2010; 14: 729–40.
14. Suciu L, Popescu LM, Gherghiceanu M, Regalia T, Nicolescu M, Hinescu M, Faussone-Pellegrini MS. Telocytes in human term placenta: morphology and phenotype. Cells Tissue Org 2010; 192: 325–39.
15. Popescu LM, Manole CG, Gherghiceanu M, Ardelean A, Nicolescu MI, Hinescu ME, Kostin S. Telocytes in human epicardium. J Cell Mol Med 2010; 14: 2085–93.
16. Gherghiceanu M, Manole CG, Popescu LM. Telocytes in endocardium: electron microscope evidence. J Cell Mol Med 2010; 14: 2330–4.
17. Hinescu ME, Gherghiceanu M, Suciu L, Popescu LM. Telocytes in pleura: two- and three-dimensional imaging by transmission electron microscopy. Cell Tissue Res 2010; 343: 389–97.
18. Popescu LM, Manole E, Şerboiu CS, Manole CG, Suciu LC, Gherghiceanu M, Popescu BO. Identification of telocytes in skeletal muscle interstitium: implication for muscle regeneration. J Cell Mol Med 2011; 15: 1379–92.
19. Kostin S. Myocardial telocytes: a specific new cellular entity. J Cell Mol Med 2010; 14: 1917–21.
20. Bani D, Formigli L, Gherghiceanu M, Faussone-Pellegrini MS. Telocytes as supporting cells for myocardial tissue organization in developing and adult heart. J Cell Mol Med 2010; 14: 2531–8.
21. Carmona IC, Bartolomé MJ, Escribano CJ. Identification of telocytes in the lamina propria of rat duodenum: transmission electron microscopy. J Cell Mol Med 2011; 15: 26–30.
22. Cantarero CI, Luesma BMJ, Junquera EC. The primary cilium of telocytes in the vasculature: electron microscope imaging. J Cell Mol Med 2011; Mar 24. doi: 10.1111/j.1582-4934.2011.01312.x.
23. Zhou J, Zhang Y, Wen X, Cao J, Li D, Lin Q, Wang H, Liu Z, Duan C, Wu K, Wang C. Telocytes accompanying cardiomyocyte in primary culture: two- and three-dimensional culture environment. J Cell Mol Med 2010; 14: 2641–5.
24. Eyden B, Curry A, Wang G. Stromal cells in the human gut show ultrastructural features of fibroblasts and smooth muscle cells but not myofibroblasts. J Cell Mol Med 2011; 15: 1483–91.
25. Gherghiceanu M, Popescu LM. Heterocellular communication in the heart: electron tomography of telocyte-myocyte junctions. J Cell Mol Med 2011; 15: 1005–11.
26. Mandache E, Popescu LM, Gherghiceanu M. Myocardial interstitial Cajal-like cells (ICLC) and their nanostructural relationships with intercalated discs: shed vesicles as intermediates. J Cell Mol Med 2007; 11: 1175–84.
27. Popescu LM, Gherghiceanu M, Manole GC, Faussone-Pellegrini MS. Cardiac renewing: interstitial Cajal-like cells nurse cardiomyocyte progenitors in epicardial stem cell niches. J Cell Mol Med 2009; 13: 866–86.
28. Popescu LM, Gherghiceanu M, Hinescu ME, Cretoiu D, Ceafalan L, Regalia T, Popescu AC, Ardeleanu C, Mandache E. Insights into the interstitium of ventricular myocardium: interstitial Cajal-like cells (ICLC). J Cell Mol Med 2006; 10: 429–58.
29. Hinescu ME, Gherghiceanu M, Mandache E, Ciontea SM, Popescu LM. Interstitial Cajal-like cells (ICLC) in atrial myocardium: ultrastructural and immunohistochemical characterization. J Cell Mol Med 2006; 10: 243–57.
30. Kostin S, Popescu LM. A distinct type of cell in myocardium: interstitial Cajal-like cells (ICLCs). J Cell Mol Med 2009; 13: 295–308.
31. Suciu LC, Popescu LM, Regalia T, Ardelean A, Manole CG. Epicardium: interstitial Cajal-like cells (ICLC) highlighted by immunofluorescence. J Cell Mol Med 2009; 13: 771–7.
32. Hinescu ME, Ardeleanu C, Gherghiceanu M, Popescu LM. Interstitial Cajal-like cells in human gallbladder. J Mol Histol 2007; 38: 275–84.
33. Popescu LM, Ciontea SM, Cretoiu D. Interstitial Cajal-like cells in human uterus and fallopian tube. Ann N Y Acad Sci 2007; 1101: 139–65.
34. Cretoiu D, Ciontea SM, Popescu LM, Ceafalan L, Ardeleanu C. Interstitial Cajal-like cells (ICLC) as steroid hormone sensors in human myometrium: immunocytochemical approach. J Cell Mol Med 2006; 10: 789–95.
35. Cretoiu SM, Cretoiu D, Suciu L, Popescu LM. Interstitial Cajal-like cells of human Fallopian tube express estrogen and progesterone receptors. J Mol Histol 2009; 40: 387–94.
36. Gherghiceanu M, Hinescu ME, Andrei F, Mandache E, Macarie CE, Faussone-Pellegrini MS, Popescu LM. Interstitial Cajal-like cells (ICLC) in myocardial sleeves of human pulmonary veins. J Cell Mol Med 2008; 12: 1777–81.
37. Hinescu ME, Popescu LM, Gherghiceanu M, Faussone-Pellegrini MS. Interstitial Cajal-like cells in rat mesentery: an ultrastructural and immunohistochemical approach. J Cell Mol Med 2008; 12: 260–70.
38. Gabella G. Innervation of the gastrointestinal tract. Int Rev Cytol 1979; 59: 129–93.
39. Cişmaşiu VB, Radu E, Popescu LM. miR-193 expression differentiates telocytes from other stromal cells. J Cell Mol Med 2011; 15: 1071–4.
40. Herzog EL, Bucala R. Fibrocytes in health and disease. Exp Hematol 2010; 38: 548–56.
41. Marchand F. Die örtlichen reaktiven Vorgänge (Lehre von der Entzündung). In: Krehl L and Marchand F, editors: Handbuch der allgemeinen pathologie, vol. 4, part 1. Leipzig, 1924; 78.
42. Faussone-Pellegrini MS, Bani D. Relationships between telocytes and cardiomyocytes during pre- and post-natal life. J Cell Mol Med 2010; 14: 1061–3.
43. Faussone-Pellegrini MS. Cytodifferentiation of the interstitial cells of Cajal of mouse colonic circular muscle layer. An E.M. study from fetal to adult life. Acta Anat 1987; 128: 98–109.
44. Faussone-Pellegrini MS, Vannucchi MG, Ledder O, Tian-Ying Huang T-Y, Hanani M. Plasticity of interstitial cells of Cajal: a study of mouse colon. Cell Tissue Res 2006; 325: 211–7.
45. Faussone-Pellegrini MS, Vannucchi MG, Alaggio R, Strojna A, Midrio P. Morphology of the interstitial cells of Cajal of the human ileum from foetal to neonatal life. J Cell Mol Med 2007; 11: 482–94.
46. Lorincz A, Redelman D, Horváth VJ, Bardsley MR, Chen H, Ordög T. Progenitors of interstitial cells of Cajal in the postnatal murine stomach. Gastroenterology 2008; 134: 1083–93.
47. Huizinga JD, White EJ. Progenitor cells of interstitial cells of Cajal: on the road to tissue repair. Gastroenterology 2008; 134: 1252–4.
48. Gherghiceanu M, Popescu LM. Human epicardium: ultrastructural ancestry of mesothelium and mesenchymal cells. J Cell Mol Med 2009; 13: 2949–51.

49. Gherghiceanu M, Popescu LM. Cardiomyocyte precursors and telocytes in epicardial stem cell niche: electron microscope images. J Cell Mol Med 2010; 14: 871–7.
50. Yamazaki K, Eyden BP. Gap junctions and nerve terminals among stromal cells in human fallopian tube ampullary mucosa. J Submicrosc Cytol Pathol 1998: 30: 399–408.
51. Gibbons SJ, De Giorgio R, Faussone-Pellegrini MS, Garrity-Park MM, Miller SM, Schmalz PF, Young-Fadok TM, Larson DW, Dozois EJ, Camilleri M, Stanghellini V, Szurszewski JH, Farrugia G. Apoptotic cell death of human interstitial cells of Cajal. Neurogastroenterol Motil 2009; 21: 85–93.
52. Mandache E, Gherghiceanu M, Macarie C, Kostin S, Popescu LM. Telocytes in human isolated atrial amyloidosis: ultrastructural remodelling. J Cell Mol Med 2010; 14: 2739–47.
53. Gevaert T, De Vos R, Everaerts W, Libbrecht L, Van Der Aa F, van den Oord J, Roskams T, De Ridder D. Characterization of upper lamina propria interstitial cells in bladders from patients with neurogenic detrusor overactivity and bladder pain syndrome. J Cell Mol Med 2011; Jan 20. doi: 10.1111/j.1582-4934.2011.01262.x.
54. Gherghiceanu M, Hinescu M, Popescu LM. Myocardial interstitial Cajal-like cells (ICLC) in caveolin-1 KO mice. J Cell Mol Med 2009; 13: 202–6.
55. Cipriani G, Serboiu CS, Gherghiceanu M, Faussone-Pellegrini MS, Vannucchi MG. NK-receptors, Substance P, Ano1 expression and ultrastructural features of the muscle coat in Cav-1$^{-/-}$ mouse ileum. J Cell Mol Med 2011. May 2. doi: 10.1111/j.1582-4934.2011.01333.x.
56. Klumpp D, Horch RE, Kneser U, Beier JP. Engineering skeletal muscle tissue—new perspectives in vitro and in vivo. J Cell Mol Med 2010; 14: 2622–9.
57. Polykandriotis E, Popescu LM, Horch RE. Regenerative medicine: then and now—an update of recent history into future possibilities. J Cell Mol Med 2010; 14: 2350–8.
58. Popescu LM, Gherghiceanu M, Kostin S, Faussone-Pellegrini MS. Telocytes and heart renewing. In: Wang P, Kuo CH, Takeda N, Singal PK, editors. Adaptation biology and medicine, vol 6. Cell adaptations and challenges. New Delhi: Narosa, 2010: 17–39.
59. Gittenberger-de Groot AC, Winter EM, Poelmann R. Epicardium-derived cells (EPDCs) in development, cardiac disease and repair of ischemia. J Cell Mol Med 2010; 14: 1056–60.
60. Li TS, Cheng K, Lee ST, Matsushita S, Davis D, Malliaras K, Zhang Y, Matsushita N, Smith RR, Marbán E. Cardiospheres recapitulate a niche-like microenvironment rich in stemness and cell-matrix interactions, rationalizing their enhanced functional potency for myocardial repair. Stem Cells 2010; 28: 2088–98.
61. Rupp H, Rupp TP, Alter P, Jung N, Pankuweit S, Maisch B. Intrapericardial procedures for cardiac regeneration by stem cells: need for minimal invasive access (Attach Lifter) to the normal pericardial cavity. Herz 2010; 35: 458–65.
62. Limana F, Capogrossi MC, Germani A. The epicardium in cardiac repair: from the stem cell view. Pharmacol Ther 2011; 129: 82–96.
63. Kostin S. Types of cardiomyocyte death and clinical outcomes in patients with heart failure. J Am Coll Cardiol 2011; 57: 1532–4.
64. Russell JL, Goetsch SC, Gaiano NR, Hill JA, Olson EN, Schneider JW. A dynamic notch injury response activates epicardium and contributes to fibrosis repair. Circ Res 2011; 108: 51–9.
65. Popescu LM. The tandem: telocytes—stem cells. Int J Biol Biomed Eng 2011; 2/5: 83–92.
66. Popescu LM, Gherghiceanu M, Suciu LC, Manole CG, Hinescu, ME. Telocytes and putative stem cells in the lungs: electron microscopy, electron tomography, and laser scanning microscopy. Cell Tissue Res 2011; doi: 10.1007/s0041-011-1229-z.

Received June 28, 2011; accepted August 3, 2011

Maria-Simonetta Faussone-Pellegrini, Professor Emeritus of Histology and Embriology at the Faculty of Medicine of the University of Florence, is member of the Editorial Board of the Journal of Cellular and Molecular Medicine, Assistant Editor of the Italian Journal of Anatomy and Embryology, Honorary Foreign Member of the Romanian Academy of Medical Science. Her main researches deal on the interstitial cells of Cajal that in 1977 she successfully proposed to be the intestinal pacemaker cells. She also studies enteric and cerebral neuronal and glial cells, gastrointestinal muscles, stromal cells formerly named interstitial Cajal-like cells and now telocytes. All these topics have been studied by electron microscope and histochemistry in normal and pathological conditions and during differentiation. Her publications are about 200, most of which in Journals with IF.

L.M. Popescu, MD, PhD, Dr. h.c.mult., is currently Professor of Cellular and Molecular Medicine, 'Davila' University of Medicine, Bucharest, Romania and Head of the National Institute of Pathology, Bucharest, Romania. He is fellow of the National Academy of Sciences and the President of Academy of Medical Sciences. Recently, he became President Elect of the Federation of European Academies of Medicine, and of the International Society for Adaptive Medicine. He published over 100 scientific articles in international peer-review journals and is cited more than 1500 times. He has a Hirsch Index of about 30. Professor Popescu is Editor-in-Chief (and founder) of the Journal of Cellular and Molecular Medicine (Wiley/Blackwell), with a 5-year IF of 5. He is credited with the discovery of Telocytes.