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Critical review: Cardiac telocytes vs cardiac lymphatic endothelial cells☆

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ABSTRACT

The study of cardiac interstitial Cajal-like cells (ICLCs) began in 2005 and continued until 2010, when these cells were renamed as telocytes (TCs). Since then, numerous papers on cardiac ICLCs and TCs have been published. However, in the initial descriptions upon which further research was based, lymphatic endothelial cells (LECs) and initial lymphatics were not considered. No specific antibodies for LECs (such as podoplanin or LYVE-1) were used in cardiac TC studies, although ultrastructurally, LECs and TCs have similar morphological traits, including the lack of a basal lamina. When tissues are longitudinally cut, migrating LECs involved in adult lymphangiogenesis have an ICLC or TC morphology, both in light and transmission electron microscopy. In this paper, we present evidence that at least some cardiac TCs are actually LECs. Therefore, a clear-cut distinction should be made between TCs and LECs, at both the molecular and the ultrastructural levels, in order to avoid obtaining invalid data.

Contents

Abbreviations: AF, anchorage filament; Ang-1, angiopoietin-1; Ang-2, angiopoietin-2; BL, basal lamina; CRU, calcium-release unit; EC, (blood vascular) endothelial cell; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; FGF, fibroblast growth factor; ICC, interstitial Cajal cell; ICLC, interstitial Cajal-like cell; LEC, lymphatic endothelial cell; LYVE-1, lymphatic vessel endothelial hyaluronan receptor-1; NO, nitric oxide; NOS, nitric oxide synthase; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; Prox-1, prospero homeobox protein-1; SEM, scanning electron microscope/microscopy; TC, telocyte; TEM, transmission electron microscope/microscopy; Tp, telopode; VEGF, Vascular Endothelial Growth Factor; VEGFR, Vascular Endothelial Growth Factor receptor; WPB, Weibel–Palade body.

☆ This paper belongs to the special issue Human lymph vessels.

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1. Introduction

The true nature of cardiac interstitial cells, especially those collectively named fibroblasts, is a hot topic and is under active investigation (Tallquist and Molkentin, 2017). For this reason, terms and concepts should be carefully used.

Telocytes (TCs) are stromal cells that are found in numerous locations and display a potentially wide spectrum of differentiation and function (Ardeleanu and Bussolati, 2011). They are defined by their peculiar long, thin and moniliform prolongations, termed telopodes (Rusu et al., 2012a, 2014, 2012b, 2012c). Telopodes (Tps) consist of dilations (podoms) which are serially linked by thin segments, termed "podomeres" (Rusu, 2014; Rusu et al., 2014, 2012b, 2012c) or "podomers" (Cretoiu and Popescu, 2014; Li et al., 2014, 2015; Popescu et al., 2011). An overestimation in the interpretation of the static pictures offered by transmission electron microscopy (TEM) could be observed in most previous papers on TCs and previous acknowledgement of TC function mainly on electron microscopy pictures was exaggerated.

Various markers label TCs (Dobra et al., 2018; Faussone Pellegrini and Popescu, 2011). It was recently stated that the immunophenotype of TCs "is similar to that of interstitial, endothelial, smooth muscle, mast and haematopoietic stem cells and neurons" (Mitrofanova et al., 2017), therefore not indicative of a particular cell type. Most markers considered to be TC-specific also label endothelial cells or progenitors (Rusu et al., 2018a). For example, c-kit, a marker of hematopoietic stem cells (HSCs) (Murry et al., 2004), as well as of stem or progenitor cells (Didilescu et al., 2013), was indicated also as expressed in cardiac TCs (Bei et al., 2015; Chang et al., 2015; Varga et al., 2017; Zhao et al., 2013; Zhaofu and Dongqing, 2016). However, c-kit-positive HSCs could not transdifferentiate into cardiac myocytes in myocardial infarcts (Murry et al., 2004). The studies linking myocardial infarction and TCs have failed to show, beyond a reasonable doubt, that TCs do actually have significant roles in myocardial regeneration (Hostiuc et al., 2018a). Nor is the role of cardiac TCs in atrial fibrillation currently clear (Hostiuc et al., 2018b).

The peculiar morphology ascribed to TCs (a small cell body containing a nucleus and extremely thin prolongations of $\geq$60 μm) and c-kit expression were used as standards to identify and quantify cardiac telocytes in the myocardium (Zhao et al., 2013). This although the respective authors indicated that "currently, no specific biomarkers exist for the identification of cardiac telocytes" (Zhao et al., 2013). As CD34 positive expression is also indicative of HSCs, a CD34+ or c-kit+ phenotype could indicate either TCs or haematopoietic stem cells. The term "hematopoietic" was not found in that paper (Zhao et al., 2013). On the other hand, CD34 is a well-known endothelial marker and several studies suggested that subsets of TCs could belong to the endothelial lineage, in the cardiac niche (Grigoriu et al., 2016; Rusu et al., 2017a) or in other niches (Petrea et al., 2018a, 2018b; Rusu et al., 2018a, 2018b).

A series of papers promoted the idea that human resident CD34+ stromal cells are a main source of mesenchymal cells, but these CD34+ cells were just labelled with a different term (e.g., fibroblasts,

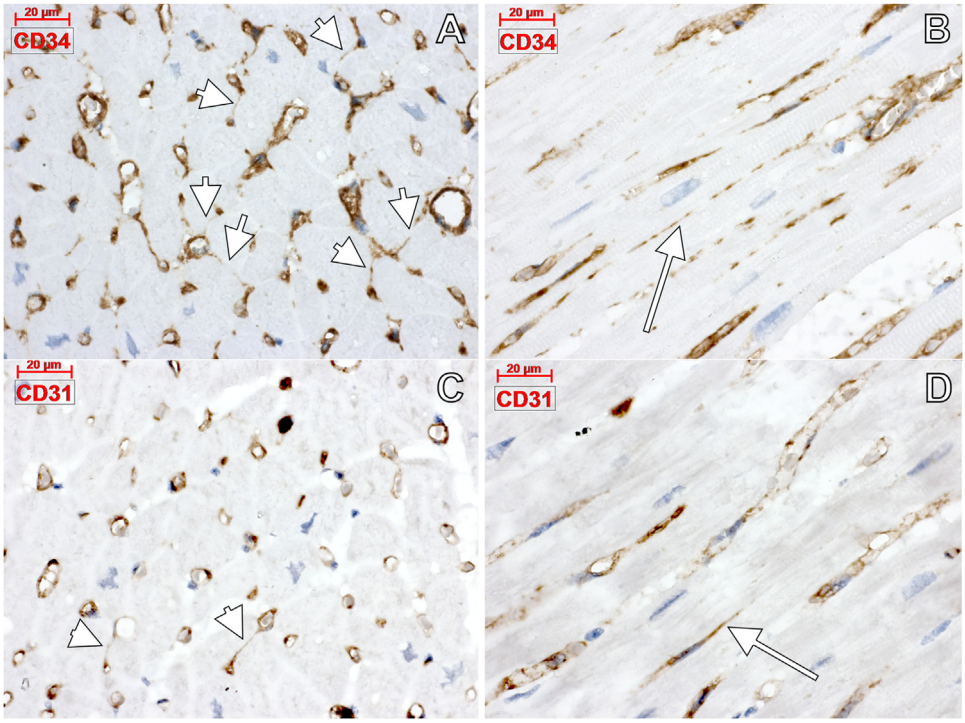

Fig. 1. Immunohistochemistry of a human adult cardiac papillary muscle sample, from a previously studied lot (Rusu et al., 2017a). Slides were labeled with CD34 (A, B) and CD31 (C, D) antibodies, on transverse cuts (A, C) and longitudinal cuts (B, D). The arrowheads indicate interstitial moniliform thin cells uniting vascular, or lymphatic, lumina. The arrows indicate seemingly longitudinal tangential cuts of vascular or lymphatic endothelia, appearing as false TCs, especially if their connection to a vessel is not in the same plane.

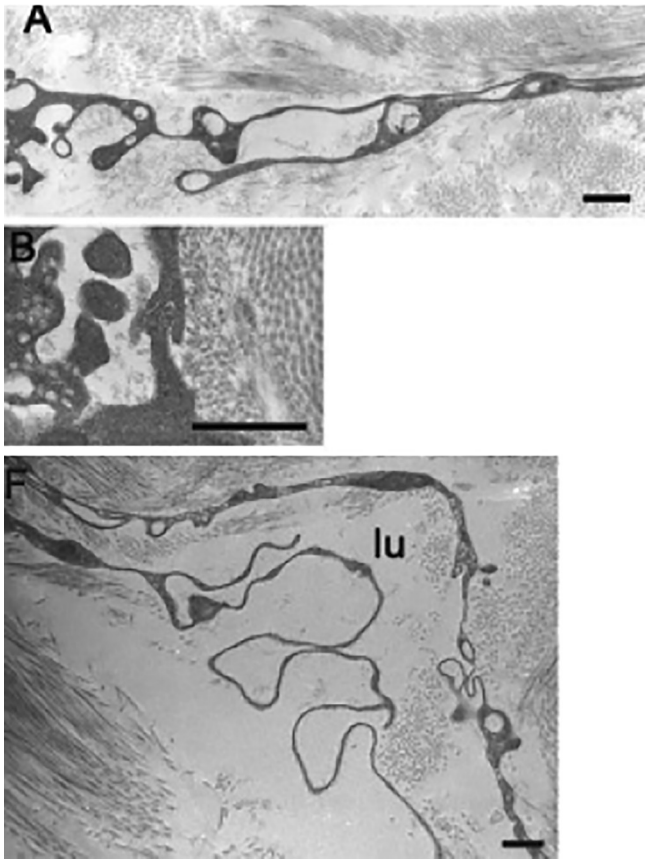

Fig. 2. Reprinted from Detry et al. BMC Cell Biology 2011, CC BY 4.0 license. These are electron microscopy pictures of lymphangiogenesis *in vivo*. [. . .] (A): Lymphatic endothelial cells (LEC) form long processes containing vesicles and delimitating extracellular spaces devoid of matrix or with reminiscent matrix fragments. Note the presence of intracellular vesicles in endothelial processes. (B): Endothelial cells are joined by interdigitations. (F): Tubular structures containing a lumen (lu) are lined by long cytoplasmic extensions of LEC. Scale bars: 1 μm.

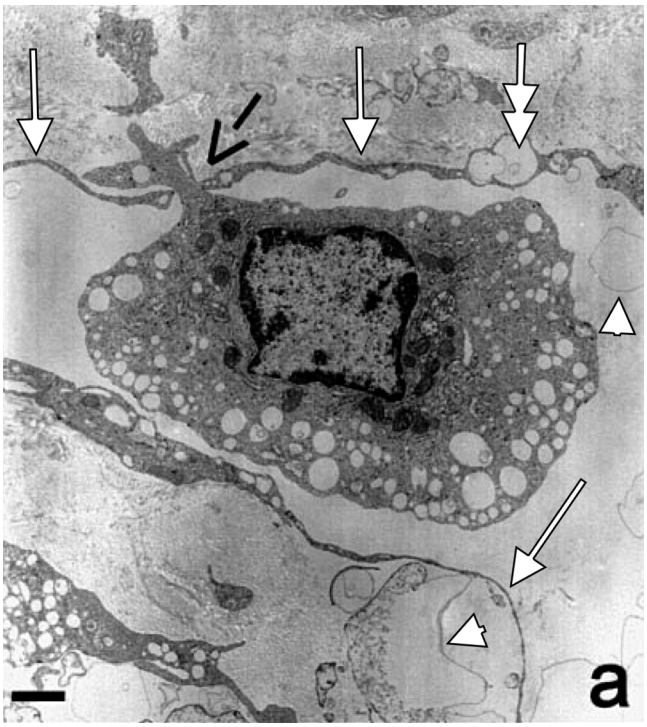

Fig. 3. Reprinted with permission from John Wiley and Sons (License Number: 4255211271377; Licensed Content Publication: *Journal of Cellular and Molecular Medicine*) from (Stoitzner et al., 2002). It is presented a dendritic cell which enters a dermal lymphatic. The cell body of the transmigrating dendritic cell is already inside the lumen of a lymph vessel but a cytoplasmic process is still extending into the dermal connective tissue. The black arrow points at an area of close apposition of dendritic cell and endothelial cell surfaces. It is obvious the TC-like morphology of the LECs which are extremely thin and moniliform (white arrows) and can be easily misjudged as TCs. Shedded vesicles (white arrowheads) are located on both ab- and adluminal sides of those LECs and intracytoplasmic matrix-filled vacuoles are found (double-headed arrow). The collagenic ECM can be easily distinguished from the matrix-filled lymphatic lumen.

fibrocytes or TCs) by authors who were perhaps unaware that the cell populations they described were identical (Barth and Westhoff, 2007; Diaz-Flores et al., 2014). Nevertheless, TCs are morphologically similar to the "veil cells" (Petre et al., 2016; Rusu et al., 2017a) that were found by Joris and Majno (1974) in the perivascular niche of the coronary arteries.

2. From interstitial Cajal-like cells (ICLCs) to telocytes (TCs)

In an editorial (article) published in *Journal of Cellular and Molecular Medicine*, Popescu and Faussone-Pellegrini (2010) relabelled the previously named interstitial Cajal-like cells (ICLCs) to telocytes (Popescu and Faussone-Pellegrini, 2010). This was done after a series of studies identifying cardiac ICLCs had been published by Popescu's group in the same journal (Gherghiceanu et al., 2008; Hinescu et al., 2006; Kostin and Popescu, 2009; Mandache et al., 2007; Popescu et al., 2006; Suciu et al., 2009). Since then, numerous studies dealing with ICLCs and TCs have referred to these pioneering works when presenting TCs' basic morphological and immunophenotypical traits.

Most of the pioneering studies of *in situ* cardiac ICLCs or cardiac TCs were done on bidimensional cuts, under light or electron microscopy. However, the possibility of longitudinal tangential cuts displaying single spindle-shaped ECs but false TCs could not be eliminated. See Fig. 1.

3. Similar ultrastructural standards for the identification of ICLCs and TCs

The structural and ultrastructural characteristics of cardiac ICLCs were documented in a study of the myocardium in which other studies on the digestive tract, the human detrusor and the myocardium were also discussed (Kostin and Popescu, 2009). Most of the features of ICLCs there (Kostin and Popescu, 2009), were repeated later as features of TCs by Popescu and Faussone-Pellegrini (2010) (Table 1). In the initial standardisation as ICLCs (Kostin and Popescu, 2009), they were assigned a "labyrinthic" profile of cell processes. This was changed when ICLCs were renamed to TCs that were shown to form a network that presented as a labyrinthine system generated by 3D convolution and overlapping (Popescu and Faussone-Pellegrini, 2010). However, bidimensional TEM identification could not reasonably support these 3D convolutions.

It is interesting to note here that the terms "podoms" and "podomeres" did not appear in the editorial in which TCs were proposed as a new cell type (Popescu and Faussone-Pellegrini, 2010), but later, in a subsequent paper that evaluated cardiac TCs in cultures (Suciu et al., 2010a). When ICLCs were defined, they were shown to possess Ca^{2+}-handling units consisting of caveolae, endoplasmic reticulum and mitochondria (Kostin and Popescu, 2009) that could be regarded as a common feature of different cell types, including of endothelial cells (ECs) (Vrapciu and Rusu, 2017). Afterwards, TCs were shown to be equipped with Ca^{2+}-release units (CRUs) (Popescu and Faussone-Pellegrini, 2010). To our knowledge, the CRUs are a common feature of skeletal and cardiac muscles

Table 1
The standard of identification of interstitial Cajal-like cells (ICLCs) indicated by Kostin and Popescu (2009) is compared to the standard of identification of telocytes (TCs) indicated by Popescu and Faussone-Pellegrini (2010).

	ICLCs characteristics	TCs characteristics
Morphology of the cell body	1. Spindle-shaped, or pyriform, or triangular, or stellate 2. High nucleocytoplasmic ratio	1. Spindle-shaped, or pyriform, or triangular, or stellate 2. High nucleocytoplasmic ratio
Nucleus	Oval	Oval
Chromatin	Heterochromatin and euchromatin	Clustered marginal heterochromatin
Mitochondria	1. In the perinuclear cytoplasm 2. In the dilations (knobs) of the cells processes	1. In the perinuclear cytoplasm 2. In the dilations of the TCs processes
Golgi complexes	Small	Small
ER	Smooth and rough ER, also in cell processes and their knobs	Smooth and rough ER, also in cell processes and their dilations
Cell processes	1. Prolongations 2. Extremely long (*"tens up to hundreds of micrometres")* 3. Very thin (0.2–0.4 μm)[a] 4. Suddenly thin at the starting point from the cell body 5. Uneven calibre with specific moniliform aspect: dilations (knobs) alternating with thin narrow segments 6. Profile: labyrinthic 7. Numerous ramifications, with dichotomic pattern	1. Prolongations 2. Extremely long (*"tens up to hundreds of micrometres*") 3. Very thin (mostly below 0.2 μm) 4. Thin emergence from the cell body 5. Moniliform aspect, with many dilations along 6. Organization in a network (labyrinthine system) 7. Branching, with a dichotomous pattern
Cytoskeleton	Thin filaments Intermediate filaments	Thin filaments Intermediate filaments
Caveolae	Numerous	Numerous (2–3% of the cytoplasmic volume)
Ca^{2+} handling units	1. Consist of caveolae, ER and mitochondria 2. Within the dilations of the processes	Within the dilations of the processes, consisting of mitochondria, ER and caveolae
Shedding microvesicles	Present	Present
Basal lamina	Inconstant	Thin and discontinuous, or absent
Markers	CD34 (constant feature) c-kit (occasional)	CD34 c-kit
Junctions	1. Gap-like junctions 2. "Stromal synapses" with connective cells and immunoreactive cells	1. Gap junctions 2. Connective connections or "stromal synapses" with connective cells and immunoreactive cells
Proliferative potential	Uncertain (?), as the authors indicate: (1) *(Adult) mesenchymal stem cells?*; (2) *Uncommitted progenitor cells?*; (3) *Cardiac repair/regeneration?.*	As the authors state, "*Hypothetically, many roles were ascribed to telocytes (formerly, ICLC). However, there is no reasonable evidence to support them*".

[a] In the original paper of Kostin and Popescu (2009) the length of ICLCs processes is erroneously indicated in millimetres (mm).

(Boncompagni et al., 2009; Cabra et al., 2016; Felder and Franzini-Armstrong, 2002; McGrath et al., 2009; Takekura et al., 1994), being built upon the dihydropyridine and ryanodine receptors that are Ca^{2+} channels (Franzini-Armstrong et al., 1999). ICLCs were compared with fibroblasts, these later being documented by Kostin and Popescu (2009) as lacking caveolae in *in vivo* conditions.

4. Lymphatic vessels

The circulatory system in vertebrates is composed of two morphologically and functionally distinct vascular networks, the lymphatic vessel system and the blood vessel network (Yu et al., 2014). The first anatomical description of the lymphatic vessels was published by Aselli (1627), quoted in Ribatti and Crivellato (2010). The lymphatic vascular system contains a unidirectional system of conduits interrupted by lymph nodes that run parallel with the blood vascular system (Teijeira et al., 2013). The lymphatic vessels are essential for returning interstitial fluid and digested lipids (collectively known as lymph) back into the blood circulation and they play important roles in maintaining health (Chen et al., 2014). Lymphatic vessels deliver immune cells from tissues to lymph nodes (Teijeira et al., 2013). The lymphatic system is paramount in a number of physiological and pathological processes (Yu et al., 2014).

The tissue channels of the pre-lymphatic system are low-resistance pathways within the extracellular matrix (ECM), appearing as regular interstitial spaces of 25–100 μm lined by networks of matrix fibres on which occasionally apply widely-spaced endothelial-like cells with filopodes which are connected with collagen fibres (Zoltzer, 2003). These tissue channels further drain into the initial lymphatics (Ribatti and Crivellato, 2010) exclusively built up by LECs that have a peculiar oak leaf-shaped circumference (Baluk et al., 2007; Zoltzer, 2003). Between the LECs of the initial lymphatics are found numerous open junctions or wide intercellular clefts. The cell borders overlap to form inlet or primary valves that provide unidirectional fluid flux towards the lymphatic vessels (Baluk et al., 2007; Leak and Jamuar, 1983; Zoltzer, 2003). The endothelium of the initial lymphatics has an extremely attenuated cytoplasm, except in the perinuclear region (Ribatti and Crivellato, 2010). These initial lymphatics are commonly associated with structures that have smooth muscle or are neighbours to microvessels and nerves within the interstitia. They are readily identified in normal tissue based on their morphology and specific location (Shepro, 2005). The initial lymphatics empty into down-

stream contractile lymphatics (Shepro, 2005), i.e., precollectors and collecting lymphatic vessels, vessels that have a basal lamina, valves and an irregular and discontinuous smooth muscle layer (Alitalo et al., 2005; Leak and Jamuar, 1983; Sacchi et al., 1999).

5. Cardiac lymphatics

The heart has a well-developed lymphatic system (Miller, 2011) with its own role in fluid homeostasis of the heart interstitia, namely, in the balance between fluid filtration from blood capillaries into the cardiac interstitia and fluid removal from the interstitia through the lymphatic vessels (Ishikawa et al., 2007). The mammalian heart has an extensive lymphatic system through which the lymph flows from the endocardium to the epicardium and mostly drains into the right lymphatic duct (Miller, 1963, 2011). The left ventricle has the highest lymphatic density (Miller, 2011). Cardiac lymphatics have been investigated using dye-injection techniques, electron microscopy, lymphangiography and immunohistochemistry on paraffin-embedded samples (Ishikawa et al., 2007).

The cardiac lymph is drained through the initial lymphatics from the subendocardial lymphatic plexus to the subepicardial lymphatic plexus (Sappey's plexus, authors' note) by intramyocardial lymphatic channels (Ishikawa et al., 2007). Precollecting vessels originate in the subepicardial plexus and drain into the collecting vessels that are neighbours of major coronary branches (Sacchi et al., 1999). The TEM features of cardiac lymphatics are determined by an adaptation to dynamic forces and the anatomy of lymphatics supports the theory that they originate from the coalescence of mesenchymal lacunae (Sacchi et al., 1999). During adult cardiac lymphangiogenesis in patients with terminal heart failure, there is a substantial recruitment of additional initial lymphatics; lymphatics grow by appositional growth rather than by sprouting or developing new vessels from pluripotent progenitor cells (Dashkevich et al., 2009).

Podoplanin is a transmembrane mucin-type glycoprotein that is strongly expressed in podocytes, keratinocytes, cells of the choroid plexus, alveolar lung cells and LECs (Alitalo et al., 2005). Podoplanin is a reliable marker of lymphatic vessels in the myocardium (Zhikun et al., 2013) but was never used in studies on TCs. In normal cardiac tissue, podoplanin (D2-40)-expressing lymphatics are frequent in subepicardium, including the perivascular interstitia of the subepicardial fat (Ishikawa et al., 2007). The myocardial initial lymphatics are sporadically scattered among cardiomyocytes but are abundant around arteries and veins, being larger than blood vessels (Ishikawa et al., 2007). The subendocardial lymphatics are also abundant (Ishikawa et al., 2007). Overall, in the normal myocardium, blood vessels seem more numerous than lymphatics (Ishikawa et al., 2007).

It was recently demonstrated that the podoplanin-expressing cardiac cell populations of the heart are phenotypically heterogeneous and capable of generating lymphatic endothelium and profibrotic cells (Cimini et al., 2017). Some of the markers associated with podoplanin-expressing cells were found in TCs (Table 2).

6. Omission of cardiac lymphatics in cardiac TC characterisation

The terms "*lymphatic*" and "*Weibel–Palade*" do not appear—neither in the editorial renaming ICLCs to TCs (Popescu and Faussone-Pellegrini, 2010), nor in papers describing cardiac ICLCs or cardiac TCs (Bei et al., 2015; Chang et al., 2015; Cismasiu et al., 2011; Cretoiu et al., 2014; Cretoiu and Popescu, 2014; Fertig et al., 2014; Gherghiceanu et al., 2008, 2010; Gherghiceanu and Popescu, 2012; Hinescu et al., 2006; Hinescu and Popescu, 2005; Kostin, 2010; Kostin and Popescu, 2009; Li et al., 2015, 2016;

Table 2
Molecular and ultrastructural specific traits of LECs are compared with demonstrated features of TCs. NT: not tested. CD31 and the von Willebrand Factor are pan-endothelial markers while CD34 is not an absolutely specific endothelial marker (Figs. 4–8, 10, 12–14).

LECs ultrastructural features	Also in ICLCs/TCs
high nucleocytoplasmic ratio (Poggi et al., 1995; Ribatti and Crivellato, 2010)	+
ribosomes (Poggi et al., 1995)	+
WPBs (Poggi et al., 1995; Sacchi et al., 1999)	**Fig.11**
mitochondria (Poggi et al., 1995)	+
SER	+
RER	+
Golgi apparatus (Poggi et al., 1995)	+
caveolae (plasmalemmal vesicles) (Poggi et al., 1995)	+
pinocytotic vesicles (Leak and Burke, 1966; Poggi et al., 1995)	+ (Diaz-Flores et al., 2014a)
interlocking and overlapping of LECs (Leak, 1971; Poggi et al., 1986)	**Fig.14**
matrix-filled (condensed or precipitated lymph) lumen	**Figs.6, 10, 12, 14**
AFs attached to the abluminal side of LECs (Leak and Burke, 1968; Leak and Jones, 1993; Leak et al., 1978)	**Figs.6, 13**
occasional extraendothelial elastin fibers (Arkill et al., 2010; Poggi et al., 1995; Sacchi et al., 1999)	**Fig.9**
cytoplasmic filaments (Sacchi et al., 1999) - actin (Shepro, 2005) - intermediate filaments (Shepro, 2005) - microtubules (Shepro, 2005)	+ + + + (Gevaert et al., 2012)
lumina-limiting (Poggi et al., 1986) - large, irregular lumina (Shepro, 2005) - (completely) collapsed lumina (Detry et al., 2011)	**Figs.4, 5, 6, 10, 13** **Figs.7, 8, 11, 12, 14**
cell processes, intraluminal and abluminal (Zhikun et al., 2013)	**Figs. 10, 13**
absent or inconsistent basal lamina (Ribatti and Crivellato, 2010)	+
open junctions or wide interendothelial clefts (Baluk et al., 2007; Leak and Jamuar, 1983; Zoltzer, 2003)	**Figs.7, 10, 14**
inlet (primary) valves due to LECs overlapping	**Fig.14**
oak leaf-shaped (Baluk et al., 2007; Kakei et al., 2014; Zoltzer, 2003)	NT
focal points of adhesion (Ribatti and Crivellato, 2010)	**Fig.14**
immunocompetent cells transmigrate between LECs (Stoitzner et al., 2002)	+ (Popescu et al., 2005)
contacts with immunocompetent cells	**Figs.5, 6**
no covering pericytes (Shepro, 2005)	**Figs. 5-14**
mitotic LECs (Detry et al., 2011)	NT
LECs molecular markers	
podoplanin (D2-40) (Cimini et al., 2017; Ishikawa et al., 2007; Ribatti and Crivellato, 2010; Zhang et al., 2017)	NT
LYVE-1 (Bruyere et al., 2008; Cimini et al., 2017; Ribatti and Crivellato, 2010; Zhang et al., 2017)	NT
VEGFR-3 (Bruyere et al., 2008; Ribatti and Crivellato, 2010; Zhang et al., 2017)	NT
VEGF-C (Moldobaeva et al., 2017)	NT
VEGF-D (Moldobaeva et al., 2017)	NT
von Willebrand Factor (Bruyere et al., 2008)	NT
Prox-1 (Cimini et al., 2017; Ribatti and Crivellato, 2010; Zhang et al., 2017)	NT
desmoplakin (Ribatti and Crivellato, 2010)	NT
PDGFR-α (Cimini et al., 2017)	+ (Cretoiu and Popescu, 2014; Li et al., 2016; Manole et al., 2015; Milia et al., 2013; Rusu et al., 2017a)
PDGFR-β (Cimini et al., 2017)	+ (Liu et al., 2016; Sheng et al., 2014)
CD34 (Cimini et al., 2017)	+ (Diaz-Flores et al., 2014a; Diaz-Flores et al., 2014b; Dobra et al., 2018; Faussone Pellegrini and Popescu, 2011; Grigoriu et al., 2016; Popescu and Faussone-Pellegrini, 2010; Vannucchi and Faussone-Pellegrini, 2016; Vannucchi et al., 2014; Vannucchi et al., 2013; Xiao et al., 2016; Xiao et al., 2013; Yang et al., 2014; Zhao et al., 2014; Zhaofu and Dongqing, 2016)
PECAM-1 (CD31) (Sawa et al., 1999)	– (Manetti et al., 2013)
EGFR (Marino et al., 2013)	+ (Hinescu and Popescu, 2005; Popescu et al., 2006)

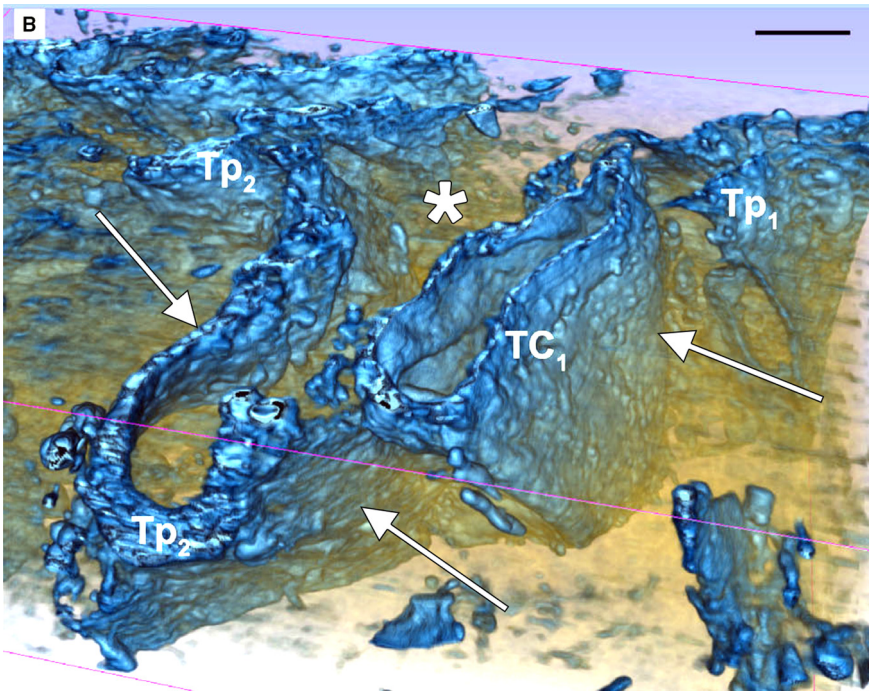

Fig. 4. Reprinted from John Wiley and Sons, CC BY License (Cretoiu et al., 2014). The original legend indicates: *"Automated segmentation of the stack containing the telocyte TC1 [. . .] shows that the telopode Tp2 is long (20 μm), narrow (0.2–1 μm) and flat, given a ribbon appearance of the cell. [. . .] Scale bars: 2 μm"*. However, those so-termed ribbons, as well as the cell body limit (arrows) a lumen (*). This 3D reconstruction proves that telopodes appear as thin cell processes only on bidimensional cuts and are in fact cuts of flattened cells with attenuated cytoplasm, such as are the LECs.

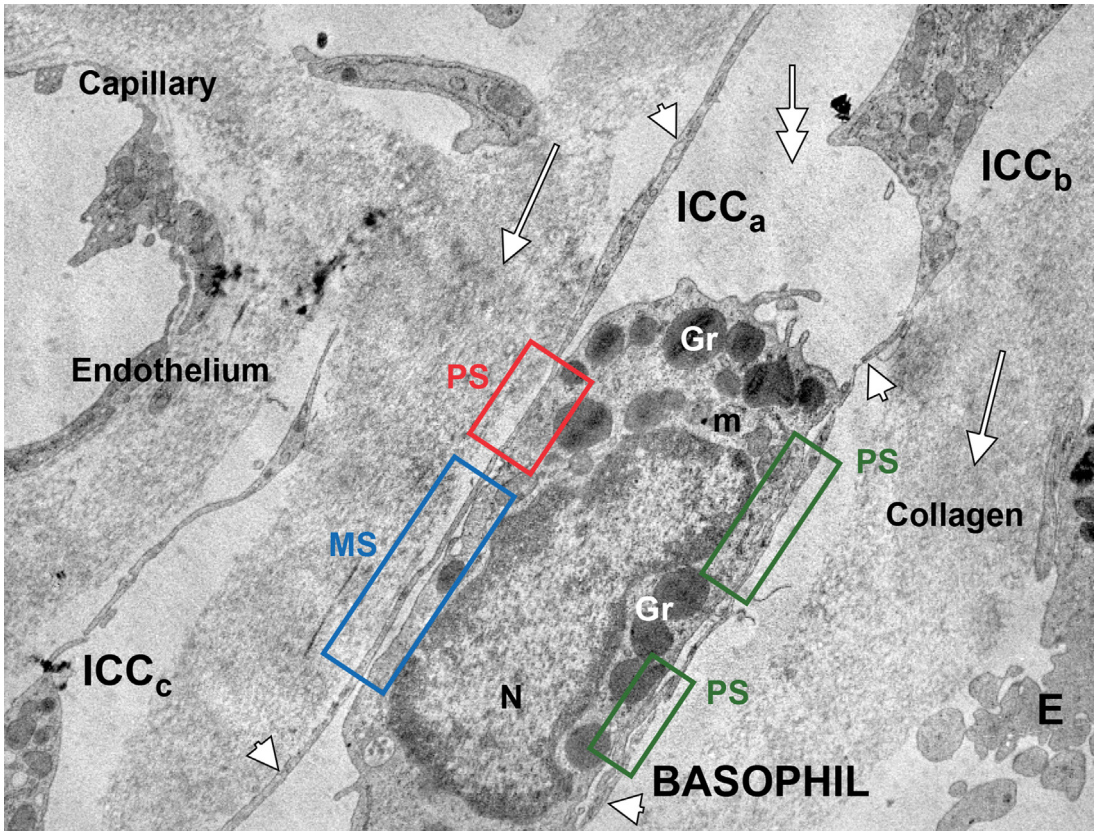

Fig. 5. Reprinted with permission from John Wiley and Sons from (Popescu et al., 2005). In the original legend (black indicators) is presented: *"Rat stomach muscularis mucosae: TEM; original magnification 7100×. A basophil establishes several synapses with cell processes belonging to 2 different ICC (ICCa and ICCb). Red and green outlines indicate plain synapses (PS), while the blue rectangle shows a multicontact synapse (MS). Another ICC is also present (ICCc) in proximity of a blood vessel. N, nucleus; Gr, granules of irregular shape and variable electron-density, which are specific for basophils; m, mitochondria"*. The so-identified ICCs are in fact LECs (arrowheads) which border a collagen-free lymphatic lumen (double-headed arrow) which contains that basophil. Those LECs lack basal laminae and their adluminal side is directly contacting the collagen fibers (arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

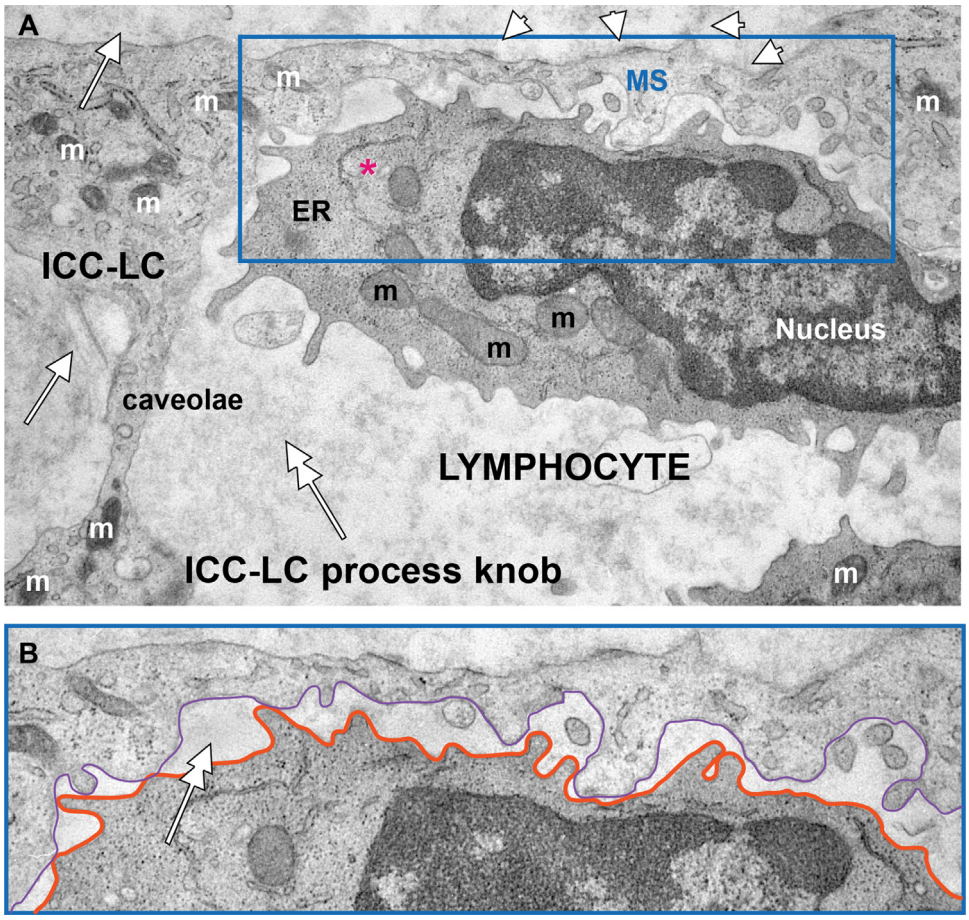

Fig. 6. Reprinted with permission from John Wiley and Sons (License Number: 4255211271377) (Popescu et al., 2005). In the original legend (black indicators) is presented: *"Human mammary gland stroma: TEM; original magnification 9100×. A: Lymphocyte establishing a multicontact synapse (MS) with an ICC-LC. The blue rectangle delimits the synaptic "kiss and run" region. Contours of the two cell membranes appear traced in B (with violet for ICC-LC and orange for lymphocyte) and the distances measured between membranes are shown in C. Note (asterisk) a peculiar conformation of the endoplasmic reticulum (ER) connecting mitochondria with the cell surface, suggestive for a possible role in synaptic Ca2+ homeostasis. m, mitochondria"*. However, those ICLCs are LECs, with the abluminal side facing a collagen-free, matrix-filled lumen (double-headed arrows) and the opposite, adluminal side facing the collagenic ECM (arrow) and, seemingly (the images have low resolution), attaching anchoring filaments (arrowheads). The lymphatic intraluminal lymphocyte further supports this TEM diagnosis.

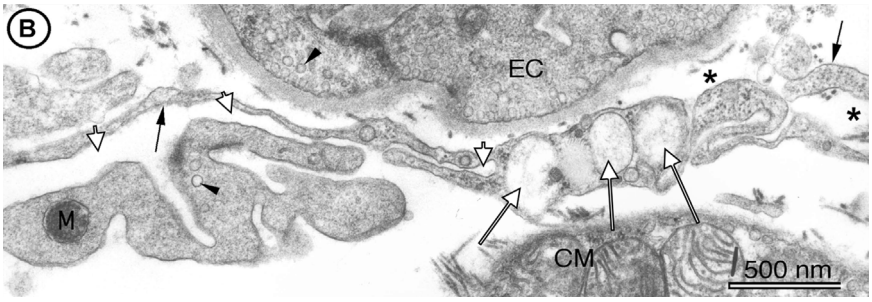

Fig. 7. Reprinted with permission from John Wiley and Sons (License Number: 4254870244791) (Kostin and Popescu, 2009). In the original legend (black indicators) is presented: *"A typical example of ICLC processes (arrows) located in vicinity of endothelial cells (EC) and cardiomyocytes. The presence of caveolae (arrowheads) is a typical feature of ICLCs and ECs. Note the cross-section of intermediate filaments (asterisk) inside ICLC processes."* However, the matrix-filled large vacuoles (white arrows) and the narrow collagen-free space between the respective processes (white arrowheads) could be as well the lumen of an initial lymphatic with wide-spaced LECs. Caveolae and lack of basal lamina could equally indicate LECs.

Mandache et al., 2010, 2007; Popescu et al., 2005, 2006, 2010; Rusu et al., 2012d; Sheng et al., 2014; Suciu et al., 2009; Varga et al., 2016; Yang et al., 2017; Zhao et al., 2013, 2014; Zhou et al., 2015). Also, only one set of relevant findings was found for the term "*lymphatic*" by searching through a recent book about these cells, named "Telocytes Connecting Cells" (2016), namely, that of Milia et al. (2013), who identified a network of TCs around lymphatic vessels in ileal samples (Milia et al., 2013). That study did not use TEM, TCs being identified exclusively by the positive expression of CD34 and PDGFRα. It is worth noting that CD34 is also expressed in endothelial cells, while the PDGFs, like the VEGF family, FGF2, Ang-1 and Ang-2 are also lymphangiogenic growth factors (Da et al., 2008). Overall, this is critical, because intramyocardial lymphatic and blood capillaries abundantly co-exist and interweave to build a complicated network (Zhikun et al., 2013).

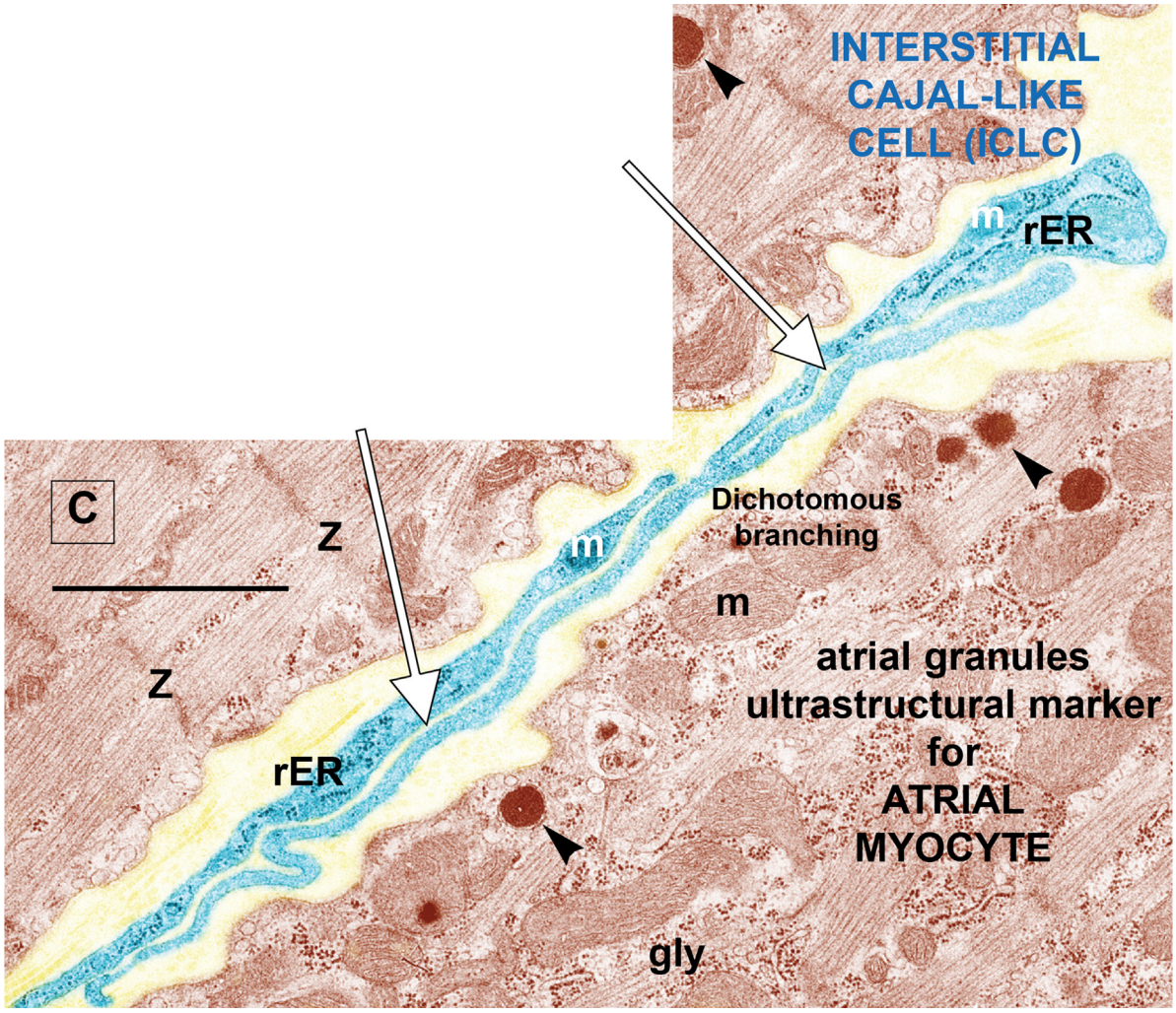

Fig. 8. Reprinted with permission (License Number: 4255550538015; Licensed Content Publisher: John Wiley and Sons; Licensed Content Publication: *Journal of Cellular and Molecular Medicine*) from (Hinescu et al., 2006). In the original legend of the figure is indicated: *"Some cell processes surround their "own" myocardial cell bundle while others lie between several bundles. Note in C, at higher magnification, two ICLC thin processes"*. However, the space between the two cell processes could as well be a collapsed lymphatic lumen (arrows).

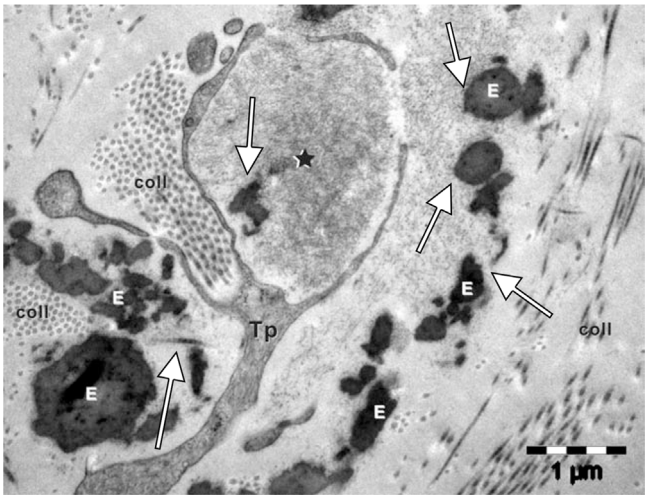

Fig. 9. Reprinted with permission from John Wiley and Sons (License Number: 4255631442022) from (Mandache et al., 2010). The authors indicate: *"Electron microscopy of atrial interstitial area. A telopode (Tp) surrounds a bunch of amyloid fibrils (star). Coll, collagen fibres; E, elastin"*. However, the amyloid fibrils the authors indicate, do not comply with the usual standard, of *"long, nonbranched filaments with diameters of 6–12 nm"* (Greenwald and Riek, 2010). The telopode presented as evidence is rather a LEC devoid of basal lamina and embedded within an interstitial matrix consisting of elastic fibers interwoven between collagen fibrils (arrows).

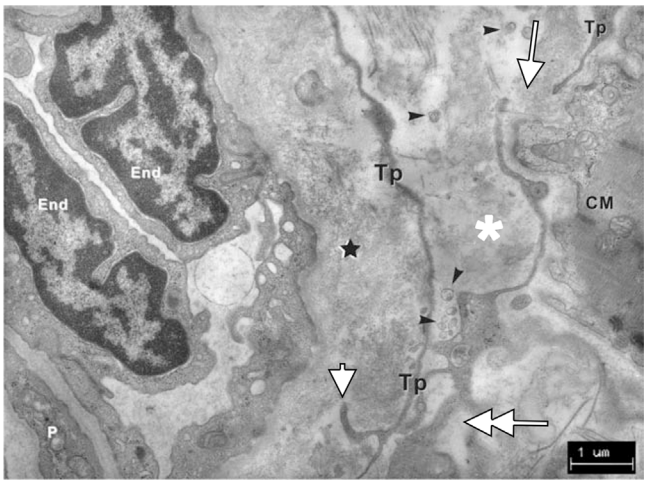

Fig. 10. Reprinted with permission from John Wiley and Sons (License Number: 4255631442022) from (Mandache et al., 2010). The authors indicate: *"Telopodes (Tp) surrounding an amyloid deposit (stars) in the periphery of a blood vessel. Small shed vesicles (arrowheads) can be seen in the vicinity of telopodes. CM, cardiomyocyte; End, endothelium; P, pericyte"*. However, the amyloid fibrils do not comply with the usual standard, of *"long, nonbranched filaments with diameters of 6–12 nm"* (Greenwald and Riek, 2010). The telopodes they indicate are rather LECs which border a less dense lumen (*) of an initial lymphatic. Between LECs there are gaps (arrow). An intracytoplasmic sac (double-headed arrow) and an abluminal short process (arrowhead) are observed, these being common features of initial lymphatics.

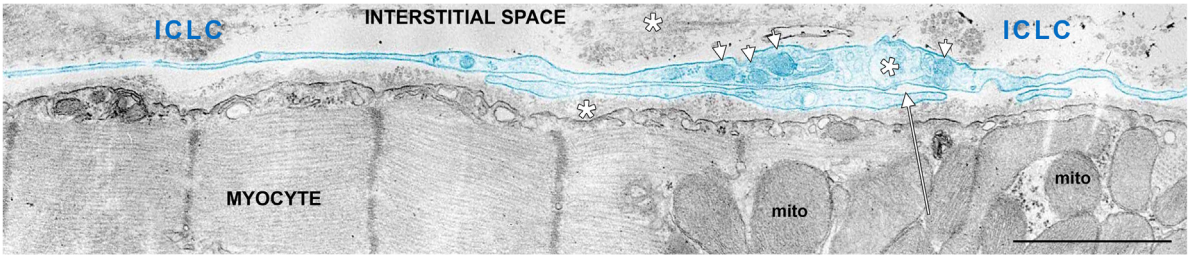

Fig. 11. Reprinted with permission from John Wiley and Sons (License Number: 4255851174272) from (Popescu et al., 2006). Cropped area of Fig. 6 A in that article (we noticed that between Figs. 5 and 6 there an additional unnumbered one), which was originally described: *"Longitudinal section through ventricular muscle fibers. A. A 20 μm long ICLC process (blue) running parallel with the basal lamina of a ventricular myocyte overlapping with a 3 μm short ICLC process"*. However, those cells limit a collapsed collagen-free lymphatic lumen (arrow) while, adluminally, the initial lymphatic devoid of basal lamina is surrounded by a collagenic interstitial matrix (*). Seemingly, although blurred by digital supracolouring, one of those cells contains Weibel–Palade bodies (arrowheads) which are clathrin-coated, display a tubular content, and were not indicated as mitochondria (*mito*) by the authors, such as they did within myocytes. Moreover, the authors supracoloured an extracellular space, seemingly luminal, and included it to the cell body (*), although the plasmalemmal contours are obvious.

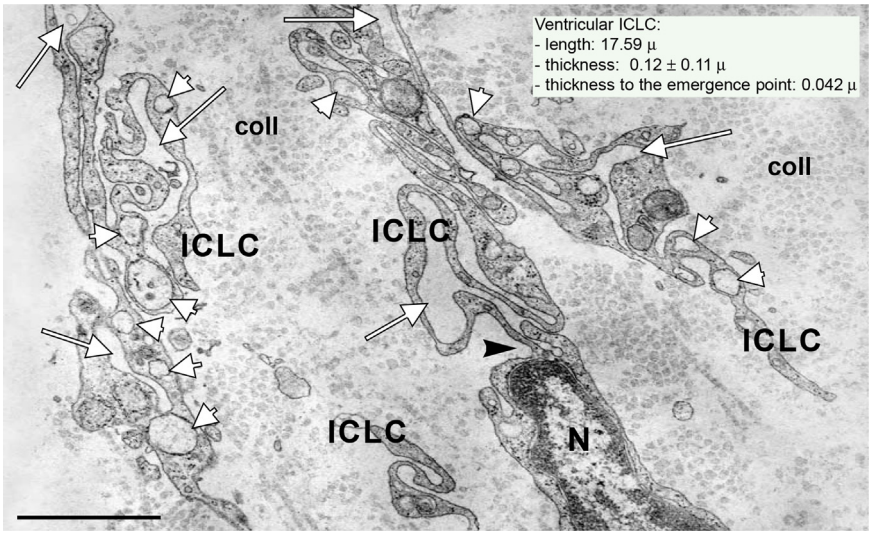

Fig. 12. Reprinted with permission from John Wiley and Sons (License Number: 4255851174272) from (Popescu et al., 2006). The authors originally noted: *"Several retracted veil-like cytoplasmic extensions belonging to ICLC, containing free ribosomes, a few mitochondria, caveolae and enlarged sER. Note that the cytoplasmic processes are slender at their emergence point (arrowhead). The cells are placed in a collagen fibers meshwork. coll = collagen; N = nucleus. Scale bar = 1 μm"*. However, they did not indicate those sER cisterns, nor they detailed these at higher magnification. In fact, the image presents collagen-embedded and basal lamina-free LECs which limit lumina filled with collagen-free lymph matrix (arrows) and contain numerous intracytoplasmic sacs (arrowheads) which are characteristic to LECs but were presumably misjudged as sER.

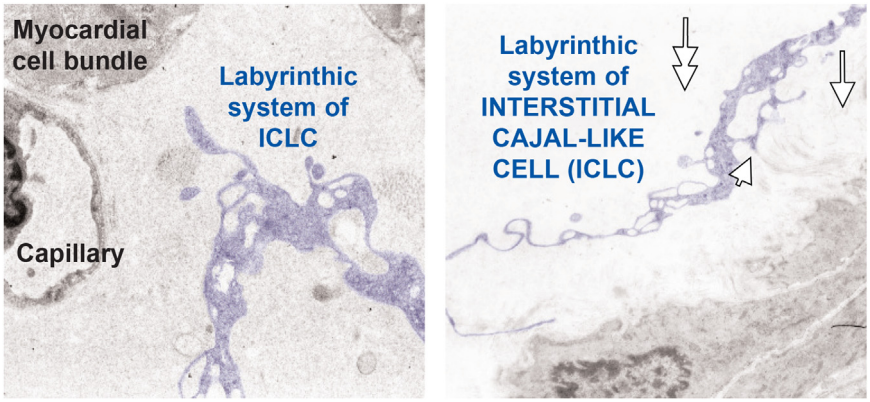

Fig. 13. Reprinted with permission from John Wiley and Sons (License Number: 4256140563037) from (Hinescu and Popescu, 2005). The authors evaluated rat myocardial ICLCs in TEM and concluded that a *"striking ultrastructural match with cells of human origin was observed concerning the extent of the labyrinthic system"*. It can be easily observed that the so-identified ICLCs, which lack a basal lamina, limit a collagen-free lumen (double-headed arrow), display numerous intracytoplasmic vacuoles, and adluminally are related to the collagenic interstitial matrix (arrow) and, seemingly, attach anchoring filaments (arrowhead). An abluminal process of a LEC can be observed in the left panel.

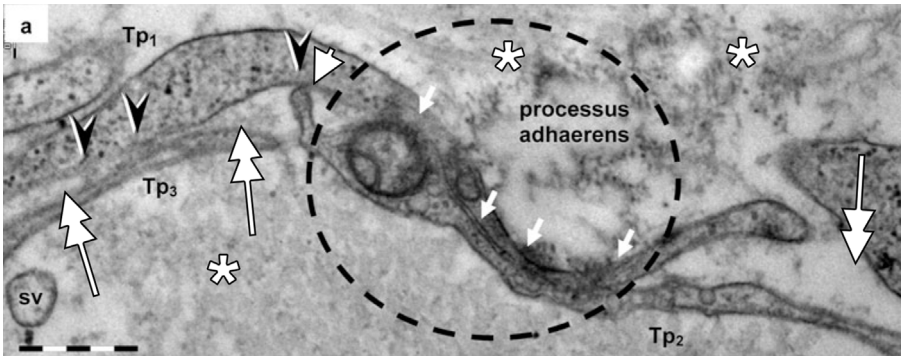

Fig. 14. Reprinted from John Wiley and Sons (Gherghiceanu and Popescu, 2012) which is licenced under CC BY. The authors indicated: *"Two overlapping telopodes (Tp1, Tp2) are connected by a sequence of puncta adherentia minima (small arrows) in 1.2 μm long contact sector (white arrows in dotted circle) – processus adhaerens. Minute adjoining points of the plasma membrane of telopodes (Tp1-Tp2 and Tp1-Tp3) are also visible (black arrowheads)"*. However, the TEM micrograph could as well present a collagen-embedded (*) initial lymphatic devoid of basal lamina, with a non-collagenic matrix-filled collapsed lumen (double-headed white arrows), an inlet valve (white arrowhead), and overlapped LECs with focal points of adhesion in the original dotted circle.

Lymphatics were overlooked in studies of stromal niche populations that include TCs in organs that have lymphatic drainage. For example: "TCs occupy a strategic position in relation to stem cell niches, blood capillaries, and/or nerve bundles" and telopodes "establish contacts with other cells such as mast cells, basophils, lymphocytes, eosinophils, plasma cells, or macrophages, and non-cellular elements" (Cretoiu and Popescu, 2014). It is easy to notice that lymphatics were not included among the TC-containing niches.

7. LECs vs ICLCs and TCs

7.1. The identifiers of LECs are quite similar to those of ICLCs or TCs

Detry et al. (2011, 2012) studied using a convincing rigorous methodology lymphatic vessel formation *in vivo* (Fig. 2) and *in vitro*. The ultrastructural features they found for LECs (Detry et al., 2011, 2012) include: (1) long cell processes containing vesicles (that can also be described as intracytoplasmic sacs, or vacuoles); (2) extracellular spaces that either are devoid of interstitial matrix, or that contain reminiscent fragments of collagen fibrils, these being due to the extensive remodelling of the ECM; (3) intracellular vesicles containing matrix fragments; (4) LECs joined by interdigitations; (5) aligned LECs with long, thin and moniliform cytoplasmic extensions limit in TEM narrow lumina; (6) some LECs being mitotic; and (7) anchorage filaments (AFs) attaching LECs to the ECM. The content of the lymphatic capillary lumen may appear as a grey flocculent material that is precipitated lymph that resulted during the fixation process. That grey substance is continuous with the interstitium through open junctions between LECs (Leak, 1970). Immunoreactive cells are able of transmigrating through gaps between LECs (Fig. 3) from the luminal space towards more electron-dense connective tissue (Stoitzner et al., 2002).

The ultrastructural and molecular features assigned to LECs were also identified in cardiac TC studies. See Table 2 for details. We observe that most of the LEC-specific molecular markers were not tested in TCs.

7.2. The basal lamina and the anchorage filaments

The initial lymphatics built up by LECs can be differentiated from blood capillaries by the type of ECM each vessel adjoins (Detry et al., 2012). While the blood vascular endothelium is in direct contact with components of the endothelial basal lamina (laminin and type IV collagen), initial lymphatics do not have a basal lamina and thus interact with the interstitial matrix, being attached to it through AFs. These AFs, of about 100 Å in width, either appear as individual units, or are aggregated into bundles, running parallel with the long axis of the lymphatic capillary, similar to the microfibrils of the ECM (Leak and Burke, 1968).

Beyond the limits of 2D exploration of TCs that could result from longitudinal tangential cuts of endothelial tubes and could appear as collagen-embedded cells with long prolongations and no basal lamina, there could be two other possible inappropriate identifi-

cations of an LEC as a TC: (1) omitting the matrix-filled lumen of lymphatics and the extracellular spaces devoid of interstitial matrix, which are common features of lymphatics and (2) overlooking the fact that LECs change their overall shape during the stages of lymphedema. Mihara et al. show that collecting lymphatic vessels change through successive stages of ectasis, contraction and sclerosis (Mihara et al., 2012). Normal LECs protrude in the lymphatic lumen; ectatic LECs are smooth and do not protrude intraluminally, which corresponds to lymphangiectasia, whereas in sclerotic vessels the LECs are completely disassembled and extraendothelial collagen fibres are found within the lymphatic lumen (Mihara et al., 2012). Therefore an LEC could appear as completely collagen-embedded, but this would not modify the cell type.

7.3. Weibel–Palade bodies

Weibel–Palade bodies (WPBs), known as panendothelial ultrastructural markers (Rusu et al., 2017b; Weibel, 2012; Zhou et al., 2012), were not used to differentiate between ECs and TCs. However, TC-like cells were found containing Weibel-Palade bodies (Petrea et al., 2018a, 2018b; Rusu et al., 2018a, 2017b). In articles, as images depicting ICLCs and TCs has usually been shown at low resolutions and has been digitally supracoloured, the cytoplasmic content of these cells has often hardly been distinguishable (Gherghiceanu et al., 2010; Hinescu et al., 2006; Mandache et al., 2007; Popescu et al., 2006, 2010). As such, they are not convincing candidate LECs. Although the cigar shape of longitudinally cut WPBs is specific, we should not ignore that, if transversally cut, they are rounded and display tubular content (Carlile et al., 2000; Weibel, 2012; Weibel and Palade, 1964; Zenner et al., 2007) embedded in a dense matrix with a clathrin coat (Valentijn et al., 2011, 2008). Therefore, transversally cut WPBs could easily be misidentified as mitochondria, especially when their double membranes are not clearly distinguishable. WPB-containing cardiac ICLCs were identifiable (Fig. 11) in a study of the ventricular myocardium.

7.4. Lymphatics and elastin

LECs are characterised not only by Weibel-Palade bodies, cytoplasmic filaments and focal adhesions but also by an extraendothelial layer that contains not only collagen but also elastin (Arkill et al., 2010; Ryan, 1989; Sacchi et al., 1999) that builds a "fibrillar elastic apparatus" (Poggi et al., 1995). Elastin, which interweaves between the collagen fibres (Arkill et al., 2010), is either directly connected with LECs, or with AFs (Ryan and De Berker, 1995), forming small and rare clusters within the heart tissue (Poggi et al., 1995). It is therefore possible to fail to identify elastin in the adjoining interstitial matrix of the small lymphatic vessels (Poggi et al., 1995). Elastin was found (Mandache et al., 2010) in neighbouring atrial TCs (Fig. 9) in samples in which interstitial amyloid deposits were identified exclusively in TEM (Mandache et al., 2010). Atrial natriuretic peptide, the main constituent of isolated amyloid deposits, is known to inhibit lymph transport by decreasing spontaneous contractions and relaxing lymphatic smooth muscles through a guanosine 3′,5′ cyclic monophosphate signalling pathway (Ohhashi et al., 1990).

7.5. Interlocking and overlapping of TCs and of LECs

Cytoplasmic overlapping was described as a distinctive feature of cardiac TCs (Kostin, 2010; Varga et al., 2016). Also, cardiac Tps were described as inserting in a tight-fitting manner into deep plasma membrane invaginations called *recessus adhaerentes*, forming a long continuous cuff-like junction (Gherghiceanu and Popescu, 2012; Varga et al., 2016).

However, the LECs of the cardiac initial lymphatics were shown by TEM also to interlock and overlap with neighbouring LECs (Poggi et al., 1986). Three types of contacts between cardiac LECs were shown: end-to-end contact, overlap and interdigitation (Marchetti et al., 1987). Lymphatics also have intraendothelial channels that are bordered by multiple cytoplasmic protrusions (Marchetti et al., 1999). Therefore, cardiac TCs and LECs could have similar intercellular contacts.

7.6. LECs and vesicles

The primary direction of transport in the lymphatic capillary is from the interstitial area of the connective tissue into the lymphatic lumen (Leak, 1971). The passage of materials across the LECs in smooth-surfaced pinocytotic vesicles was suggested by Palade (1953) and Bennett (1956) (quoted in (Leak and Burke, 1966)), who both hypothesised that membrane flow and vesiculation are important mechanisms for carrying molecules and particles into and out of the cells by way of vesicles. The major passage for the removal of interstitial fluids and large molecules by the lymphatic capillary is the intercellular cleft (Leak, 1971). Although caveolae (plasmalemmal vesicles) occur equally ad- and abluminally, the movement of ingested particles is towards the central cytoplasmic matrix of LECs, where engulfed particles are deposited in autophagic-like vacuoles for digestion and possible distribution within or from the lymphatic endothelium (Leak, 1971).

Rat cardiac TCs were evaluated in cultures after the hearts were mechanically minced (Fertig et al., 2014), which did not exclude lymphatics, vessels and nerves. Those TCs were not sorted by any criteria and the authors just indicated that TCs were identified by TEM in interstitial cardiac cell cultures (Fertig et al., 2014). These cells were found in culture to release at least three types of extracellular vesicles, exosomes, ectosomes and multivesicular cargos (Fertig et al., 2014). These features were stated to be suggestive for a paracrine type of secretion of TCs (Cismasiu and Popescu, 2015; Cretoiu and Popescu, 2014; Varga et al., 2016); however, to state this with a reasonable degree of certainty, the cells should have been adequately sorted and differentiated from LECs (and other potential cellular types).

7.7. Mechanisms of adult lymphangiogenesis: migrating LECs are similar to TCs

During adult lymphangiogenesis, which can be abnormal in pathological tissues, LECs sprout from pre-existing lymph vessels and migrate through the interstitial matrix as single collagen-embedded cells (Detry et al., 2012). Migrating LECs that contain intracellular vesicles extrude long processes that probe the environment, similarly to endothelial tip cells (Rusu et al., 2013a, 2013b). Unlike them, however, LECs progressively align to form a cord (Detry et al., 2012) and, after populating a region, coalesce into lymphatic vessels (Rutkowski et al., 2006). In neoformed lymphatics, collagen-free gaps are frequently encountered between neighbouring LECs; these gaps are caused by an extensively remodelled collagen matrix (Detry et al., 2012). Due to the AFs that link LECs with the interstitial matrix, fluid accumulation in the tissue opens these gaps and enhances the uptake of interstitial fluid (Adams and Alitalo, 2007). Briefly, lymphangiogenesis is a process of cell migration and subsequent organisation, rather than of sprouting, with basal lamina developing after the vessels becoming functional (Rutkowski et al., 2006).

Therefore, while LECs migrate and organise unidirectionally in the direction of interstitial fluid flow, they do not sprout into that region, but rather migrate as single cells and later join together into vessels. In a "shunted flow" model, infiltrated LECs failed to organise into functional vessels, which indicates that interstitial

Table 3
Expression of VEGF was tested, and found in TCs. However, most of the studies are not replicable as the data on the markers that were used are incomplete.

Study of VEGF expression in ICLCs or TCs	Ref.	manufacturer, as stated by authors	clone catalogue	dilution
Telocytes in Human Term Placenta: Morphology and Phenotype	(Suciu et al., 2010)	Santa Cruz	polyclonal Sc-152	1:100
Identification of telocytes in skeletal muscle interstitium: implication for muscle regeneration	(Popescu et al., 2011b)	Santa Cruz	?	1:75
Experimental acute myocardial infarction: telocytes involvement in neo-angiogenesis	(Manole et al., 2011)	Santa Cruz	?	?
The secretome of myocardial telocytes modulates the activity of cardiac stem cells	(Albulescu et al., 2015)	MERCK RECYTMAG-65K | MILLIPLEX MAP - Immunology Multiplex Assay	-	-
Telocytes in human oesophagus	(Chen et al., 2013)	ELISA kit, eBioscinece, San Diego, CA 92121, USA	?	?
Phenotypical and ultrastructural features of Oct4-positive cells in the adult mouse lung	(Galiger et al., 2014)	Santa Cruz	polyclonal Sc-152	1:100
Platelet-derived growth factor receptor-b-positive telocytes in skeletal muscle interstitium	(Suciu et al., 2012)	Abcam	?	?
Human lung telocytes could promote the proliferation and angiogenesis of human pulmonary microvascular endothelial cells in vitro	(Zheng et al., 2014)	ELISA kit, eBioscience (California, USA)	?	?

fluid flow is necessary for lymphatic organisation (Rutkowski et al., 2006). In these regards, finding TCs devoid of a basal lamina even as single cells (Gherghiceanu et al., 2008, 2010; Gherghiceanu and Popescu, 2012; Hinescu et al., 2006; Hinescu and Popescu, 2005; Kostin and Popescu, 2009; Mandache et al., 2010, 2007; Popescu et al., 2006, 2010) within the interstitial matrix should raise the question whether they are LECs, especially when they have the ultrastructural pattern of endothelial cells. Previous studies found subsets of TCs that belonged to the endothelial lineage (Grigoriu et al., 2016; Rusu et al., 2017a) but did not go further and attempt to distinguish between endothelial progenitors and LECs.

7.8. Tangentially cut lymphendothelial tubes generate false evidence

According to histology textbooks, the initial lymphatics begin as "blind-ended" tubes in the microcapillary beds. Initial lymphatics are essentially tubes of endothelium that lack a continuous basal lamina. Therefore, one could claim that endothelial cells cannot be confused with a mesenchymal cell under the electron microscope. However, on bidimensional cuts, false spindle-shaped TCs appearances either correspond to collapsed lymphatic lumina or are resulted after grazing longitudinal cuts of lymphatics (Manta et al., 2018).

7.9. Molecular markers, methods, lymphangiogenesis and ICLCs or TCs

The molecular phenotypes of TCs are extremely variable and until now a specific set of markers for TCs has not been universally accepted. Although highly specific lymphatic markers were not previously tested in ICLCs and TCs, several markers that identify LECs were shown to be positive in TCs (Table 2). Until now, only one immunoelectron study on cells with telopodial prolongations has been published, that by Pieri et al. (2008). The evidence of CD34+ cell processes that resulted was further propagated in the editorial by Popescu and Faussone-Pellegrini (2010), in which ICLCs were renamed as TCs (Pieri et al., 2008). Although in the study of Pieri et al. (2008), the CD34+ ICLCs in the human GI tract were differentiated from c-kit+ ICCs, they were not distinguished from lymphatics.

Increased expression of both Vascular Endothelial Growth Factor (VEGF)-A (usually known as a regulator of angiogenesis that enhances the migration of blood vascular endothelial cells (ECs), but also a known EC mitogen) and VEGF-C signalling might be most important in the early stages of initiation of lymphangiogenesis, rather than in the later stages of organisation and maturation of lymphatic vessels (Rutkowski et al., 2006). VEGF-C is a critical regulator of lymphatic regeneration during adult lymphangiogenesis; macrophages not only produce VEGF-C during lymphatic regeneration but also directly contribute to lymphangiogenesis by transdifferentiating in LECs (Maruyama et al., 2005; Rutkowski et al., 2006; Yan et al., 2011). In this context, it is interesting to note that, although overlooked by the respective authors, TEM evidence of telopode-projecting macrophages was provided previously in a study of TCs (Zheng et al., 2012); those macrophages with telopodes could equally be transdifferentiating in LECs and contributing to lymphangiogenesis.

VEGF family members have important roles in myocardial lymphatic development and function and in cardiac diseases. VEGF-C binds to VEGFR-2 and VEGFR-3 and is a major regulator in the development of lymphatic vasculature. Inflammatory cells such as macrophages, dendritic cells and CD4-expressing T lymphocytes are a rich source of VEGF-C. VEGF-C may also have angiogenic

effects by attracting VEGF-A-producing macrophages (Dashkevich et al., 2016).

The positive expression of VEGF-A, which was found in TCs (Galiger et al., 2014; Suciu et al., 2010b), could support TCs affiliation to an endothelial lineage. Unfortunately, most of the studies evaluating the expression of VEGF in ICLCs or TCs are not completely replicable due to incomplete or discordant data regarding the used markers (Table 3). Also, members of the VEGF family are lymphangiogenic growth factors (Da et al., 2008). The LECs are able to release nitric oxide (NO), an endothelium-derived relaxant factor (Marchetti et al., 1997). The expression of inducible nitric oxide synthase (iNOS) was found in TCs that express VEGF-A that were not tested for the expression of eNOS (Suciu et al., 2010b). Although it was known that VEGF-A induces the expression of eNOS and iNOS in endothelial cells, the results of that TC study (Suciu et al., 2010b) were not corroborated towards the reasonable suspicion of a subset of TCs being in fact LECs.

That ICLCs are instead LECs is supported by the Popescu group's results, which found the expression of EGFR in ICLCs (Hinescu et al., 2006; Popescu et al., 2006). EGFR is known to be expressed in human LECs and in podoplanin-positive lymphatic vessels, and EGF promotes lymphangiogenesis *in vivo* (Marino et al., 2013).

7.10. TCs belong to the "interstitial organ"

A structural evaluation of the interstitial space structures in tissues that are subject to intermittent or rhythmic compression found that cells with TC morphology line up along one side of bundles of collagen and have no basal membrane (Benias et al., 2018). Such cells border a form of interstitial space in which interstitial fluid or "pre-lymph" forms or accumulates (Benias et al., 2018). Immunostaining showed positive CD34 and D2-40 (podoplanin) staining on one side of each collagen bundle and was negative for other lymphendothelial markers (CD31, ERG, LYVE-1) and it was uniformly positive for the mesenchymal marker vimentin (Benias et al., 2018). These cells did not express smooth muscle actin or CD117/c-kit (Benias et al., 2018).

8. Concluding remarks

In studies on cardiac TCs, the anatomic characterisation of a fundamental tissue structure was not included, namely, that of the lymph vessel. In further studies on cardiac TCs, specific lymphatic markers should be used, such as podoplanin, LYVE-1 and Prox-1. In addition, ultrastructural traits that do not fit lymphatic endothelial cells should be investigated in order to prevent mischaracterisation.

A comparative study is necessary to ascertain whether TCs are indeed TCs or other cell types. However, for this, it is necessary to have a reliably identified, well-characterised TC population that, as far as we know, is not yet available.

Acknowledgements

None.

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