Histol Histopathol (2018) 33: 1151-1165

http://www.hh.um.es

Histology and Histopathology

From Cell Biology to Tissue Engineering

Review

Telocytes in skeletal, cardiac and smooth muscle interstitium: morphological and functional aspects

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Summary. Telocytes (TCs) represent a new distinct type of cells found in the stromal compartment of many organs, including the skeletal, cardiac and smooth muscles. TCs are morphologically defined as interstitial cells with a small cellular body from which arise very long (up to hundreds of micrometers) and thin moniliform processes (named telopodes) featuring the alternation of slender segments (called podomers) and small dilated portions (called podoms) accommodating some organelles. Although these stromal cells are mainly characterized by their ultrastructural traits, in the last few years TCs have been increasingly studied for their immunophenotypes, microRNA profiles, and gene expression and proteomic signatures. By their long-distance spreading telopodes, TCs build a three-dimensional network throughout the whole stromal space and communicate with each other and neighboring cells through homocellular and heterocellular junctions, respectively. Moreover, increasing evidence suggests that TCs may exert paracrine functions being able to transfer genetic information and signaling molecules to other cells *via* the release of different types of extracellular vesicles. A close relationship between TCs and stem/progenitor cell niches has also been described in several organs. However, the specific functions of TCs located in the muscle interstitium remain to be unraveled. Here, we review the morphological and possible functional aspects of TCs in skeletal, cardiac and smooth muscle tissues. The potential involvement of TCs in muscle tissue pathological changes and future possibilities for targeting TCs as a novel promising therapeutic strategy to foster muscle tissue regeneration and repair are also discussed.

Key words: Telocytes, Interstitial cells, Skeletal muscle, Cardiac muscle, Smooth muscle

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DOI: 10.14670/HH-11-994

Introduction

The stromal space (interstitium) has the main function of connecting the specific structures of an organ (Popescu and Nicolescu, 2013). 'Interstitial cells' is a morphological term denoting cells of direct or indirect (hematopoietic) mesenchymal origin which includes different cell populations residing in the connective tissue of a variety of organs (Bani and Nistri, 2014). Interstitial (stromal) cells commonly exhibit an ability to produce and organize in space correctly the macromolecular components constituting the extracellular matrix in which they are embedded (Bani and Nistri, 2014). In particular, fibroblasts are considered the most abundant stromal cells provided with structural functionality, being mainly responsible for the production of extracellular matrix components, including collagen and elastic fibers, ground substance and cytokines (Popescu and Nicolescu, 2013; Kang et al., 2015).

Stromal cells appear to be endowed with the unique ability to shape a proper three-dimensional (3D) scaffold

and stimulate the correct growth and differentiation of parenchymal precursors to give rise to tissues and organs, thus playing an essential role during organ morphogenesis. Moreover, in particular conditions this ability can be resumed to foster tissue and organ regeneration and repair following injury (Bani and Nistri, 2014). Therefore, a deeper knowledge of the biological properties of stromal cells and their role as key regulators of the 3D architecture of multiple organs seems essential to lay the foundations for new therapeutic approaches in regenerative medicine (Bani and Nistri, 2014; Bani, 2016). In this context, the role of the stromal compartment in the pathophysiology and regulatory mechanisms of different types of muscle tissues (i.e. skeletal, cardiac and smooth muscle) has been largely investigated. The skeletal muscle interstitium is crucial for regulation of blood flow, passage of substances from capillaries to myocytes and muscle regeneration (Popescu et al., 2011b). The cardiac stroma also plays a critical role either in the maintenance of the normal heart architecture or in the pathophysiological alterations occurring in cardiac diseases (e.g. post-infarction myocardial remodeling and cardiac fibrosis) (Bani and Nistri, 2014). Finally, the smooth muscle found in different organ systems is a complex tissue containing a variety of stromal cells besides smooth muscle fibers, such as fibroblasts, mast cells, macrophages, and interstitial cells of Cajal (Sanders et al., 2014). These stromal cells seem to contribute to the normal functions and remodeling of smooth muscle, while their loss can lead to a variety of motor disorders (Sanders et al., 2014).

In the most recent years, a new stromal cell type, named telocytes (TCs), has been described in the stromal compartment of several organs, including the skeletal, cardiac and smooth muscle interstitium (Faussone Pellegrini and Popescu, 2011; Cretoiu and Popescu, 2014; Díaz-Flores et al., 2014). Compelling evidence indicates that TCs are rather different from 'classical' fibroblasts and other types of interstitial cells as supported by their peculiar ultrastructural characteristics, immunohistochemical features, gene expression and proteomic profiles, and microRNA (miRNA) signatures (Faussone Pellegrini and Popescu, 2011; Cretoiu and Popescu, 2014; Díaz-Flores et al., 2014; Song et al., 2016; Cretoiu et al., 2017; Marini et al., 2017a). Ultrastructurally, the distinctiveness of TCs is given by their particular cellular prolongations called telopodes (Tps) (Cretoiu and Popescu, 2014). Tps are very long (up to hundreds of micrometers) and slender prolongations that abruptly emerge from a small nucleated cellular body and display a moniliform silhouette featuring the alternation of thin segments (called podomers) and small dilated portions (called podoms) (Faussone Pellegrini and Popescu, 2011; Cretoiu and Popescu, 2014). By their long-distance spreading Tps, TCs can shape a 3D network within the stromal space where they communicate with each other and neighboring cells through homocellular and heterocellular junctions, respectively (Faussone-Pellegrini and Gherghiceanu, 2016). In addition, TCs may exert paracrine functions being able to transfer genetic information and signaling molecules to other cells *via* the release of different types of extracellular vesicles, namely exosomes, ectosomes and multivesicular cargos (Cretoiu et al. 2016; Marini et al., 2017a). Indeed, owing to their close spatial and paracrine relationships with multiple tissue-resident cell types, TCs are generally considered as 'connecting cells' mostly endowed with intercellular signaling functions by converting the interstitium into an integrated system that contributes to either proper organ morphogenesis or subsequent maintenance of local tissue homeostasis (Ibba-Manneschi et al., 2016a; Wollheim, 2016). Of note, the presence and activity of ion channels and pumps in TCs from some organs also suggest the possible involvement of these cells in morphogenetic bioelectrical signaling (Cretoiu et al., 2015; Radu et al., 2017). Moreover, it appears that TCs may cooperate with tissue-resident stem/progenitor cells to foster organ repair and regeneration, and that TC damage and dysfunction may occur in several disorders (Díaz-Flores et al., 2014, 2015, 2016; Ibba-Manneschi et al., 2016a,b; Song et al., 2016; Marini et al., 2017a).

The goal of this review is to provide a summary of recent research findings on the morphological and possible functional aspects of TCs in the skeletal, cardiac and smooth muscle interstitium. We also provide an overview of the potential involvement of TCs in muscle tissue pathological changes and future possibilities for targeting TCs as a novel promising therapeutic strategy to foster muscle tissue regeneration and repair.

General characteristics of telocytes

The gold standard for the identification of TCs is transmission electron microscopy (TEM), a technique that allowed their discovery in the stroma of many tissues and organs of humans and other vertebrates, and led to their shortest possible definition, namely 'stromal cells with Tps' (Popescu and Faussone-Pellegrini, 2010; Cretoiu and Popescu, 2014). In fact, the ultrastructural identification of TCs is mostly based on the recognition of their very long and slender cellular prolongations, named Tps, which are characterized by a narrow emergence from the cellular body and a typical moniliform aspect (i.e. alternation of thin segments, termed podomers, and small dilated portions, termed podoms, which accommodate mitochondria, endoplasmic reticulum cisternae and caveolae) (Popescu and Faussone-Pellegrini, 2010; Cretoiu and Popescu, 2014). Under TEM, the TC silhouette is distinctive being characterized by a small piriform-, spindle- or triangular-shaped cell body (9-15 μm) giving rise to a variable number of extremely long (10-1000 μm), thin, tortuous, and overlapping Tps forming a stromal 3D spatial arrangement (Cretoiu and Popescu, 2014; Faussone-

Pellegrini and Gherghiceanu, 2016). The cellular body contains a large euchromatic nucleus with clusters of peripheral heterochromatin surrounded by a small amount of cytoplasm containing mitochondria, scarce cisternae of endoplasmic reticulum and a small Golgi apparatus (Faussone Pellegrini and Popescu, 2011; Cretoiu and Popescu, 2014). On the basis of the aforementioned morphological features, TCs appear definitely distinct from 'classical' stromal cells, such as fibroblasts (Popescu and Faussone-Pellegrini, 2010; Faussone Pellegrini and Popescu, 2011; Cretoiu and Popescu, 2014; Bei et al., 2015b; Kang et al., 2015).

In the interstitial space, Tps are physically arranged in a complex 3D network establishing either homocellular (between TCs) or heterocellular (between TCs and other cells, such as blood vessels, nerves, muscular cells, or other connective tissue-resident cells) junctions (Faussone Pellegrini and Popescu, 2011; Cretoiu and Popescu, 2014; Faussone-Pellegrini and Gherghiceanu, 2016). Moreover, TCs and their Tps can release different types of extracellular vesicles which act as important transporters involved in paracrine signaling, including the transfer of genetic material consisting mainly of miRNAs to neighboring cells (Cismaşiu and Popescu, 2015; Cretoiu et al., 2016; Marini et al., 2017a). Indeed, both physical and chemical interactions are suggestive of a prominent role of TCs in intercellular signaling (Cretoiu and Popescu, 2014; Cretoiu et al., 2016; Ratajczak et al., 2016; Marini et al., 2017a). Hence, TCs are believed to contribute to the maintenance of tissue homeostasis by regulating the surrounding microenvironment, and likely they participate in tissue repair and remodeling in both normal and pathological conditions (Cretoiu and Popescu, 2014; Bei et al., 2016; Ibba-Manneschi et al., 2016a,b). Interestingly, a large body of evidence supports the notion that TCs may be closely related to stem cell niches in different organs, including lung, heart, choroid plexus, skeletal muscle and skin, thus making them particularly attractive targets in the field of regenerative medicine (Popescu et al., 2009, 2011a, 2015; Popescu and Nicolescu, 2013; Bei et al., 2015a; Marini et al., 2017a).

Although TEM remains the method of choice to precisely identify TCs within tissues, it has been widely demonstrated that these cells are immunophenotypically characterized by CD34 antigen expression, being therefore also referred to as CD34-positive stromal cells/fibroblasts/fibrocytes/telocytes (Diaz-Flores et al., 2014). Since CD34 is also expressed by vascular endothelial cells, the combination of CD34 and CD31 immunostaining may help to unequivocally discriminate between TCs (CD34-positive/CD31-negative) and the endothelium (CD34-positive/CD31-positive), especially when vascular structures appear as profiles depending on the tissue section plane (Manetti et al., 2014, 2015; Rosa et al., 2018). Double immunolabeling for CD34 and c-kit/CD117, vimentin, platelet-derived growth factor receptor (PDGFR)-α or PDGFR-β may also be useful for distinguishing TCs from other stromal cells under light microscopy (Faussone Pellegrini and Popescu, 2011; Cretoiu and Popescu, 2014; Bei et al., 2016). In particular, it is widely proven that double immunopositivity for CD34 and PDGFR-α is a distinctive feature of TCs in many tissues and organs (Milia et al., 2013; Vannucchi et al., 2013; Cretoiu and Popescu, 2014; Alunno et al., 2015; Zhou et al., 2015; Marini et al., 2017b; Rosa et al., 2018). In addition, it is noteworthy that the immunophenotypical features of TCs may vary depending on the examined tissues and organs. TC subtypes characterized by the expression of different markers may even coexist within the same organ and they might have region-specific roles (Vannucchi et al., 2014; Chang et al., 2015; Vannucchi and Faussone-Pellegrini, 2016; Cretoiu et al., 2017; Marini et al., 2017b). For instance, TCs may exhibit either CD34, PDGFR-α or c-kit/CD117 in some organs, such as the heart, while they are CD34/PDGFR-α double-positive and c-kit/CD117-negative in others, such as the gastrointestinal tract (Vannucchi et al., 2013; Chang et al., 2015; Zhou et al., 2015; Vannucchi and Faussone-Pellegrini, 2016).

Besides cell morphology and immunophenotypical features, recent studies have also revealed that proteomic and gene expression profiles and miRNA imprints of TCs are rather different from those of other connective tissue-resident cells, such as fibroblasts, mesenchymal stem cells and microvascular endothelial cells (Cismasiu et al., 2011; Zheng et al., 2014; Albulescu et al., 2015; Wang et al., 2015; Zhu et al., 2015; Song et al., 2016).

Telocytes in skeletal muscle interstitium

TCs have been recently described in the skeletal muscle interstitium of mammals (rodents and humans), where they display the characteristic morphology and phenotype, both *in situ* and *in vitro* (Popescu et al., 2011b; Bei et al., 2015a; Arafat, 2016). By TEM, skeletal muscle TCs appear indeed spindle-shaped with very long and slender Tps characterized by a moniliform aspect, dichotomous branching and 3D network distribution forming a labyrinthine system alongside the striated muscle cells and vascular structures (Popescu et al., 2011b). *In situ* immunolabeling showed that these TCs constantly express different protein markers, such as c-kit/CD117, caveolin-1, CD34 (Fig. 1), vimentin, PDGFR-β and vascular endothelial growth factor (VEGF), and the same phenotypical profile was demonstrated in cell cultures (Popescu et al., 2011b; Suciu et al., 2012; Arafat, 2016). These markers and TEM data clearly differentiate TCs from other cell types, such as satellite cells (e.g. TCs are Pax7 negative) and fibroblasts (which are negative for CD34 and c-kit/CD117) (Popescu et al., 2011b; Arafat, 2016).

In the skeletal muscle interstitium, TCs are distributed throughout the perimysium and endomysium, where their Tps are in contact with nerve endings, blood vessels and myocytes (Popescu et al., 2011b; Arafat,

2016). In particular, it has been described that TCs are located parallel to the muscle fibers and often extend their Tps between small folds in the periphery of striated muscle cells (Popescu et al., 2011b; Arafat, 2016). The preferential perivascular or pericapillary location of TCs was confirmed by laminin labeling which showed that TCs and Tps are not enclosed or surrounded by a basal lamina in contrast to vascular mural cells (Popescu et al., 2011b; Suciu et al., 2012). Of note, Tps were often found to be interconnected by different types of intercellular junctions (e.g. manubria adhaerentia, puncta adhaerentia and small electron dense structures) (Popescu et al., 2011b). Shed vesicles and exosomes were frequently observed in the vicinity of Tps, suggesting a TC role in intercellular signaling (Popescu et al., 2011b). Furthermore, skeletal muscle TCs are often located in the close vicinity of satellite cells, striated muscle cells with regenerative features or even putative non-satellite progenitor cell niches, which may point toward their possible participation in muscle tissue regeneration and repair (Bojin et al., 2011; Popescu et al., 2011b).

Since a continuous interplay between stromal compartment and skeletal muscle fibers seems to take place from organogenesis to aging, it has been proposed that the 3D scaffold constituted by TCs and Tps might regulate a variety of physiological processes within the skeletal muscle tissue (Popescu et al., 2011b). Because of their unique long-distance connection attributes, TCs might play an essential part in integrating multiple signals essential for skeletal muscle fibers regulation and regeneration. Moreover, TCs might support paracrine signaling by the secretion of trophic factors (such as VEGF) for small vessels during angiogenesis and vascular remodeling (Suciu et al., 2012), and eventually guide both satellite and non-satellite progenitor cells undergoing migration and differentiation after trauma (Popescu et al., 2011b). On the basis of the expression of the stemness marker c-kit/CD117, some authors have also proposed that TCs could represent a unique progenitor cell type within human skeletal muscle stem cell niches (Bojin et al., 2011).

Interestingly, cells with ultrastructural characteristics typical of TCs are also located in the neuromuscular spindles and may play a role in the control of muscle tone and motor activity (Díaz-Flores et al., 2013). In fact, it has been shown that TCs form the innermost and partially the outermost layers of the external neuromuscular spindle capsule, as well as the entire neuromuscular spindle internal capsule. Immunohistochemically, neuromuscular spindle TCs express CD34, vimentin, and occasionally c-kit/CD117 (Díaz-Flores et al., 2013). In the internal capsule, Tps are organized in a dense network, which surround intrafusal striated muscle cells, nerve fibers and vessels, suggesting a passive and active role in controlling neuromuscular spindle activity, including their participation in cell-to-cell signaling. This latter hypothesis is further supported by the fact that shed vesicles and exosomes were often observed being released from and in the vicinity of Tps (Díaz-Flores et al., 2013). Finally, it was speculated that TCs may also participate in neuromuscular spindle development. Indeed, in human fetuses (22-23 weeks of gestational age) TCs and perineural cells seem to form a sheath, serving as an interconnection guide for the intrafusal

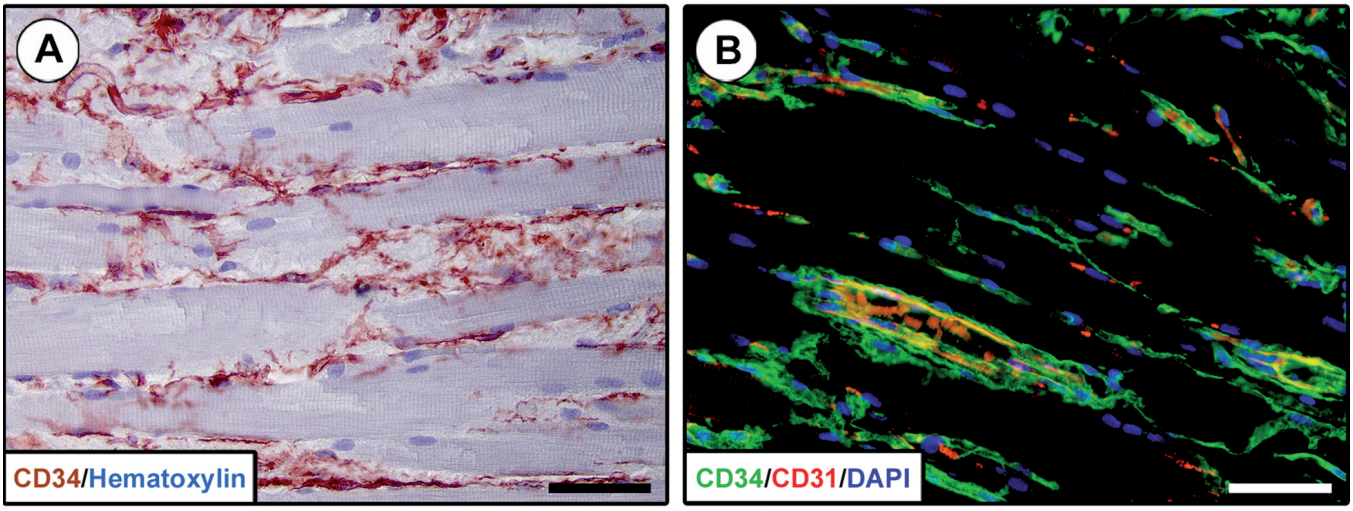

Fig. 1. Presence of CD34-positive telocytes (TCs) in skeletal muscle interstitium. Representative photomicrographs of human skeletal muscle tissue sections subjected to CD34 immunoperoxidase-based immunohistochemistry with hematoxylin counterstain **(A)**, and double immunofluorescence labeling for CD34 (green) and CD31 (red) with 4',6-diamidino-2-phenylindole (DAPI; blue) counterstain for nuclei **(B)**. CD34-positive TCs with long and moniliform processes surround skeletal muscle fibers and microvessels **(A, B)**. TCs are CD34-positive/CD31-negative, while vascular endothelial cells are CD34-positive/CD31-positive **(B)**. Scale bars: 50 μm.

structures (Díaz-Flores et al., 2013). A possible implication of neuromuscular spindle TCs in skeletal muscle pathologies has also been suggested. In particular, Díaz-Flores et al. (2013) reported that the number of CD34-positive TCs is increased in residual neuromuscular spindles between infiltrative musculoaponeurotic fibromatosis and varied in neuromuscular spindles surrounded by lymphocytic infiltrate in inflammatory myopathy.

Telocytes in cardiac muscle interstitium

The presence of typical TCs has been demonstrated in different anatomical parts of human, rat, mouse and pig heart, including the atrial and ventricular myocardial interstitium, epicardium and endocardium, where these stromal cells are supposed to participate in the regulation of cardiac homeostasis and regeneration (Bani et al., 2010; Kostin, 2010; Rusu et al., 2012c; Bani and Nistri, 2014; Bani, 2016; Bei et al., 2016; Tao et al., 2016; Tay et al., 2017; Varga et al., 2017). As far as the cardiac valves are concerned, it is proven that TCs do exist in human mitral, tricuspid and aortic valve (Yang et al., 2014). In addition, in humans it has been recently found that the sinoatrial node contains TCs establishing contacts with contractile myocardium and pacemaker cells, with Tps being mainly located near the specialized cells of the cardiac conduction system and close to blood vessels (Mitrofanova et al., 2018). However, the distribution of TCs does not appear homogeneous throughout the cardiac tissue, as it is supposed that atria are more abundant in TCs than ventricles (Kostin, 2010; Kucybala et al., 2017). Moreover, there is a significantly more numerous population of TCs in epicardium than in myocardium (Kucybala et al., 2017). TCs and their Tps are strategically placed near different cells including cardiomyocytes, cardiac stem cells, blood capillaries, nerve endings and other cells found in the cardiac stromal compartment (Bei et al., 2015a; Bani, 2016; Marini et al., 2017a). Noteworthy, a close association between TCs and either immature cardiomyocytes or putative stem/progenitor cells has also been observed in the subepicardium and epicardium, particularly in the part close to the coronary artery branching (Bani et al., 2010; Bani, 2016).

At present, cardiac TCs are the best *ex vivo, in vitro* and *in vivo* characterized TCs. Adult cardiac TCs express different markers such as CD34 (Fig. 2), c-

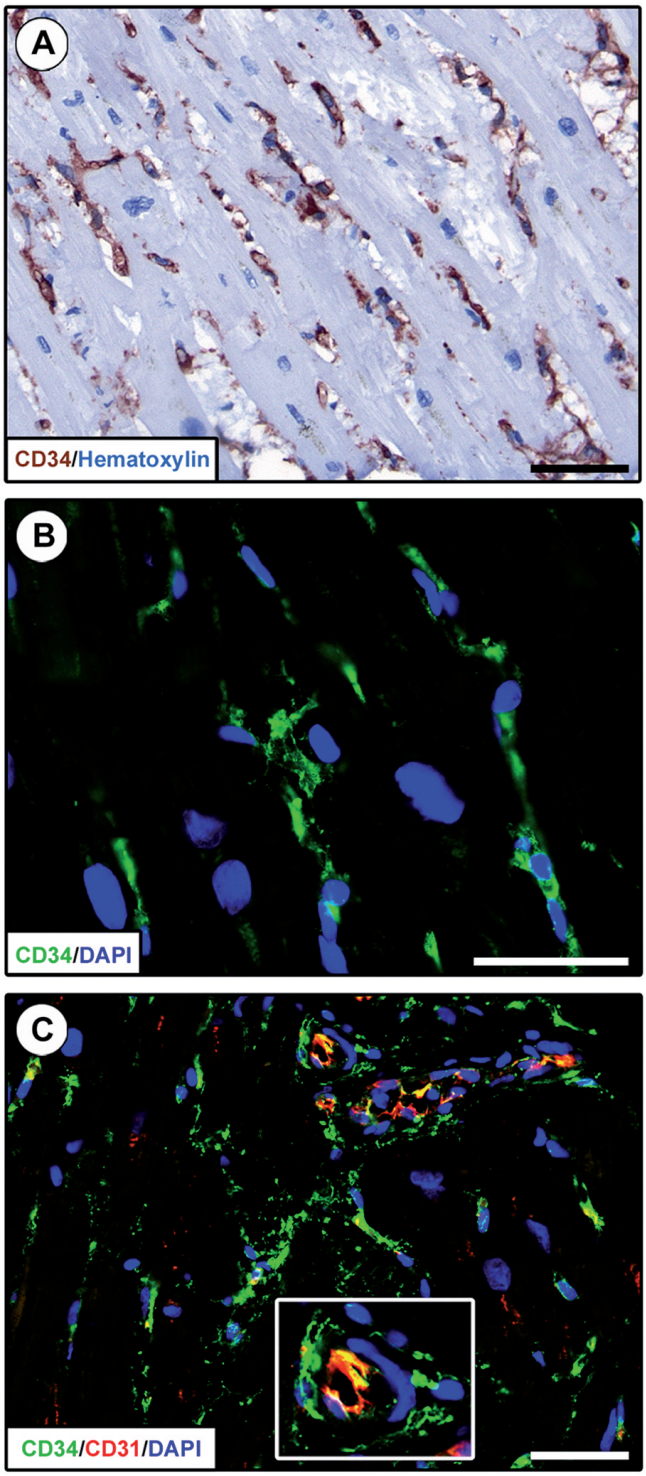

Fig. 2. Presence of CD34-positive telocytes (TCs) in cardiac muscle interstitium. Representative photomicrographs of human myocardium sections subjected to CD34 immunoperoxidase-based immunohistochemistry with hematoxylin counterstain **(A)**, immunofluorescence labeling for CD34 (green) with 4',6-diamidino-2-phenylindole (DAPI; blue) counterstain for nuclei **(B)**, and double immunofluorescence labeling for CD34 (green) and CD31 (red) with DAPI (blue) counterstain **(C)**. CD34-positive TCs with long and moniliform processes are located in the myocardial stromal space between cardiomyocytes **(A, B)**. TCs are CD34-positive/CD31-negative, while vascular endothelial cells are CD34-positive/CD31-positive **(C)**. Inset: higher magnification view of a CD34-positive/CD31-positive microvessel surrounded by CD34-positive TCs. Scale bars: 50 μm.

kit/CD117, PDGFR-α and -β and vimentin (Bani et al., 2010; Kostin, 2010; Rusu et al., 2012c; Richter and Kostin, 2015; Zhou et al., 2015; Bei et al., 2016). Furthermore, cardiac TCs in primary culture have been reported to express the embryonic stem cell marker Nanog and the myocardial stem cell marker Sca-1, suggesting that these cells may possess pluripotent properties (Chang et al, 2015; Bei et al., 2016). Cardiac TCs are also homogenously positive for the mesenchymal marker CD29, but negative for the hematopoietic marker CD45, indicating that TCs could be a source of cardiac mesenchymal cells (Bei et al., 2015b).

Although TCs seem to represent a small fraction of interstitial cells in the human heart, they are characterized by the presence of lengthy moniliform Tps which form a complex 3D network within the myocardial stromal space (Rusu et al., 2012c; Marini et al., 2017a). By using focused ion beam scanning electron microscopy (FIB-SEM), Cretoiu et al. (2014) have recently documented for the first time the whole ultrastructural anatomy of cardiac TCs. The 3D reconstruction of cardiac TCs by FIB-SEM tomography confirmed that these cells have long, narrow but flattened (ribbon-like) Tps, with humps generated by the podoms (Cretoiu et al., 2014). These TCs communicate with adjacent cells either through direct physical contacts (intercellular junctions) or by means of paracrine signaling (Marini et al., 2017a). In particular, cardiac TCs establish two types of intercellular junctions, namely homocellular and heterocellular junctions. The first are non-characteristic contacts between two neighboring TCs formed by simple appositions of plasmalemmas or by complex junctional areas accomplishing mechanical functions or allowing functional intercellular exchanges (Gherghiceanu and Popescu, 2012; Faussone-Pellegrini and Gherghiceanu, 2016; Marini et al., 2017a). Specifically, both TEM imaging and FIB-SEM tomography showed that TCs are interconnected by different types of adherens junctions, such as puncta adhaerentia minima, processus adhaerens (which connects overlapping Tps), recessus adhaerens (observed either between two Tps or between Tp and cell body) and manubria adhaerentia (Gherghiceanu and Popescu, 2012; Cretoiu et al., 2014; Faussone-Pellegrini and Gherghiceanu, 2016). TCs also form gap junctions allowing the transport of ions and small molecules between cells, which might be associated with a calcium-dependent mechanism of synchronic release of extracellular vesicles from numerous TCs. In addition, TCs may establish heterocellular junctions with stem cells, nerves, fibroblasts, endothelial cells, pericytes, macrophages and mast cells (Gherghiceanu and Popescu, 2012; Faussone-Pellegrini and Gherghiceanu, 2016; Marini et al., 2017a). Finally, *ex vivo* and *in vitro* evidence indicates that cardiac TCs may participate in intercellular signaling by shedding at least three different types of extracellular vesicles, namely exosomes, ectosomes and the so-called multivesicular cargos (Fertig et al., 2014; Cretoiu et al., 2016; Marini et al., 2017a).

As far as cardiac TC functions are concerned, these cells have been proposed to guide or 'nurse' putative stem cells and cardiomyocyte progenitors within cardiac stem cell niches (Popescu et al., 2009; Gherghiceanu and Popescu, 2010; Cismaşiu and Popescu, 2015). Of note, experimental evidence indicates that during organogenesis, TCs may coordinate the process of heart compaction from embryonic myocardial trabeculae by building a scaffold which may serve as guide for cardiomyocyte progenitors during their proliferation, differentiation and tissue integration (Bani et al., 2010; Popescu et al., 2015; Bani, 2016; Marini et al., 2017a). TCs presumably participate also in myocardial neoangiogenesis (Popescu et al., 2015). Moreover, considering that cardiac TCs and epicardial progenitor cells share the expression of some stemness markers (e.g. c-kit/CD117), TCs might represent a subpopulation of progenitor cells which could therefore be directly implicated in cardiac development and regenerative processes (Bani et al., 2010; Bei et al., 2015a; Bani, 2016). Interstingly, in zebrafish or newt the heart regenerates after amputation of the ventricle apex and TCs might be the first cells involved in this process (Popescu et al., 2015). During the lifespan, TCs seem to help in maintaining the homeostasis of stem cell niches by influencing the survival and activity of stem/progenitor cells (Bei et al., 2016). This important function may be mediated by a complex intercellular shuttle mechanism which involves bidirectional paracrine signals either between TCs and tissue-resident stem/progenitor cells or between TCs and cardiomyocytes mainly through the release of extracellular vesicles (Marini et al., 2017a). In particular, TC-released exosomes containing a cell-specific cargo of proteins, lipids and nucleic acids such as mRNAs, miRNAs and long non-coding RNAs seem to play a key role in the crosstalk between TCs and other cardiac cells during heart morphogenesis, cardiac physiology and injury response (Bei et al., 2015a, 2016; Cismaşiu and Popescu, 2015; Marini et al., 2017a). Indeed, depending on the specific types of miRNAs, cardiac TCs might substantially contribute to the local balance between quiescent and proliferative states of stem cells, as well as between self-renewal and differentiation of putative cardiomyocyte progenitors, with important implications in cardiac regeneration and repair (Cismaşiu and Popescu, 2015; Marini et al., 2017a). However, a decrease in TCs and tissue-resident stem cells occurs in the adult heart with respect to newborns, which may in part explain the reduction in the regenerative potential of the heart during aging (Popescu et al., 2015). Noteworthy, a recent experimental study in mice has shown that physical exercise may significantly increase the number of cardiac TCs, suggesting that the TC-mediated tissue regenerative capacity may be implicated in exercise-induced cardiac growth (Xiao et al., 2016).

Accumulating evidence indicates that cardiac TCs may be involved in a variety of cardiovascular diseases, such as myocardial infarction, cardiomyopathies, heart

failure, atrial fibrillation, isolated atrial amyloidosis and myxomatous valve degeneration (Mandache et al., 2010; Richter and Kostin, 2015; Ibba-Manneschi et al., 2016a; Kucybala et al., 2017). For instance, a possible association between the presence of amyloidosis in atrial tissue and TCs has been described in patients with long-standing atrial fibrillation. Specifically, Tps appear to surround and gather amyloid deposits likely trying to prevent their expansion in the adjacent areas of the cardiac interstitium (Mandache et al., 2010). In addition, heart failure due to dilated, ischemic or inflammatory cardiomyopathy is associated with a severe decrease in the number of myocardial TCs (Richter and Kostin, 2015). The reduction and loss of TCs in the failing human heart are not completely understood, but it has been proposed that such a severe impairment of the TC interstitial network could largely contribute to the alteration of the normal 3D myocardial organization and complex TC-mediated intercellular signaling mechanisms (Richter and Kostin, 2015; Ibba-Manneschi et al., 2016a). Moreover, given that TCs seem vital to intercellular signaling in the heart interstitium, it has been hypothesized that a decrease in their number may lead to important disturbances in bioelectrical communication contributing to arrhythmogenesis (Kucybala et al., 2017). In myocardial infarction, tissue ischemia and fibrosis have been suggested as the main causes of TC ultrastructural degenerative changes culminating in apoptotic cell death (Richter and Kostin, 2015). In fact, abnormal collagen deposition in areas of fibrosis is associated with reduction and loss of TCs and Tps, with the few remaining TCs displaying various ultrastructural alterations such as cytoplasmic vacuolization and shrinkage/shortening of the Tps resulting in the destruction of their typical three-dimensional interstitial network (Richter and Kostin, 2015). Instead, in stromal areas rich in amorphous material, TCs were more numerous and exhibited typical morphological characteristics with a Tp labyrinthine spatial arrangement (Richter and Kostin, 2015). As a consequence of TC reduction in the infarcted heart, the ability of these cells to maintain cardiac stem cell niche is unavoidably impaired, thus provoking depletion of cardiac stem cells and putative cardiomyocyte progenitors and likely exacerbating existing abnormalities.

The implication of cardiac TCs in heart pathology is further corroborated by recent *in vivo* studies (Manole et al., 2011; Zhao et al., 2013, 2014; Galrinho et al., 2016; Ibba-Manneschi et al., 2016a; Marini et al., 2017a; Varga et al., 2017). In rat experimental myocardial infarction, TCs were strongly reduced in fibrotic zones of the myocardium while a significant increase in TC number was reported in the border zone of infarction with respect to normal myocardium (Zhao et al., 2013). Of note, using different techniques (i.e. immunohistochemistry, electron microscopy and miRNA analysis) it has been demonstrated that the TCs located in the border zone were actively involved in neoangiogenesis either directly by physical nanocontacts with capillaries or indirectly by paracrine secretion of proangiogenic miRNAs and VEGF, as well as increased expression of nitric oxide synthase-2 (Manole et al., 2011; Galrinho et al., 2016). In this context, Zhao et al. (2013, 2014) reported that exogenous transplantation of cardiac TCs in the border and central zones decreased the infarction size and substantially improved cardiac function. In particular, histological analyses clearly revealed a reconstruction of the stromal network of TCs paralleled by an impressive reduction in myocardial tissue fibrosis (Zhao et al., 2013, 2014). The authors proposed that the aforementioned positive effects could also depend on the ability of transplanted cardiac TCs to promote the expansion, recruitment and differentiation of local cardiomyocyte progenitors (Zhao et al., 2013, 2014; Galrinho et al., 2016; Marini et al., 2017a). Further experiments were conducted to evaluate *in vivo* the possible beneficial effects of exosomes isolated from cardiac TCs in rats subjected to myocardial infarction (Yang et al., 2017). Strikingly, the administration of cardiac TC-derived exosomes resulted in decreased cardiac fibrosis, improved cardiac function, and increased angiogenesis (Yang et al., 2017). Moreover, endothelial cells cultured with cardiac TC supernatants or exosomes exhibited increased proliferation, migration, and formation of capillary-like structures, and these effects were all attenuated when exosomes were depleted from TC supernatants. These data provided novel insights into the cardiac TC function, suggesting that they may communicate with neighboring endothelial cells *via* the secretion of exosomes that potentially exert beneficial effects (Yang et al., 2017). Taken together, although the complex molecular mechanisms whereby the cardioprotective and reparative effects of TCs are accomplished remain to be fully elucidated, the aforementioned experimental data strongly put forward that cardiac TCs could represent a reliable source of cell therapy in cardiac regenerative medicine (Galrinho et al., 2016; Varga et al., 2017).

Telocytes in smooth muscle interstitium

Respiratory system

TCs have been identified by scanning and transmission electron microscopy in mouse and rat tracheal wall (Zheng et al., 2011; Rusu et al., 2012a) and in human and mouse terminal and respiratory bronchioles, as well as alveolar ducts (Popescu et al., 2011a). Tracheal and respiratory tree TCs are characterized by typical Tps, thin and long moniliform prolongations which abruptly emerge from a small cellular body and follow a longitudinal course alongside the airway tree and vascular system (Popescu et al., 2011a; Zheng et al., 2011; Rusu et al., 2012a). Tps ramify dichotomously, making a 3D labyrinthine network with complex homocellular and heterocellular junctions (Popescu et al., 2011a). Moreover,

immunohistochemistry revealed that airway TCs are c-kit-, vimentin- and CD34-positive (Popescu et al., 2011a; Zheng et al., 2011), and release shed vesicles or exosomes, likely sending macromolecular signals to neighboring cells and eventually modifying their transcriptional activity (Popescu et al., 2011a).

TCs have been detected in all stromal compartments of the tracheal wall, where they appear serially arranged with end-to-end connections of Tps and occasionally present primary cilia. Within the tracheal wall, TCs are preferentially located in the vicinity of blood vessels and smooth muscle cells, with Tps lining collagen bundles and frequently establishing stromal synapses with mast cells (Zheng et al., 2011; Rusu et al., 2012a). Moreover, TCs are numerous among smooth muscle cells in the wall of terminal bronchioles and often establish contacts with the basal lamina of smooth muscle cells (Popescu et al. 2011a). TCs also extend Tps along the basement membrane of the bronchiolar epithelium, surround nerves and have a close relationship with immune cells and stem cell niches in the peribronchiolar space (Popescu et al. 2011a).

All the aforementioned characteristics of airway TCs support the hypothesis of an integrative role for these cells in lung physiology, including mechanical support, regulation of airway secretion and contractility, intercellular signaling, immune surveillance and stem cell guidance, with potential implications in the pathogenesis of lung diseases (Popescu et al., 2011a; Zheng et al., 2011, 2012a; Rusu et al., 2012a; Shi et al., 2016; Song et al., 2016). For instance, it was hypothesized that TCs may be damaged in chronic obstructive pulmonary disease possibly contributing to loss of pulmonary tissue integrity and consequent development of emphysema (Cretoiu and Popescu, 2014). Moreover, a severe reduction in TCs has been reported in fibrotic pulmonary tissue from patients with scleroderma, suggesting that TCs may be implicated in the development of interstitial lung disease (Manetti et al., 2014). Of note, a recent experimental study in a mouse model of ovalbumin-induced asthma demonstrated that intravenous administration of lung-isolated TCs, alone or in combination with mesenchymal stem cells, could improve the allergen-induced airway inflammation and hyperresponsiveness, suggesting that exogenous TC transplantation might represent a new alternative for asthma therapy (Ye et al., 2017).

Gastrointestinal tract

Coordinated motor activity of gastrointestinal tract requires a complex interplay among various cell types including inhibitory and excitatory neurons, smooth muscle cells, interstitial cells of Cajal and other interstitial cell types (Vannucchi et al., 2013). In particular, three different interstitial cell types forming networks within the gastrointestinal muscle coat have been identified. Among them, the interstitial cells of Cajal, which are immunophenotypically positive for c-kit/CD117 and negative for CD34 and PDGFR-α, are considered pacemaker cells and main mediators of neurotransmission in the gastrointestinal tract (Faussone-Pellegrini and Thuneberg, 1999; Vannucchi et al., 2013). Another interstitial cell type, referred to as 'fibroblast-like cells' and likely implicated in enteric neurotransmission as suggested by the expression of SK3 channel which is involved in the control of neuronal excitability, is PDGFR-α-positive and c-kit/CD117-negative (Kurahashi et al., 2012; Vannucchi et al., 2013). Finally, cells with typical ultrastructural features of TCs (i.e. cells with Tps) were described to be CD34-positive (Fig. 3A-E) and c-kit/CD117-negative, and also express SK3 (Pieri et al., 2008; Vannucchi et al., 2013). Of note the described PDGFR-α-positive 'fibroblast-like cells' and CD34-positive TCs appear to share the same locations in the gastrointestinal tract wall (Pieri et al., 2008; Kurahashi et al., 2012; Vannucchi et al., 2013). Indeed, PDGFR-α/CD34 double immunolabeling has subsequently revealed that TCs and PDGFR-α-positive 'fibroblast-like cells' are the same interstitial cell type in the muscularis mucosae, submucosa and muscle coat of human oesophagus, stomach and small and large intestines (Fig. 3F) (Vannucchi et al., 2013).

In the human gastrointestinal tract, CD34/PDGFR-α double-positive TCs form a 3D interstitial network in the muscolaris mucosae, submucosa and in the interstitium between muscle layers, and an almost continuous layer at the submucosal border of the circular muscle layer (Vannucchi et al., 2013). Specifically, TCs surround smooth muscle bundles, nerve structures of the myenteric plexus, blood vessels, funds of gastric glands and intestinal crypts (Vannucchi et al., 2013). Moreover, the TCs located within the smooth muscle layers displayed the same location of interstitial cells of Cajal, running intermingled with them (Vannucchi et al., 2013).

Typical TCs were also identified by TEM both in rat and human esophagus (Rusu et al., 2012b; Chen et al., 2013), particularly beneath the basal epithelial layer, in submucosa, closely related to smooth and striated muscular fibers, and also in the adventitia. Within the esophageal muscle coat, TCs seem to have strategic positions, enwrapping bundles of smooth muscle cells or being situated between smooth muscle cells and blood vessels (Chen et al., 2013). Moreover, Small electron-dense nanostructures have been described between the membranes of smooth muscle cells and Tps (Chen et al., 2013). Esophageal TCs differed from interstitial cells of Cajal due to their typical ultrastructure characteristics (Rusu et al., 2012b). Using TEM, the presence of TCs was also demonstrated in the lamina propria of rat duodenum and jejunum just beneath the epithelial layer of the mucosal crypts and in between the smooth muscle cells of the muscularis mucosae (Cantarero Carmona et al., 2011; Cretoiu et al., 2012). In particular, their Tps display dichotomous branching and form a 3D network close to immune cells, smooth muscle cells or nerve bundles.

Several roles have been proposed for gastrointestinal TCs, including structural support, spatial relationships with different cell types, intercellular signaling and modulation of intestinal motility. Indeed, the TC networks might play a mechanical and supporting role being resistant and deformable following intestine movements, likely acting as stretch sensors (Cretoiu et al., 2012; Vannucchi et al., 2013). In addition, the

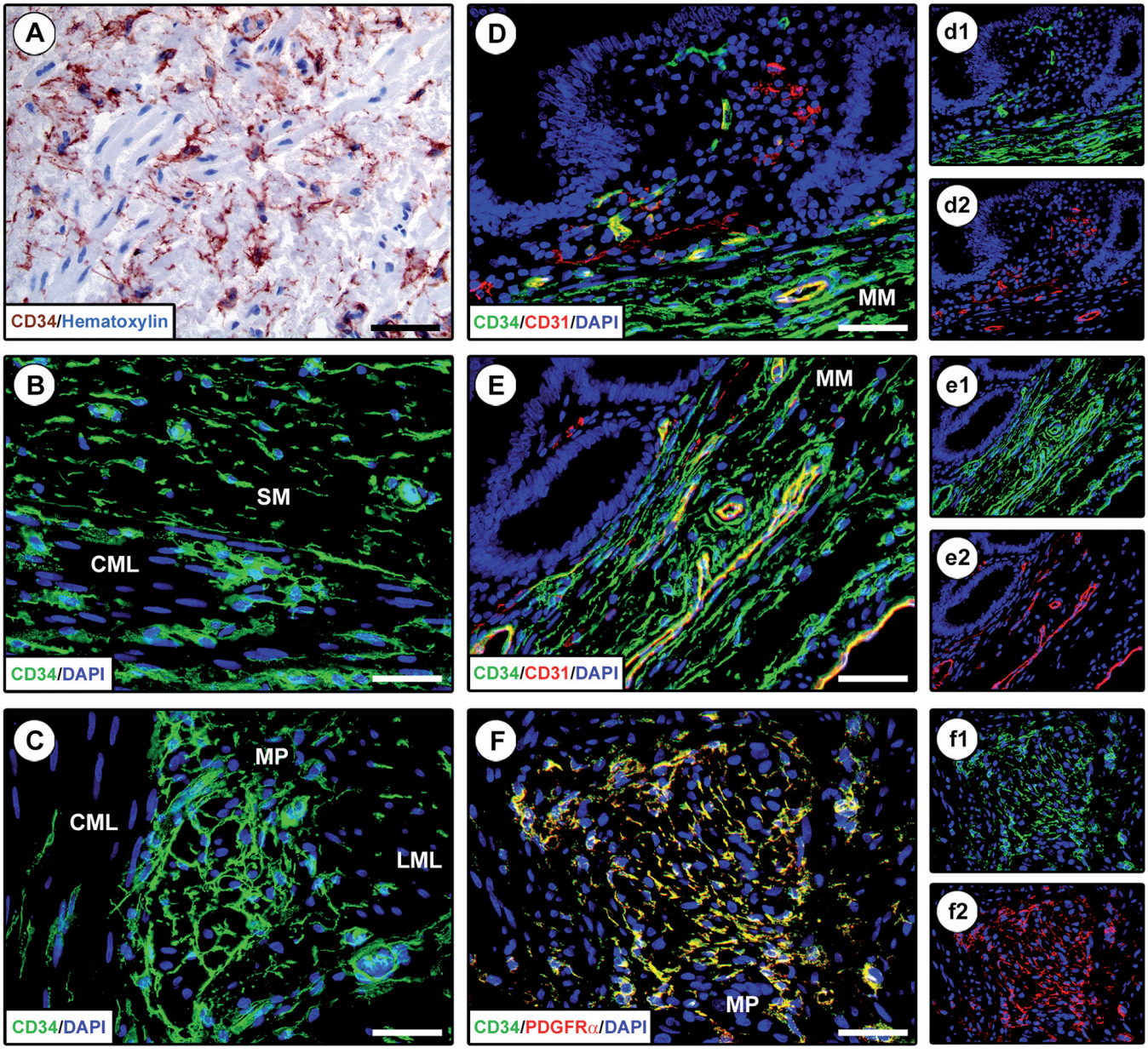

Fig. 3. Presence of CD34-positive telocytes (TCs) in gastrointestinal tract smooth muscle interstitium. Representative photomicrographs of human bowel sections subjected to CD34 immunoperoxidase-based immunohistochemistry with hematoxylin counterstain **(A)**, immunofluorescence labeling for CD34 (green) with 4',6-diamidino-2-phenylindole (DAPI; blue) counterstain for nuclei **(B, C)**, double immunofluorescence labeling for CD34 (green) and CD31 (red) with DAPI (blue) counterstain **(D, E)**, and double immunofluorescence labeling for CD34 (green) and PDGFR-α (red) with DAPI (blue) counterstain **(F)**. CD34-positive TCs with long and moniliform processes are demonstrated in the muscularis propria of esophagus **(A)** and muscularis propria **(B, C)** and muscularis mucosae **(D, E)** of ileum. TCs are CD34-positive/CD31-negative, while vascular endothelial cells are CD34-positive/CD31-positive **(D, E)**. CD34-positive/PDGFR-α-positive TCs form a network around colonic myenteric plexus ganglia **(F)**. The small panels on the right **(d1-2,e1-2,f1-2)** depict green and red fluorescence split channels from the respective merge panels **(D-F)**. CML, circular muscle layer; LML, longitudinal muscle layer; MM, muscularis mucosae; MP, myenteric plexus; SM, submucosa. Scale bars: 50 μm.

evidence that intramuscular TCs and interstitial cells of Cajal form intermingled networks surrounding smooth muscle cells and ganglia suggests that TCs might play a role in neurotransmission and regulation of gastrointestinal peristalsis, possibly contributing to spread the slow waves generated by the interstitial cells of Cajal (Vannucchi et al., 2013; Banciu et al., 2016). As proposed in other organs, gastrointestinal TCs could also have a role in intercellular signaling and control of local tissue homeostasis, especially when located near immune cells and stem cells of the intestinal niche, possibly acting as stem/progenitor cell adjutants involved in intestinal epithelium renewal (Cretoiu et al., 2012).

Recent histopathological investigations suggested that an impairment of the TC network might have important pathophysiological implications contributing to the architectural derangement of the gastrointestinal wall and gut dysmotility in different disorders (Milia et al., 2013; Manetti et al., 2015; Ibba-Manneschi et al., 2016a,b). In fact, a severe reduction in TCs has been reported during fibrotic remodeling of the gastric wall in scleroderma, as well as of the small and large intestine wall in Crohn's disease and ulcerative colitis, respectively (Milia et al., 2013; Manetti et al., 2014, 2015; Ibba-Manneschi et al., 2016a,b). In particular, in the terminal ileum of patients with Crohn's disease, TCs seem to selectively disappear in histopathologically affected areas, where fibrosis and architectural derangement of the intestinal wall are evident (Milia et al., 2013). Few TCs entrapped in a fibrotic extracellular matrix were present in the thickened muscularis mucosae and submucosa, and a discontinuous network of TCs was observed around smooth muscle bundles, ganglia and nerve strands in the affected muscularis propria (Milia et al., 2013). A similar loss of TCs accompaining the fibrotic remodeling of the colonic wall and likely contributing to colonic dysmotility was detected in specimens from ulcerative colitis patients (Manetti et al., 2015). Indeed, in the muscularis propria of advanced fibrotic ulcerative colitis, the TC network was found to be reduced or even completely absent around smooth muscle bundles and myenteric plexus ganglia (Manetti et al., 2015). Interestingly, at the myenteric plexus, the loss of the TC network was paralleled by the loss of interstitial cells of Cajal both in Crohn's disease and ulcerative colitis (Milia et al., 2013; Manetti et al., 2015). The close association between the TC reduction and the development of tissue fibrosis led to hypothesize that TCs could exert anti-fibrotic functions preventing abnormal activation of immune cells and fibroblasts and helping to maintain the normal organization of the extracellular matrix, or alternatively that TCs could represent a source of α-smooth muscle actin (SMA)-expressing profibrotic myofibroblasts (Díaz-Flores et al., 2015; Ibba-Manneschi et al., 2016a,b). Finally, it has been proposed that in the digestive tract TCs might represent the common cell of origin of both gastrointestinal stromal tumors and perivascular epithelioid cell tumors (Ardeleanu and Bussolati, 2011).

Urinary tract

TCs have been described in the upper lamina propria of the renal pelvis, ureter and urethra, as well as in kidney and urinary bladder of human and rodents (Zheng et al., 2012b; Vannucchi et al., 2014; Dobra et al., 2018). In the ureter and urinary bladder, it appears that numerous TCs are located between smooth muscle bundles, where their long Tps form a 3D network establishing intercellular contacts with smooth muscle cells, capillaries and nerve endings (Zheng et al., 2012b; Vannucchi et al., 2014). Furthermore, different subtypes of TCs have been identified by immunohistochemical studies in the human ureter and urinary bladder wall (Vannucchi et al., 2014; Vannucchi and Faussone-Pellegrini, 2016; Dobra et al., 2018). In particular, the TC subtype found around detrusor muscle bundles appears to be CD34/calretinin-positive and PDGFR-α/α-SMA/c-kit-negative (Vannucchi et al., 2014; Vannucchi and Faussone-Pellegrini, 2016).

Although the functions of TCs in the urinary system are not yet fully understood, the fact that detrusor muscle TCs are in close vicinity of and communicate with smooth muscle cells and nerve endings, and possess SK channels and receptors for growth factors and hormones suggests that they might be involved in bladder reflexes (Vannucchi et al., 2014; Wolnicki et al., 2016). Moreover, it has been hypothesized that TCs in the upper lamina propria of the bladder could act as signal transductors between the urothelium and the underlying nerve endings during bladder filling and emptying (Wolnicki et al., 2016). Of note, a recent study has demonstrated that neurogenic detrusor overactivity causes significant changes in TCs consisting mainly in a functional TC activation without cell loss or interruption of their 3D stromal network, suggesting that urinary bladder TCs may display an intrinsic adaptability to the pathological condition likely preserving their peculiar functions (Traini et al., 2018).

Female reproductive organs

TCs have been investigated in the female reproductive organs such as the uterus and fallopian tubes (Cretoiu and Cretoiu, 2016). In particular, TCs were described in human uterus and, recently, in the uterus and oviduct of rat and Chinese soft-shelled turtle (Ullah et al., 2014; Yang et al., 2015a,b; Cretoiu and Cretoiu, 2016). In humans, TCs were found in the endometrial stroma of the stratum functionalis and in the basal endometrium after menstruation, as well as in the myometrial interstitium (Aleksandrovych et al., 2016). Although ultrastructural analyses are currently the method of choice to precisely identify uterine TCs, the immunophenotypes reported for these cells include numerous markers such as CD34, c-kit/CD117, PDGFR-

α and -β, vimentin, CD44, desmin, cadherin-11, and nestin (Roatesi et al., 2015). The possible presence of different TC subpopulations has also been suggested (Aleksandrovych et al., 2016). *In vitro*, uterine TCs express the same markers as *in situ*. Moreover, uterine TCs were found to be double-positive for CD34 and PDGFR-α, as well as to express T-type Ca^{2+} channels and the gap junction protein connexin-43 (Cretoiu et al., 2013; Roatesi et al., 2015; Cretoiu and Cretoiu, 2016).

In human myometrium, TCs form a 3D network with multiple homocellular and heterocellular contacts as evidenced by TEM (Popescu et al., 2007; Cretoiu et al. 2013; Cretoiu, 2016; Cretoiu and Cretoiu, 2016). In particular, Tps dimensions appear different between non-pregnant and pregnant myometrium, with podomers being thicker in non-pregnant myometrium and podoms thicker in pregnant myometrium (Cretoiu and Cretoiu, 2016). Moreover, experimental studies in the rat have shown that TC number in endometrium and myometrium changes depending on the reproductive state (Salama, 2013). Specifically, endometrial TCs seem to increase and myometrial TCs decrease in pregnant respect to non-pregnant uteri. Conversely, the number of myometrial TCs increases significantly in postpartum uteri, while the immature uteri show the lowest number of TCs in both endometrium and myometrium (Salama, 2013). Given that TCs are believed to control smooth muscle cell contractions, the decrease in myometrial TCs in the pregnant uterus could in part contribute to the impediment of uterine contractility before term. Instead, their increase after delivery could be related with the uterus involution accompanied by myometrial contractions (Hatta et al., 2012; Salama, 2013). Similarly, in human uterus, the number of c-kit-positive TCs is reduced during pregnancy likely preventing myogenic contractions and early delivery (Horn et al., 2012). In fact, TCs seem to be involved in the electrical modulation of uterus smooth muscle cells, thus regulating myogenic contractile mechanisms during pregnancy (Aleksandrovych et al., 2016; Cretoiu and Cretoiu, 2016). This is strongly supported by the evidence that T-type calcium channels ($Ca_V3.1$ and $Ca_V3.2$) and SK3 small-conductance calcium-activated potassium channels are present in human myometrium TCs. Of note, the molecular expression of these channels changes in pregnant respect to non-pregnant myometrium, suggesting that TCs could play an important role in controlling the excitability of the uterine musculature in pregnancy and labor, and possibly act as sensors for mechanical stretching during uterine enlargement in pregnancy (Aleksandrovych et al., 2016; Cretoiu and Cretoiu, 2016). $Ca_V3.2$ is highly expressed in the TCs of the pregnant myometrium since steroid hormones and oxytocin might induce its expression leading to frequent and sustained contractions during labor (Cretoiu and Cretoiu, 2016). Instead, SK3 channels have been more often detected in non-pregnant myometrium (Cretoiu and Cretoiu, 2016). Stromal contacts between TCs and immune cells (e.g. eosinophils, macrophages, and plasma cells) have frequently been observed in the myometrial interstitium suggesting a possible role for TCs in the immune surveillance process which is crucial for the maintenance of pregnancy and uterine activation during labor (Roatesi et al., 2015). Uterine TCs could also serve as 'hormonal sensors', since there is evidence that some uterine stromal cells may play a role in endometrial growth and differentiation in a hormone-dependent manner. It has also been proposed that TCs could participate in proliferation of myometrial tissue and be involved in endometrium hyperplasia (Aleksandrovych et al., 2016; Cretoiu et al., 2013). Finally, a recent study suggested that the loss of TCs may have important implications in the pathogenesis of uterine leiomyoma, a benign tumor which originates from the muscle layer of the uterus (Varga et al., 2018).

In the fallopian tubes, TCs have been described either in humans (Popescu et al., 2007) or in different animal species such as mice (Dixon et al., 2010), rats (Yang et al., 2015a,b), turtles (Ullah et al., 2014) and hens (Gandahi et al., 2012). Tubal TCs are in close contact not only with one another but also with smooth muscle cells, nerve fibers and blood capillaries (Popescu et al., 2007). In particular, in the human fallopian tubes, TCs have been mainly described in the ampullar region, specifically in the lamina propria of the mucosa and within the tunica muscularis (Cretoiu and Cretoiu, 2016; Urban et al., 2016). Human tubal TCs express CD34, vimentin and c-kit/CD117 antigens, as well as progesterone and estrogen receptors (Cretoiu, 2016). TCs are considered as neuroeffector cells involved in smooth muscle activity of fallopian tubes (Gandahi et al, 2012). Moreover, the presence of estrogen and progesterone receptors on oviduct TCs allows to speculate that they could act as steroid sensors (Cretoiu et al., 2009). TCs could indeed behave as sensors of hormone levels which control smooth muscle cell contraction and movement of fallopian tube cilia by intercellular junctions or paracrine pathways (Cretoiu et al., 2009). Noteworthy, the number of oviduct TCs declines in women with endometriosis, tubal ectopic pregnancy and acute salpingitis (Cretoiu and Cretoiu, 2016). While in normal rat oviducts numerous TCs run parallel to each other and sometimes encircle microvessels and/or establish junctions with fibrocytes and pericytes, in endometriosis-affected rat oviducts TCs display typical features of cell degeneration (e.g. loss of organelles, swollen cell nucleus and mitochondria, and cytoplasmic vacuolization) with derangement of their 3D interstitial network which might promote tissue fibrosis and potentially impact on fertility (Yang et al., 2015b). Similar tubal TC ultrastructural modifications were found in a model of acute salpingitis-affected oviduct, where the relationship between TCs and tissue-resident stem cells resulted disrupted in the myosalpinx. The authors proposed that tubal TC decrease or loss are presumably due to local inflammation and are followed by interstitial fibrosis (Yang et al., 2015a).

Prostate

By means of light, transmission and scanning electron microscopy, recent *in vivo* and *in vitro* investigations provided evidence for the presence of TCs in the prostate of Mongolian gerbil, used as a rodent experimental model (Corradi et al., 2013; Sanches et al., 2017). Interestingly, it was noted that the gerbil prostate TCs acquire their typical morphology only in the postnatal period simultaneously with the differentiation of histological compartments of the gland. Prostate TCs have a small and fusiform cellular body with very thin and extremely long Tps and are present in the subepithelial area and also at the periphery of smooth muscle layers, where closely interconnected Tps form a complex network (Sanches et al., 2017). An important role in tissue organization during prostate development has been attributed to TCs (Sanches et al., 2017). Indeed, during prostate morphogenesis, CD34-positive TCs are initially found at the periphery of the developing alveoli, while later c-kit/CD117-positive and double-positive TCs can be observed. CD34-positive TCs also appear numerous in the interalveolar stroma and the region around the periductal smooth muscle (Sanches et al., 2017). Moreover, prostate TCs express estrogen receptors β and secrete transforming growth factor-β1, a factor that promotes the differentiation of the periductal and perialveolar smooth muscle and reduces epithelial proliferation during prostate development, thus stimulating prostatic gland morphological differentiation (Sanches et al., 2016, 2017). Therefore, it has been proposed that TCs could play differential roles during different stages of prostate development. Hence, initially TCs may support the differentiation of periductal and perialveolar smooth muscle, whereas subsequently these cells produce dense networks that compartmentalize the prostatic stroma microenvironment and alveoli and form a barrier between the interalveolar region and the periurethral smooth muscle (Sanches et al., 2017). Prostate TCs might accomplish these functions mainly through paracrine signaling. In addition, prostate TCs might have an auxiliary function in the regulation of gland contractility, as supported by the presence of numerous caveolae as well as gap junctions between TCs and smooth muscle cells (Sanches et al., 2016). A role of TCs in prostate remodeling and/or regeneration including their possible action as adult progenitor cells have also been suggested (Sanches et al., 2016). However, further studies aimed at understanding the biological functions of TCs and their possible implication in prostate pathology (e.g. benign prostatic hyperplasia and cancer) should be conducted.

Conclusions and perspectives

In the last few years great efforts have been made in investigating the morphological and functional features of TCs, a unique interstitial cell type that appears to participate in development, homeostasis and pathophysiology of a variety of organs and tissues, including the skeletal, cardiac and smooth muscles. The strategic tissue location of TCs and the ability of their Tps to build a complex stromal 3D network establishing multiple homocellular and heterocellular contacts with tissue-resident stem/progenitor cells, nerves, capillaries and muscle cells, along with the release of microvesicles suggest a special role for these cells in intercellular signaling. Besides being implicated in guiding and 'nursing' of immature cells during organogenesis and tissue regeneration/repair, it is believed that TCs could themselves represent a pool of precursors for various mesenchyme-derived cells in adulthood. Although these cells are still partly enigmatic, growing evidence indicates that TCs cannot be further considered negligible players in muscle tissue contraction coordination and regeneration. Indeed, presently TCs are attracting increasing attention for their potential applications in tissue engineering and regenerative medicine (Bei et al., 2015a; Boos et al., 2016; Mirancea, 2016). This represents an exciting area of future investigation, especially in the field of pathophysiology of muscle tissues which are endowed with poor regenerative potential after injury. Therefore, it is expected that a better understanding of the complex mechanistic insights underlying TC biology will provide useful directions for their potential therapeutic applications in a variety of skeletal, cardiac and smooth muscle tissue pathologies.

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Accepted April 25, 2018