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Telocytes form networks in normal cardiac tissues

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Summary. Telocytes (TC) are a class of interstitial cells present in heart. Their characteristic feature is the presence of extremely long and thin prolongations (called telopodes). Therefore, we were interested to see whether or not TCs form networks in normal cardiac tissues, as previously suggested.

Autopsy samples of cardiac tissues were obtained from 13 young human cadavers, without identifiable cardiac pathology and with a negative personal history of cardiovascular disease. Immunohistochemistry on formalin-fixed paraffin-embedded tissues was performed using monoclonal antibodies for CD117/c-*kit*. Additionally, ventricular samples from 5 Sprague-Dawley rats were ultrastructurally evaluated under transmission electron microscopy.

We found c-kit positive cells with TC features in subepicardium, as well in subepicardial arteries and in subepicardial fat. TCs were also present in the subendocardium. Light and electron microscopy revealed the existence of intramyocardial networks built up by bipolar TCs. Larger c-kit positive multipolar TCs were found between cardiac muscle bundles.

Our results support the existence of a cardiac network of telocytes.

Key words: Telocytes, Myocardium, Epicardium, Endocardium, CD117

Introduction

Recently, telocytes (TC) were described as being cells with remarkably long, thin and moniliform processes named telopodes (Tp), the latter consisting of narrow segments called podomeres and dilations named podoms (Kostin and Popescu, 2009; Faussone-Pellegrini and Bani, 2010; Kostin, 2010; Suciu et al., 2010a,b; Zhou et al., 2010; Faussone-Pellegrini and Popescu, 2011). The expression of c-kit receptors differs between telocyte populations (Popescu and Faussone-Pellegrini, 2010). Such cells were identified in human atrial myocardium (Hinescu and Popescu, 2005; Hinescu et al., 2006), in rat and human ventricular myocardium (Popescu et al., 2006), and in the myocardial sleeves of the human pulmonary veins (Gherghiceanu et al., 2008; Morel et al., 2008).

As was also the case for the interstitial cells of Cajal (ICC) (Faussone-Pellegrini and Thuneberg, 1999), as well as for the interstitial Cajal-like cells, markers such as vimentin, S100 protein, and CD34 are not so well suited for firm identifications of TC (Popescu, 2011).

Immunohistochemistry revealed that TCs in ventricular myocardium positively label with CD34, and only in a few cases with CD117/c-kit (Popescu et al., 2006). In human atrial myocardium these cells were also found to be slightly and inconsistently positive for CD117/c-kit, and variably positive for CD34 (Hinescu et al., 2006). Sections of human pulmonary veins lacking myocardial sleeves are generally less positive for CD117/c-kit, as compared with sections with a thick muscular sleeve (Morel et al., 2008).

Cardiac TCs were initially considered to influence the rate and rhythm of the nodal system but without a pacemaker function (Popescu and Faussone-Pellegrini, 2010). Evidence of TCs in the pulmonary sleeves (Gherghiceanu et al., 2008; Morel et al., 2008) suggested they might also be involved in pacemaking and/or arrhythmogenesis (Popescu et al., 2011b). Possible implications in pathology were recently addressed (Mandache et al., 2010; Zheng et al., 2011, 2012).

During cardiac development, TCs were considered to be involved in nursing and guiding for myocardial precursors in order to form the correct three-dimensional tissue pattern and contribute to compaction of the

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embryonic myocardial trabeculae (Bani et al., 2010; Faussone-Pellegrini and Bani, 2010).

TCs were identified in cardiac walls in various locations (Hinescu and Popescu, 2005; Hinescu et al., 2006; Popescu et al., 2006, 2010; Morel et al., 2008; Gherghiceanu et al., 2008, 2010; Kostin, 2010; Popescu et al., 2011b; Mandache et al., 2007, 2010; Kostin and Popescu, 2009; Liu et al., 2011). Endocardial TCs were evaluated as participating in the "blood-myocardium barrier", and were demonstrated to project intramyocardial Tp (Gherghiceanu et al., 2010). Interconnected subepicardial TCs create a 3D network, connected with the myocardial TCs (Popescu et al., 2010).

Briefly, TCs are cells with Tps (Popescu et al., 2011a,b,c). Telopodes are cell prolongations with a "beads on a string" appearance (Popescu et al., 2006) and distinctive morphological features (Table 1) (Popescu and Faussone-Pellegrini, 2010).

Cells with irregular shapes and thin long processes, morphologically similar to the ICCs have also been described in the vessel walls (Formey et al., 2011; Pucovsky et al., 2007), e.g. the portal vein (Povstyan et al., 2003; Rusu et al., 2011) and the guinea-pig (Pucovsky et al., 2003) and rat mesenteric arteries (Formey et al., 2011). Such cells were considered vascular ICLCs and their processes were termed "*filopodia*" (Pucovsky et al., 2003, 2007). The long thin filopodia were discussed as being the most prominent feature of the vascular interstitial cells, by Pucovsky (2010), who documented that, in the majority of cases, filopodia do not have varicosities (Pucovsky, 2010). The latter refers to a study by Hinescu et al.(2008) as being the only one describing "*moniliform filopodia*" for interstitial cells (Pucovsky, 2010); we have to point out that in that paper, the name for those cell prolongations was "*moniliform processes*", and not "*filopodia*" (Hinescu et al., 2008).

Kit-specific immunofluorescence was detected in two distinct classes of ICCs, namely, ICC-DMP (ICCs associated with the deep muscular plexus) and ICC-MY (ICCs of the myenteric region): (a) ICC-DMP were identified as elongated, occasionally branching cells with ovoid cell bodies and little perinuclear cytoplasm. Two main processes occasionally divided into forklike secondary branches. ICC-DMP are parallel with the long axis of the circular smooth muscle cells in the deep muscular plexus; (b) ICC-MY were identified as multipolar cells forming dense two-dimensional networks in the myenteric region, enveloping ganglia and nerve trunks (Chen et al., 2007).

As c-kit labeling ICCs and ICLCs was found to be either positive or negative, and also considering that the existence of cardiac TCs is beyond any doubt at this time, we hypothesized that c-kit positive cardiac TCs could present morphological and topographical patterns that could separate them into distinctive classes, and that these cells could build extensive cardiac networks.

So we aimed to evaluate the morphological and topographical patterns of telocytes in young human healthy cardiac tissues immunostained with c-kit antibodies, and by use of transmission electron microscopy, and to refer our findings to the available references at the time.

Materials and methods

For the immunohistochemical study, autopsy samples of cardiac tissues were obtained from thirteen young human cadavers (aged 2.5 to 41 years, with a sex ratio of 8:5), in the "Mina Minovici" Institute of Legal Medicine, Bucharest. The donors died after various traumatic events without significant cardiac pathologies identified at the autopsy and a negative personal history for cardiovascular diseases. Samples from each donor cadaver included: right and left atrial anterior walls and appendages, right and left anterior ventricular walls, and interventricular septa.

For the TEM study cardiac samples (ventricular walls) were obtained from five Sprague-Dawley rats. All procedures were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* of the National Institutes of Health, and protocols were approved by the "Carol Davila" University of Medicine and Pharmacy Bioethics Committee. The *EC Directive 86/609/EEC for animal experiments and the Uniform Requirements for manuscripts submitted to Biomedical journals* were followed accordingly.

Immunohistochemistry was performed on 3-μm thick sections from 10% formalin fixed paraffin-embedded specimens. For CD117/c-kit (1:100, BIOCARE MEDICAL PME 296 AA, clone Y145) immune labeling the sections were deparaffinized in "Slide bright" and a descending series of alcohol rinses (6 min each) and then rehydrated in distilled water. Endogenous peroxidase was blocked with 3% H_2O_2 for 10 min at room temperature. This was followed by: (a) Heat Retrieval Method: retrieve sections under pressure using Biocare's Decloaking Chamber, followed by a wash in distilled water; (b) Protein Block: incubate for 10-15 minutes at room temperature with Biocare's Background Sniper; (c) incubation with the primary antibodies for 30 min at room temperature; (d) Polymer: incubate for 30 minutes at RT with a Polymer (Biocare's MACH 4 detection system); (e) the sections were incubated for 5 minutes at room temperature with Biocare's Betazoid DAB, and counterstained with hematoxylin; (f) TBS buffer was used for washing steps.

Testis germ cells (human adult) served as external positive controls. Cardiac samples treated without the respective primary antibodies served as negative controls (human, fetal and adult).

Microscopic slides were analyzed and snapshots were taken and scaled using a ZEISS working station containing an AxioImager M1 microscope with an AxioCam HRc camera and the digital image processing software AxioVision.

Cardiac (ventricular) samples of five Sprague-

Dawley rats were used for transmission electron microscopy evaluation. Small tissue fragments were fixed as previously described (Mirancea et al., 2007). Semithin sections were stained with 1% toluidine blue for light microscopy. The Formvar coated grids were examined in a Philips electron microscope EM 208S (acceleration voltage of 80 kV) and snapshots were taken using a video camera Veleta and the iTEM Olympus Soft Imaging System.

Approval for the present study was granted by the Institutional Ethics Board in the "Mina Minovici" Institute of Legal Medicine, Bucharest, and by the Bioethics Committee of the "Carol Davila" University of Medicine and Pharmacy of Bucharest, in accordance with the generally accepted international standards and national laws.

Results

Light microscopy

Within the subepicardium we found c-kit positive interstitial cells (ICs) in the following locations: (a) within the walls of the subepicardial coronary arteries, at

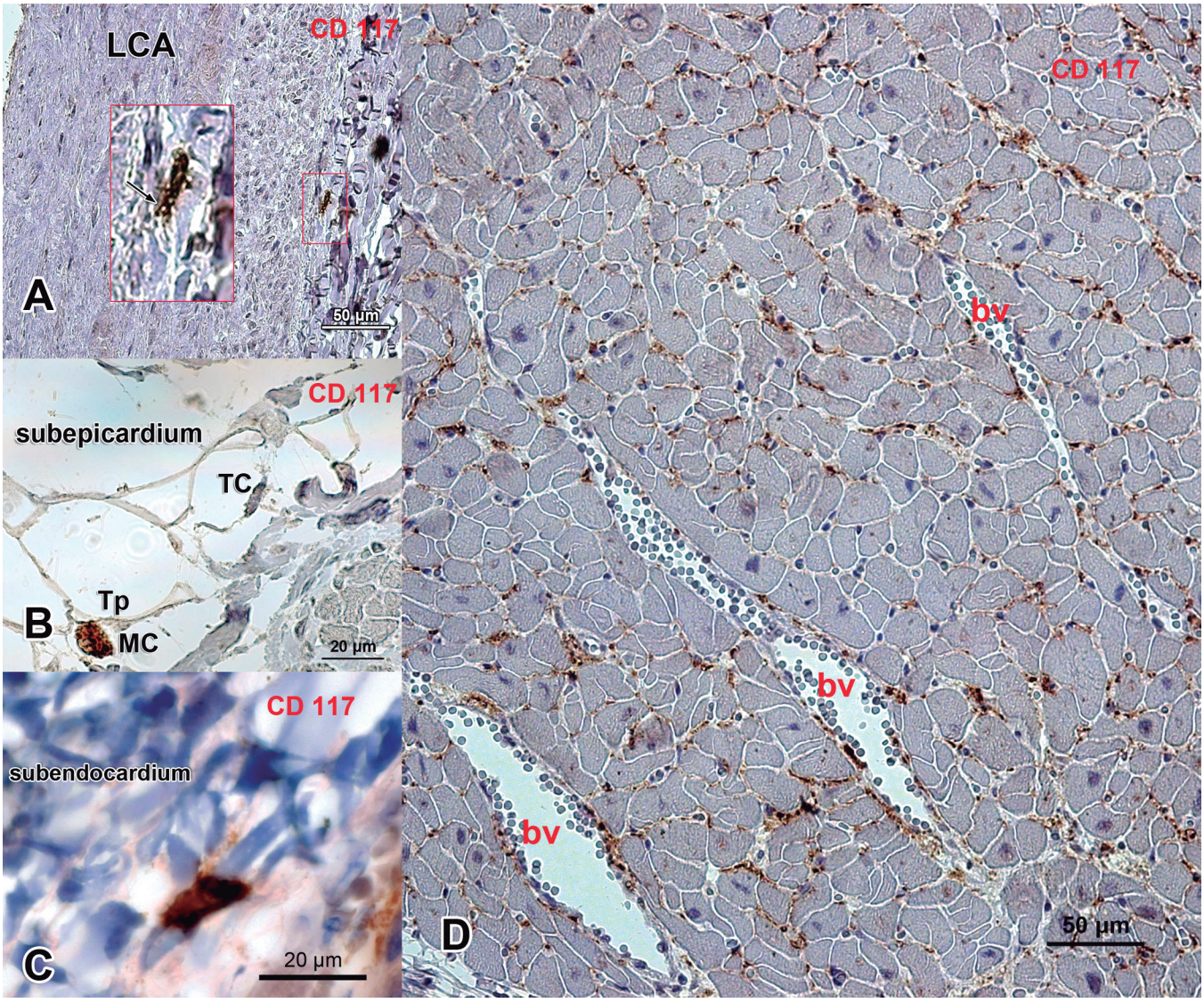

Fig. 1. A. Oblique section of the left coronary artery (LCA) demonstrating (inset) a c-kit+ multipolar telocyte at the media-adventitia border. A primary dichotomizing process (arrow) sends off two moniliform secondary processes. **B.** Deep subepicardial c-kit+ mast cell (MC), located in the vicinity of a superficial myocardial bundle. Subepicardial telocytes (TC) and a telopode (Tp) neighboring the mast cell (MC) are identified. **C.** A multipolar c-kit positive interstitial cell is identified within the subendocardial connective stroma of a pediatric heart (5 years, right atrial wall). Unspecific labeling (brown for the myocardium and blue for the connective tissue is due to the Betazoid DAB chromogen). **D.** c-kit positive intramyocardial network of the interventricular septum. bv: blood vessels.

the media-adventitia border (Fig. 1A); or (b) embedded in subepicardial fat (Fig. 1B). These subepicardial ICs had similar morphological features:

- multiple thin processes, most of them moniliform (Fig. 1A,B);
- long-distance course of the primary processes, with further dichotomizations (Fig. 1B).

As the morphological features of the c-kit positive subepicardial ICs we identified were similar to those of the telocytes, we decided that they were c-kit positive

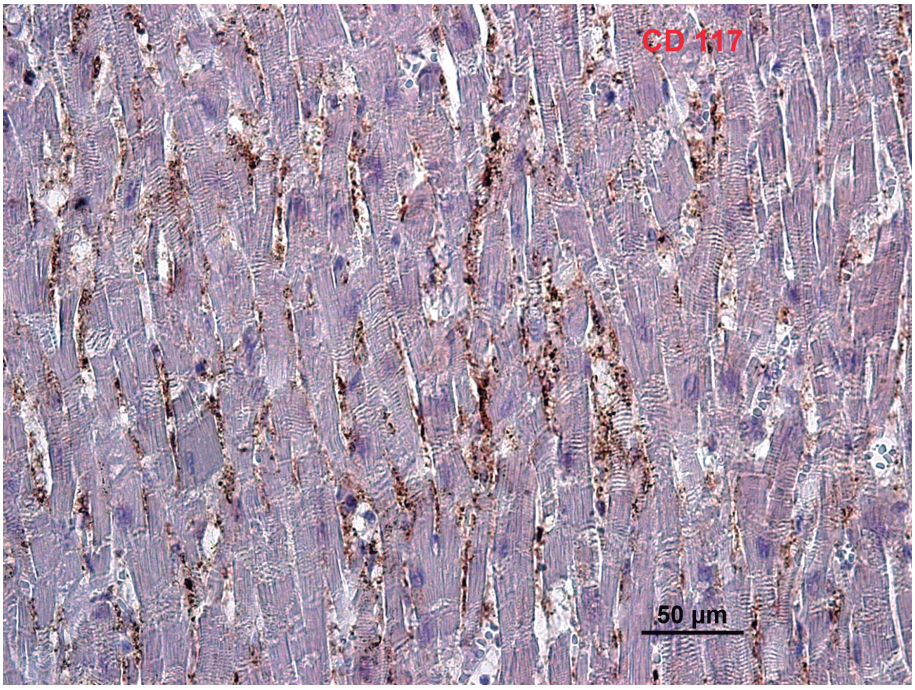

Fig. 2. c-kit positive network within the left ventricular myocardium, longitudinally cut.

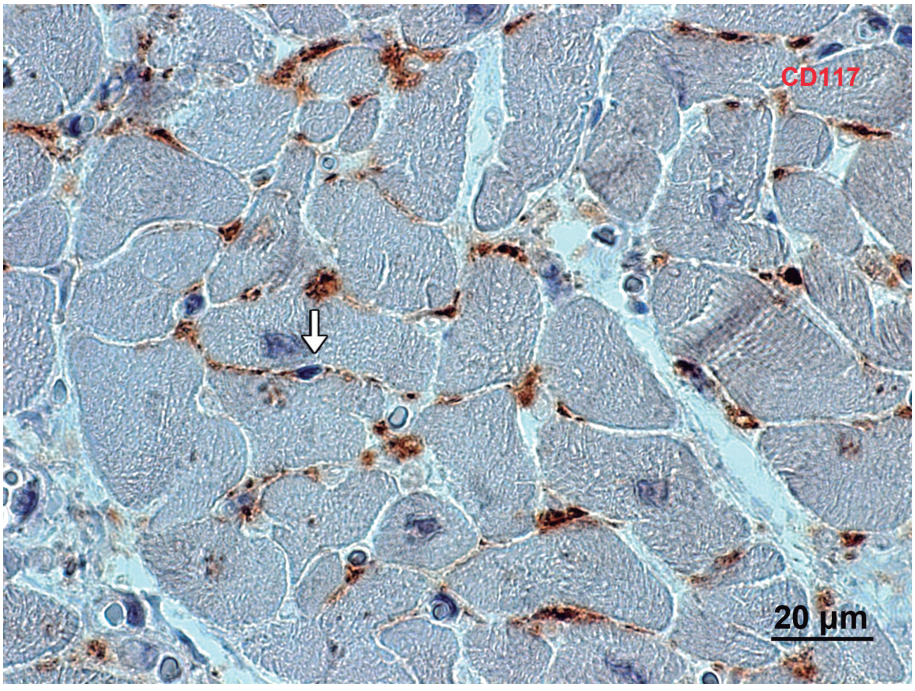

Fig. 3. A c-kit positive spindle-shaped telocyte (arrow) with two telopodes is identified.

subepicardial telocytes.

We also identified multipolar c-kit positive ICs within the subendocardium (Fig. 1C) in all samples. Their morphological features, especially the moniliform telopodes, determined us to also consider these cells as being telocytes belonged to a larger mesenchymal population of the subendocardium.

Within the myocardium we identified well-designed c-kit positive networks (Figs. 1D, 2, 3) in the walls of all four cardiac chambers. The three-dimensional organization of these networks was suggested on transverse (Figs. 1D, 3) and longitudinal (Fig. 2) sections of the myocardium. The ICs of these networks had morphological characteristics similar to those of the telocytes (Fig. 3): small-sized cell bodies, bipolar (in the plane of section) and, seemingly, serially linked.

However, a second type of larger c-kit positive ICs were identified within myocardium. These were multipolar (in the plane of section) and were usually located in the intramuscular septa.

Transmission electron microscopy

The ultrastructural examination found intramyocardial telocytes (TC) positioned between myocardial bundles (Fig. 4). These cells were usually spindle-shaped, bipolar (Figs. 4, 5) with variably developed basal lamina and with a reduced amount of cytoplasm surrounding a nucleus with eccentric condensed chromatin (Figs. 4, 5). In cell bodies and in

Table 1. The standard of identification of telopodes.

1	number	1-5, number variation is due to site and angle of section
2	length	tens-up to hundreds of microns
3	thickness	uneven caliber, mostly below 0.2 microns
4	aspect	moniliform
5	branching	dichotomous pattern
6	Organization	in networks
7	Ca^{2+} release units at the level of dilations	

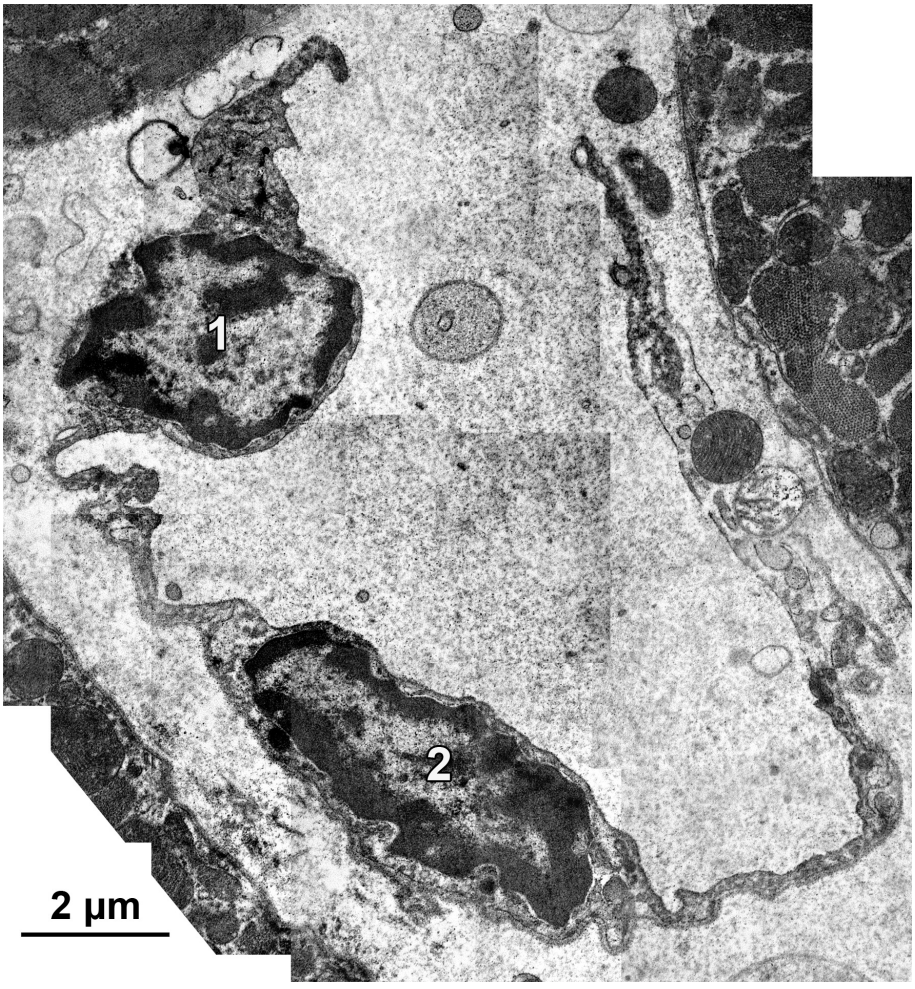

Fig. 4. Ultrathin section of a rat cardiac ventricular wall. Two telocytes (1, 2) serially linked by a stromal synapse are identified in myocardium.

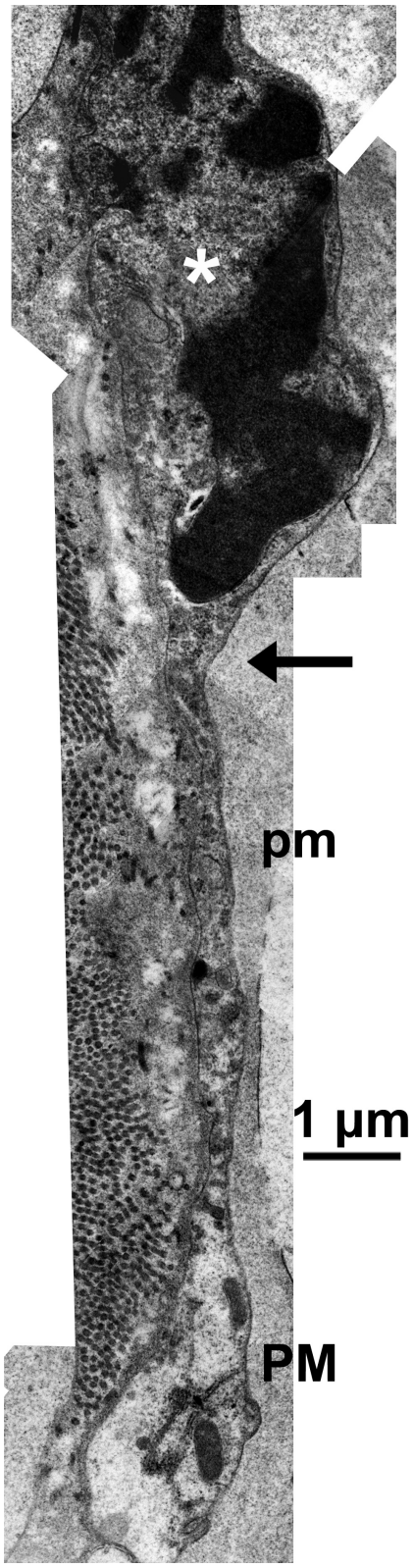

Fig. 5. Ultrathin section of a rat cardiac ventricular wall. A cardiac telocyte is shown: the cell nucleus (*) is identified, as is also a cell prolongation with characteristic telopodial emergence (arrow), podomere (tm) and podom (PM).

their processes we identified caveolae, intermediate filaments, occasionally microtubules, cisternae of endoplasmic reticulum (both smooth and rough), and ribosomes. The TC were projecting telopodes that presented dilations (podoms), usually containing endoplasmic reticulum and mitochondria (Figs. 4-6). Stromal synapses between neighbor telopodes were identified, proving the presence of cardiac TC linkage (Figs. 4, 6).

Discussion

To date there are still few studies regarding the cardiac TC (Hinescu and Popescu, 2005; Hinescu et al., 2006; Mandache et al., 2007, 2010; Gherghiceanu et al., 2008, 2010; Popescu et al., 2006, 2010; Suciu et al., 2010a,b; Zhou et al., 2010; Liu et al., 2011; Popescu, 2011). The existing studies debate the reliability of c-kit/CD117 as a distinctive marker for cardiac TCs, and the only firm diagnostic tool for TC remains the TEM.

Our TEM studies of cardiac TCs are consistent with previous studies (Rusu et al., 2011; Hinescu and Popescu, 2005, Hinescu et al., 2006, Popescu et al., 2006, Mandache et al., 2007, Gherghiceanu et al., 2008, Kostin and Popescu, 2009, Popescu and Faussone-Pellegrini, 2010, Popescu, 2011) in confirming that TCs distinguish themselves from ICCs, especially by their specific telopodes.

The telopodes, which are the processes of the telocytes with a "*beads on a string*" appearance (Popescu and Faussone-Pellegrini, 2010), accommodate in podoms mitochondria, endoplasmic reticulum and caveolae (Suciu et al., 2010a,b). We are therefore able to confirm the fact that the cardiac cells with apparently ICC ultrastructural features and telopodes are indeed cardiac telocytes, and not just canonical ICCs.

CD-117/c-kit labeling cannot exclude the possibility for c-kit negative cardiac TCs being also present within the cardiac wall, but it can offer a morphological and topographical basis for an anatomical patterning of c-kit positive cardiac TCs, which may be classified as follows: (a) subepicardial TC; (b) intramyocardial TC and (c) subendocardial TC. The subepicardial c-kit positive CTCs can be in turn viewed as vascular and subepicardial proper.

The TCc we have found in subepicardial coronary arteries may be constitutive, as was discussed elsewhere (Pucovsky, 2010). Our results support the presence of telocytes at the media-adventitia border within the arterial coronary wall, as was previously evaluated (TEM, IHC) in rat mesentery (Hinescu et al., 2008).

Even so, further studies have to be performed to evaluate whether or not vascular TCs play a normal functional role and how these may act in vascular dysfunctions of the coronary bed. Bobryshev suggested in a study on "*arterial ICCs*" (Bobryshev, 2005) that, in advanced atherosclerosis, some of these cells lose their contacts with smooth muscle cells (SMCs) and nerve fibers, migrate from media-adventitia border to the

disorganized media and atherosclerotic plaques, where they suffer destructive alterations; if the presence of ICCs between nerve fibers and SMCs is regarded as a characteristic of a normal wall, the disruption of these contacts might lead to alterations in normal arterial function. Even though Bobryshev's "*arterial ICCs*" were c-kit negative (Bobryshev, 2005) a similar pathway might be suggested for c-kit positive vascular TCs. Also the phenotypic plasticity of the c-kit positive TC has to be accounted for in pathological tissues. Nakahara (Nakahara et al., 2002), in a study regarding colon motility in diabetic patients, found a significantly decreased number of c-kit positive ICCs in the study groups compared with the controls, suggesting a possible association between diabetic gastroenteropathy and the decreased number of ICCs. If diabetes is associated with a decreased number of ICCs in the intestinal tract, a similar mechanism might lead to a decreased number of TCs in the heart, possibly altering the processes of heart repair and renewing (Popescu et al., 2009). Further research needs to be conducted in order to properly analyze the presence and pattern of these networks in different cardiac pathologies as they might play important parts in cardiovascular pathogenesis. The networks of cardiac TCs we found correlate with the previous reports and reinforce the evidences brought by studies on cell cultures – typical telocytes were found distributed among cardiomyocytes, connecting them by long telopodes and seeming to accelerate their synchronous beating (Zhou et al., 2010). It was also shown that some c-kit or CD34 immunopositive cells in engineered heart tissue have the morphology of

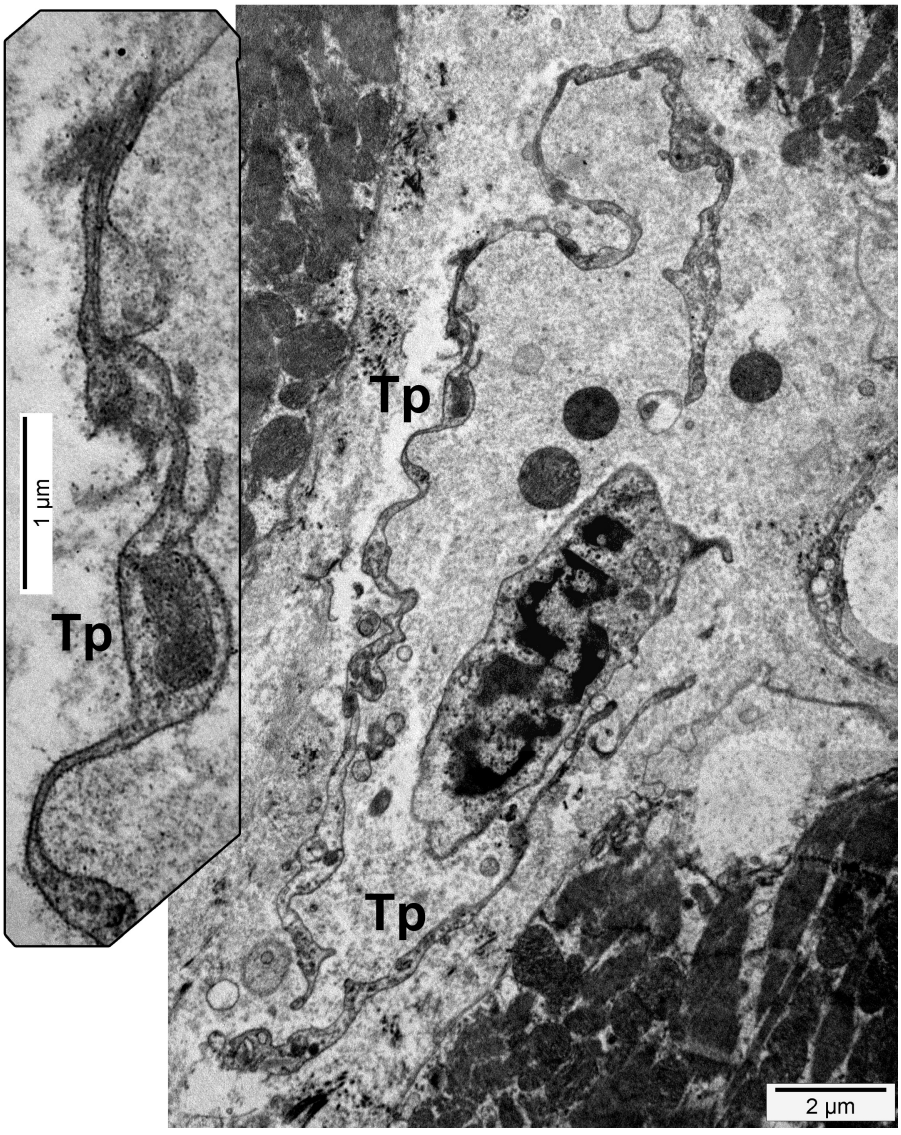

Fig. 6. Ultrathin section of a rat cardiac ventricular wall. Telopodes (Tp) are identified between muscle bundles and their peculiar appearance is detailed (inset).

telocytes, with a typical fusiform cell body and long moniliform telopodes (Zhou et al., 2010) suggesting a possible role in the heart regeneration process, and a possible value as a tool for cardiac tissue engineering (Zhou et al., 2010).

Subepicardial TCs form a network continuous within the myocardium, suggesting a possible role of these cells in signal transmission, intrinsic in the subepicardium, and/or subepicardial-to-myocardial.

The subendocardial TCs we identified may be considered analogous to TCs that were found at the vascular media-adventitia border and similarly, their role remains uncertain.

The most convincing evidence we gained were those of the intramyocardial c-kit positive networks that we found within the walls of all cardiac chambers in normal tissues. This finding is convergent with our EM evidence of TCs serially linked by stromal synapses – such connective connections were previously described (Popescu et al., 2005). A recent study used confocal microscopy of immunolabeled tissue sections for c-kit and also revealed that in the mid-myocardium interstitial c-kit positive TCs intermingle with cardiomyocytes and form a network-like distribution pattern (Kostin, 2010). These lead us to raise the following hypothesis: the cardiac function may not be regulated strictly by the extrinsic autonomic and intrinsic nodal systems; the cardiac networks of TCs could also contribute to synchronize the extrinsic and intrinsic influences.

As we found two main patterns of the c-kit positive intramyocardial TCs, small fusiform and bipolar, and larger and multipolar, it seemed reasonable to us to speculate that these may be analogous to the classes of ICCs, respectively the elongated bipolar ICC-DMP and the multipolar ICC-MY (see also Introduction). As in the small intestine ICC-DMP are known to mediate neuromuscular transmission and ICC-MY are slow wave generating ICCs (Chen et al., 2007), distinctive classes of cardiac TC may be also presumed and further investigated. This observation is reasonable as now it is generally accepted that pacemaker ICCs are primarily located between, or on the surface of smooth muscle layers, in intramuscular septa, or on the submucosal surface in the circular muscle layer (Chen et al., 2007; Kim et al., 2009), and ICLCs resident of striated muscles (Midrio et al., 2010; Popescu et al., 2011c) were also identified.

As ICLCs from the myocardial sleeves of the pulmonary veins were found to be involved in rythmogenicity (Morel et al., 2008), and cardiac TCs death was diagnosed in atrial fibrillation (Popescu et al., 2011b) a strong suspicion for the involvement of TC in heart rhythm is raised. However, the possibility for the TC involvement in reparatory processes after an arrhythmic event (Popescu et al., 2011b) or after myocardial infraction (Liu et al., 2011) cannot be discarded.

It was shown that bone marrow derived c-kit positive cells stimulate both angiogenesis and myofibroblast accumulation in infarcted hearts and that dysfunction of such cells impairs myocardial healing after infarction (Cimini et al., 2007). The growth and differentiation of c-kit positive cardiac stem cells into mature myocytes is markedly enhanced in the hypertrophied myocardium of patients with chronic aortic stenosis (Urbanek et al., 2003). c-kit positive cells were not detected in the absence of infarction and appeared after infarction in the epicardial–subepicardial region (Limana et al., 2007). However we found c-kit positive TCs in seemingly normal cardiac tissues.

A complete, exhaustive c-kit mapping of the normal human heart telocytes should be performed, in order to check for discrete regional differences. Recently the distribution of telocytes was evaluated in the rat heart (atrial walls), and that study reached the conclusion that the distribution of telocytes is different in various parts of the atrial walls (Liu et al., 2011). A limitation of the immunohistochemical method is that evidence of the c-kit positive TC does not exclude the presence of c-kit negative TCs within the cardiac walls; the possible functional analogy between TCs and the four classes of ICCs remains to be further evaluated. Also a functional switch of c-kit reactivity has to be accounted for and further investigated.

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References

Bani D., Formigli L., Gherghiceanu M. and Faussone-Pellegrini M.S. (2010). Telocytes as supporting cells for myocardial tissue organization in developing and adult heart. J. Cell. Mol. Med. 14, 2531-2538.

Bobryshev Y.V. (2005). Subset of cells immunopositive for neurokinin-1 receptor identified as arterial interstitial cells of Cajal in human large arteries. Cell Tissue Res.321, 45-55.

Chen H., Redelman D., Ro S., Ward S.M., Ordog T. and Sanders K.M. (2007). Selective labeling and isolation of functional classes of interstitial cells of Cajal of human and murine small intestine. Am. J. Physiol. Cell Physiol. 292, C497-507.

Cimini M., Fazel S., Zhuo S., Xaymardan M., Fujii H., Weisel R.D. and Li R.K. (2007). c-kit dysfunction impairs myocardial healing after infarction. Circulation 116, I77-82.

Faussone-Pellegrini M.S. and Bani D. (2010). Relationships between telocytes and cardiomyocytes during pre- and post-natal life. J. Cell. Mol. Med. 14, 1061-1063.

Faussone-Pellegrini M.S and Popescu L. (2011). Telocytes. BioMol. Concepts 2, 481-489.

Faussone-Pellegrini M.S. and Thuneberg L. (1999). Guide to the identification of interstitial cells of Cajal. Microsc. Res. Tech. 47,

248-266.

Formey A., Buscemi L., Boittin F.X., Beny J.L. and Meister J.J. (2011). Identification and functional response of interstitial Cajal-like cells from rat mesenteric artery. Cell Tissue Res. 343, 509-519.

Gherghiceanu M., Hinescu M.E., Andrei F., Mandache E., Macarie C.E., Faussone-Pellegrini M.S. and Popescu L.M. (2008). Interstitial Cajal-like cells (ICLC) in myocardial sleeves of human pulmonary veins. J. Cel. Mol. Med. 12, 1777-1781.

Gherghiceanu M., Manole C.G. and Popescu L.M. (2010). Telocytes in endocardium: electron microscope evidence. J. Cell. Mol. Med. 14, 2330-2334.

Hinescu M.E. and Popescu L.M. (2005). Interstitial Cajal-like cells (ICLC) in human atrial myocardium. J. Cell. Mol. Med. 9, 972-975.

Hinescu M.E., Gherghiceanu M., Mandache E., Ciontea S.M. and Popescu L.M. (2006). Interstitial Cajal-like cells (ICLC) in atrial myocardium: ultrastructural and immunohistochemical characterization. J. Cell. Mol. Med. 10, 243-257.

Hinescu M.E., Popescu L.M., Gherghiceanu M. and Faussone-Pellegrini M.S. (2008). Interstitial Cajal-like cells in rat mesentery: an ultrastructural and immunohistochemical approach. J. Cell. Mol. Med. 12, 260-270.

Kim Y.C., Suzuki H., Xu W.X., Choi W., Kim S.H. and Lee S.J. (2009). Ca2+-activated K+ current in freshly isolated c-Kit positive cells in guinea-pig stomach. J. Korean Med. Sci. 24, 384-391.

Kostin S. (2010). Myocardial telocytes: a specific new cellular entity. J. Cell. Mol. Med. 14, 1917-1921.

Kostin S. and Popescu L.M. (2009). A distinct type of cell in myocardium: interstitial Cajal-like cells (ICLCs). J. Cell Mol. Med. 13, 295-308.

Limana F., Zacheo A., Mocini D., Mangoni A., Borsellino G., Diamantini A., De Mori R., Battistini L., Vigna E., Santini M., Loiaconi V., Pompilio G., Germani A. and Capogrossi M.C. (2007). Identification of myocardial and vascular precursor cells in human and mouse epicardium. Circ. Res. 101, 1255-1265.

Liu J.J., Shen X.T., Zheng X., Li Z., Wang J., Qi X.F. and Cai D.Q. (2011). Distribution of telocytes in the rat heart. J. Clin. Rehab. Tiss. Eng. Res. (CRTER) 15, 3546-3548.

Mandache E., Popescu L.M. and Gherghiceanu M. (2007). Myocardial interstitial Cajal-like cells (ICLC) and their nanostructural relationships with intercalated discs: shed vesicles as intermediates. J. Cell. Mol. Med 11, 1175-1184.

Mandache E., Gherghiceanu M., Macarie C., Kostin S. and Popescu L.M. (2010). Telocytes in human isolated atrial amyloidosis: ultrastructural remodelling. J. Cell Mol. Med 14, 2739-2747.

Midrio P., Alaggio R., Strojna A., Gamba P., Giacomelli L., Pizzi S. and Faussone-Pellegrini M.S. (2010). Reduction of interstitial cells of Cajal in esophageal atresia. J. Pediatr. Gastroenterol. Nutr. 51, 610-617.

Mirancea N., Hausser I., Metze D., Stark H.J., Boukamp P. and Breitkreutz D. (2007). Junctional basement membrane anomalies of skin and mucosa in lipoid proteinosis (hyalinosis cutis et mucosae). J. Dermatol. Sci. 45, 175-185.

Morel E., Meyronet D., Thivolet-Bejuy F. and Chevalier P. (2008). Identification and distribution of interstitial Cajal cells in human pulmonary veins. Heart Rhythm. 5, 1063-1067.

Nakahara M., Isozaki K., Hirota S., Vanderwinden J-M., Takakura R., Kinoshita K., Miyagawa J-I., Chen H.U.I., Miyazaki Y., Kiyohara T., Shinomura Y. and Matsuzawa Y. (2002). Deficiency of KIT-positive cells in the colon of patients with diabetes mellitus. J. Gastroenterol-Hepatol. 17, 666-670.

Popescu L.M. (2011). The tandem: telocytes - stem cells. Int. J. Biol. Biomed. Eng. 5, 83-92.

Popescu L.M. and Faussone-Pellegrini M.S. (2010). 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. 14, 729-740.

Popescu L.M., Gherghiceanu M., Cretoiu D. and Radu E. (2005). 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. 9, 714-730.

Popescu L.M., Gherghiceanu M., Hinescu M.E., Cretoiu D., Ceafalan L., Regalia T., Popescu A.C., Ardeleanu C. and Mandache E. (2006). Insights into the interstitium of ventricular myocardium: interstitial Cajal-like cells (ICLC). J. Cell. Mol. Med. 10, 429-458.

Popescu L.M., Gherghiceanu M., Manole C.G. and Faussone-Pellegrini M.S. (2009). Cardiac renewing: interstitial Cajal-like cells nurse cardiomyocyte progenitors in epicardial stem cell niches. J. Cell. Mol. Med. 13, 866-886.

Popescu L.M., Manole C.G., Gherghiceanu M., Ardelean A., Nicolescu M.I., Hinescu M.E. and Kostin S. (2010). Telocytes in human epicardium. J. Cell. Mol. Med. 14, 2085-2093.

Popescu L.M., Gherghiceanu M., Suciu L.C., Manole C.G. and Hinescu M.E. (2011a). Telocytes and putative stem cells in the lungs: electron microscopy, electron tomography and laser scanning microscopy. Cell Tissue Res. 345, 391-403.

Popescu L.M., Gherghiceanu M.., Kostin S. and Faussone-Pellegrini M.S. (2011b). Telocytes and heart renewing. In: Cell adaptations and challenges, adaptation biology and medicine. Vol. 6. Wang P., Kuo C.-H., Takeda N. and Singal P.K. (eds). Narosa Publishing House Pvt. Ltd. New Delhi, India. pp 17-39.

Popescu L.M., Manole E., Serboiu C.S., Manole C.G., Suciu L.C., Gherghiceanu M. and Popescu B.O. (2011c). Identification of telocytes in skeletal muscle interstitium: implication for muscle regeneration. J. Cell. Mol. Med. 15, 1379-1392.

Povstyan O.V., Gordienko D.V., Harhun M.I. and Bolton T.B. (2003). Identification of interstitial cells of Cajal in the rabbit portal vein. Cell Calcium 33, 223-239.

Pucovsky V. (2010). Interstitial cells of blood vessels. ScientificWorld J. 10, 1152-1168.

Pucovsky V., Moss R.F. and Bolton T.B. (2003). Non-contractile cells with thin processes resembling interstitial cells of Cajal found in the wall of guinea-pig mesenteric arteries. J. Physiol. 552, 119-133.

Pucovsky V., Harhun M.I., Povstyan O.V., Gordienko D.V., Moss R.F. and Bolton T.B. (2007). Close relation of arterial ICC-like cells to the contractile phenotype of vascular smooth muscle cell. J. Cell. Mol. Med. 11, 764-775.

Rusu M.C., Pop F., Hostiuc S., Curca G.C. and Streinu-Cercel A. (2011). Extrahepatic and intrahepatic human portal interstitial cajal cells. Anat Rec (Hoboken) 294, 1382-1392.

Rusu M.C., Pop F., Hostiuc S., Dermengiu D., Lala A.I., Ion D.A., Manoiu V.S. and Mirancea N. (2011). The human trigeminal ganglion: c-kit positive neurons and interstitial cells. Ann. Anat. 193, 403-411.

Suciu L., Nicolescu M.I. and Popescu L.M. (2010a). Cardiac telocytes: serial dynamic images in cell culture. J. Cell Mol. Med. 14, 2687-2692.

Suciu L., Popescu L.M., Gherghiceanu M., Regalia T., Nicolescu M.I., Hinescu M.E. and Faussone-Pellegrini M.S. (2010b). Telocytes in

human term placenta: morphology and phenotype. Cells Tissues Organs 192, 325-339.

Urbanek K., Quaini F., Tasca G., Torella D., Castaldo C., Nadal-Ginard B., Leri A., Kajstura J., Quaini E. and Anversa P. (2003). Intense myocyte formation from cardiac stem cells in human cardiac hypertrophy. Proc. Natl. Acad. Sci. USA 100, 10440-10445.

Zheng Y., Li H,. Manole C.G., Sun A., Ge J. and Wang X. (2011). Telocytes in trachea and lungs. J. Cell. Mol. Med .15, 2262-2268.

Zheng Y., Bai C. and Wang X. (2012). Telocyte morphologies and potential roles in diseases. J. Cell. Physiol. 237, 2311-2317.

Zhou J., Zhang Y., Wen X., Cao J., Li D., Lin Q., Wang H., Liu Z., Duan C., Wu K. and Wang C. (2010). Telocytes accompanying cardiomyocyte in primary culture: two- and three-dimensional culture environment. J. Cell. Mol. Med. 14, 2641-2645.

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