Chapter 16
Myocardial Telocytes: A New Player in Electric Circuitry of the Heart

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Abstract The heart is an electrically conducting organ with networked bioelectric currents that transverse a large segment of interstitial space interspersed with the muscular parenchyma. Non-excitable connective cells in the interstitial space contributed importantly to many structural, biochemical, and physiological activities of cardiac homeostasis. However, contribution of interstitial cells in the cardiac niche has long been neglected. Telocyte is recently recognized as a distinct class of interstitial cell that resides in a wide array of tissues including in the epicardium, myocardium, and endocardium of the heart. They are increasingly described to conduct ionic currents that may have significant implications in bioelectric signaling. In this review, we highlight the significance of telocytes in such connectivity and conductivity within the interstitial bioelectric network in tissue homeostasis.

16.1 Background

All living cells and tissues are believed to be interlinked via bioelectric signaling mediated by ionic flow, electric fields, and voltage gradients to maintain interconnectivity [1]. The ability to maintain such bioelectric gradients across multidimensional networked cellular entities has important implications in health and disease state. Maintenance of bioelectric signaling, beyond electrical conduction per se, via differential resting membrane potentials among living cells, in particular, by non-excitable cells in the interstitial space has been highlighted to play important roles in developmental embryogenesis, tissue morphogenesis, and organ regeneration [2]. Indeed, gradients of membrane potentials within tissue niche are believed to direct

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stem cell proliferation and differentiation [3] that could have far-reaching but often underappreciated influence on cellular physiology.

The heart is an electrically conducting organ whereby known players in the parenchyma and interstitial space bridge the bioelectric gradients by electrotonic conductivity and electrical circuitry that are interconnected through connexins and gap junction and via other hitherto poorly studied intercellular adaptors/connectors. Non-excitable connective cells in the interstitial space contributed importantly to many structural, biochemical, and physiological activities of cardiac homeostasis. Heterocellular electrotonic coupling between interstitial cells such as fibroblasts, endothelial cells, smooth muscle cells, stem cells, and cardiomyocytes is only beginning to be recognized. In fact, in situ membrane connectivity of fibroblasts that juxtaposed cardiomyocytes is clearly evidenced in studies involving dye transfer experiments in sinoatrial node that signals their direct participation in physiological and perhaps pathological processes of electrical conduction in the heart [4]. The ability of cardiac fibroblasts to act as a bridge between conducting cardiomyocytes has been widely demonstrated in various coupling experiments [5, 6].

Telocytes are recently described interstitial cells with exceptionally long cellular processes found within cardiac parenchyma of the epicardium, myocardium, and endocardium that are believed to mainly act as structural supporting and nursing cells in the heart [7–9]. Despite their implicated intermediary role in the electrical activities of cardiac rhythm [7] and atrial fibrillation [10], very limited is known about the electrophysiological property of cardiac telocytes. We recently reported that human atrial and ventricular telocytes responded to H_2S by attenuating TGF-β1-stimulated KCa1.1/Kv1.1 and Kir2.1 gene expression. However, the presence of competent K^+ channels in telocytes and their implications in myocardial physiopathology remain largely unexplored. Human myometrial telocytes have been reported to express calcium-dependent hyperpolarization-activated chloride inward current [11], and SK3 outward potassium rectifier channels were reported in uterine telocytes [12]. Furthermore, transient outward potassium current that exhibited pacemaker-like activity was reportedly present in gastrointestinal telocytes [13], and hyperpolarization-activated cyclic nucleotide-gated (HCN) channel was found in telocytes of murine gastric antrum [14]. In this review, we highlight the significance of telocytes in such connectivity and conductivity within the interstitial bioelectric network in cellular homeostasis.

16.2 Telocyte: A New Player Within Interstitial Network

The seminary work by Popescu and colleagues in the last decade has identified and established telocyte as a distinct cellular entity, separate from fibroblasts [15] in the interstitial space of many organs, including the heart [16], bladder [17], lungs [18], and skeletal muscle [19]. Such telocytes are intimately contacting parenchymal tissues within the organs and are implicated in electrical conduction beyond their traditional structural supporting role in the myocardial system due to their close

proximity to nerve endings, cardiomyocytes [20], and pulmonary veins [10] in which atrial arrhythmias often originated in recurrent atrial fibrillation [21, 22].

Telocytes have previously been described as interstitial Cajal-like cells (ICLC) and were found in atrial and ventricular myocardium [23, 24] though very little was known of their function. Recently, telocytes have been increasingly recognized to participate beyond their passive supporting role but instead may play physiological diverse functions in the heart [25–27]. Telocytes have exceptionally long (10–1,000 μm), moniliform cellular processes named telopodes with intervening podoms and podomers that act as long-range cellular connector that transverses a vast interstitial network connecting different segments of the heart [28] including those of the epicardium [7, 29], myocardium [8, 26], and endocardium [9]. Their close proximity with cardiac progenitors and cardiomyocytes is believed to be important in the repair and regeneration of infarcted myocardium [7]. However, the mechanisms involving in such interactions are poorly understood.

The fact that telocytes were found widely in the developing and adult heart [16, 26] suggests that they are likely to have bioelectric modulatory function in their membrane potentials and capacitance due to their varying size and length in an adaptation towards microenvironment within cardiac niche. The extensive intercellular networks encompassed by telocytes with their long telopodes have been postulated to carry electrical signals and/or currents via intracellular cytoskeletal structures, perhaps in conjunction with transmitting electrical signals via gap junctions such as connexins that have been identified in a wide range of tissues [30, 31]. This unconventional concept is in congruent with the observed ionic species and specialized ion channels reported in telocytes found in a wide range of tissues. Indeed, telocytes were recently shown to exhibit voltage-gated ion channels whereby ion conductance characteristics of BKca and IKir currents were reported by our group [32] and ICaT by others [11, 33]. This supports that they may carry functional ionic currents that are likely contributing to important cellular cues and signaling within the interstitial network and in their electrical interaction with cardiomyocytes.

16.2.1 Telocyte: Physical Connector Bridging Electrotonic Conductivity

Human myocardial telocytes are clearly distinguishable from atrial or ventricular fibroblasts in culture whereby their characteristic long telopodes [27] with intersperse podomers and podoms that are often in contact with fibroblasts and other telocytes [34]. Consistent with distinctive telocyte identity [16, 26, 35], human telocytes express CD34, c-Kit, and PDGFR-β markers (Fig. 16.1)

We recently reported that the presence of inter-networking cardiac telocytes in the interstitial space improved myocardial strain post-myocardial transplantation of human-induced pluripotent stem cell (iPSC)-derived mesenchymal stem cells (iMSCs) into the infarcted myocardium [36]. Our results are consistent with the purported role of telocytes in mediating cardiac parenchymal and interstitial

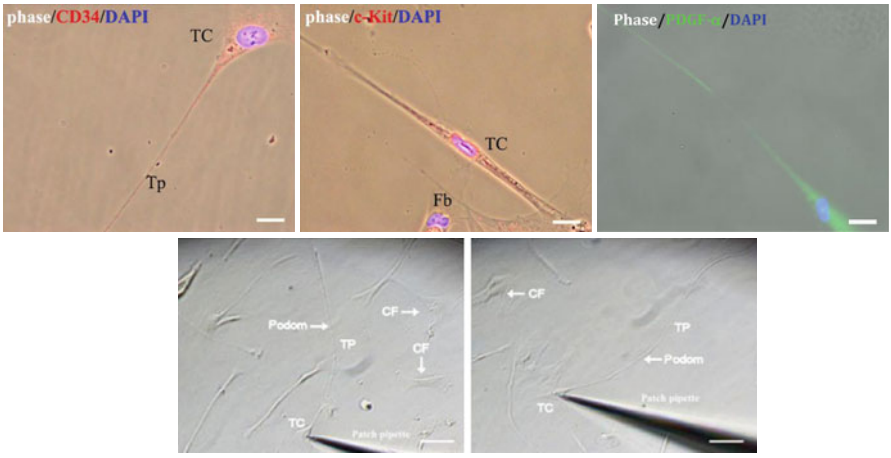

Fig. 16.1 Identification and characterization of myocardial telocytes in culture. Cells with extended telopodes that stained positive for CD34, c-kit, and PDGF-α that are characteristics of telocytes were patched with glass pipette in a whole-cell configuration for electrophysiology study (Images adapted from Sheng et al. [32])

interactions in promoting tissue repair [27]. Furthermore, we observed that myocardial telocytes intertwined with transplanted cardiac progenitors in the infarcted regions that coincided with increased angiogenesis [37] that is in agreement with beneficial effect of telocyte transplantation in recovering cardiac function [38]. The feasibility of long-range interaction between telocytes to maintain electrotonic conductivity within the cardiac niche cannot be discounted as the network of mechanical and biological interconnectivity from infarcted segment to other remote healthy segments of the myocardium was evidenced (Fig. 16.2) by close association of exogenously transplanted telocytes with resident telocytes [36, 37].

The decreased density of telocytes early post infarct (from 4 to 30 days) and their subsequent transplantation that decreased infarct size and improved cardiac function suggest physiological benefits of their present in the heart [38, 39]. Interestingly, such disappearance of telocytes coincides with the window of arrhythmogenic episodes often acutely experienced post-MI. In addition, heart failure patients experienced more than twofold decrease in the numbers of telocytes in the myocardium that coincided with remodeling of collagenous extracellular matrix in the cardiac niche [40] that is known to be a fertile substrate for pro-arrhythmogenic events [41]. Therefore, it may be tempting to surmise that loss of cardiac telocytes may compromise the three-dimensional spatial interconnectivity and perhaps conductivity of a continuous bioelectric gradient between the interstitial and parenchymal junctions within the myocardium that may further precipitate the electrical imbalance during post-MI period.

Heterocellular coupling of fibroblasts with cardiomyocytes in culture has been well documented to support wave propagation as far as 300 um through electrotonic interaction possibly via connexin43 (C×43) and C×45, though with major local

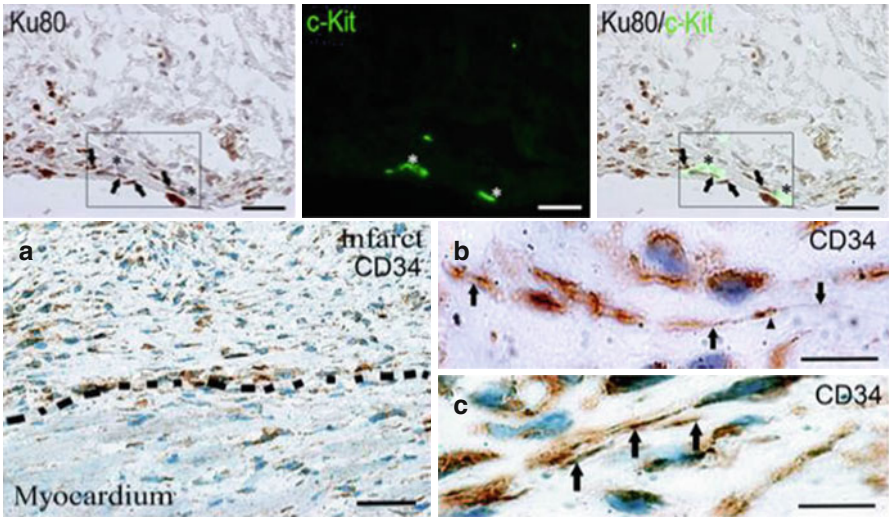

Fig. 16.2 Interconnected myocardial telocytes in infarcted murine myocardium showing connectivity of telocytes in the networked interstitial space in close proximity to cardiac progenitor cells and intact cardiac muscle fibers (Images adapted from Ja et al. [37] (*top panel*) and Miao et al. [36] (*bottom panel*))

conduction delays that may have implication in arrhythmias [5]. Similarly, telocytes are known to express C×43 [42] that may support electrotonic conduction and exert influence on cardiac arrhythmia. Therefore, more focused studies on coupling experiments between cardiomyocytes and telocytes for electrical interaction and integration within cardiac syncytium are warranted.

The elegant electron microscopy works provided by Popescu and colleagues attest to the possible existent of heterocellular coupling between telocytes and cardiomyocytes within myocardium. Indeed, beyond paracrine communication through telocytes released vesicles [43], direct heterocellular connection and coupling between telocytes and cardiomyocytes have been demonstrated previously such that atypical junctions formed by macromolecular complexes and nanopillars were observed between telopodes and sarcolemmal processes of cardiomyocytes [25]. This is in addition to the reported direct junctional connection between telocytes and cardiac progenitors [7, 9], between telocytes and cardiac stem cells via adherens junctions, puncta adherentia, and stromal synapses [44], and the existence of close apposition of telopodes against intercalated disks of cardiac muscle [22]. Collectively, these evidences support possible electrophysiological role of telocytes within the spatial architecture of cardiac syncytium.

Consistent with their intermediary function and role as bridging connector, a comprehensive proteomic analysis of cultured telocytes revealed that up to 4 % of cellular proteins were of cell junction components, thus affirming their key role in intercellular signaling and communication [15]. Tight adherens junctions were recently confirmed to exist between telopodes of telocytes in the myocardium [45],

and specific junctional contacts were noted between telocytes and cardiomyocytes and between telocytes and other interstitial cells [28] in the myocardium supporting their extended connectivity that is structurally supportive of probable electrotonic conductivity. Whether such connectivity is present or changed throughout developmental phase and disease stage or differs between species and exists within other tissues that experience distinct mechanical stress than the myocardium is largely unknown.

Besides their interconnectivity through gap junctions and adherens junctions, it is believed that telocytes could connect with cardiomyocytes through recently described intercellular nanotubes that directly link these heterogeneous cells together. Such connectivity has been reported in coupling experiments between fibroblasts and cardiomyocytes [46]. In fact, intercellular tunneling nanotubes ranging from 50 to 200 nm in length, perhaps in conjunction with connexin junctional proteins, may impart electrical signals between fibroblasts and cardiomyocytes via activation of voltage-gated calcium channels [47] and exchange of mitochondria [48]. Such interactions may partake in arrhythmogenesis as density-dependent biphasic influence of fibroblasts on conduction velocity and upstroke velocity through partial depolarization of cardiomyocytes has been previously observed [49]. Interestingly, such heterocellular connections between fibroblasts and cardiomyocytes are reminiscent of telopodes of telocytes in contacting neighboring cells in a three-dimensional cardiac niche. Nevertheless, feasibility of interstitial telocytes acting as intervening electrotonic bridge between conducting cardiomyocytes has largely been neglected thus far. Intriguingly, the ratio of cardiomyocytes to telocytes in rat myocardium was reported to be 70:1 [42], which was similar to ratiometric density reported between cardiomyocytes and fibroblasts that were observed to exert influence on arrhythmogenic events in heterocellular coupling experiments [49].

Despite the mounting evidence suggesting heterocellular connectivity between telocytes and cardiomyocytes, it is unclear if telocytes are possibly acting in the overall electrical circuitry as passive insulating bystander or active conducting player. Transfection of gap junction proteins and voltage-gated ion channels into telocytes in coupling experiments with cardiomyocytes would be of crucial interest to further elucidate such connectivity in establishing bioelectric gradient and their importance in maintaining cardiac electrical homeostasis, at least spatially within a localized interstitial to myocardial niche.

16.2.2 Telocyte: Gated Ion Channels and Function

To date, voltage-gated ion channels are increasingly being recognized in telocytes isolated from a wide range of tissues. In the human myometrium, patch-clamp recordings revealed a calcium-dependent hyperpolarization-activated chloride inward current but absence of L-type calcium channels, which was postulated to modulate myometrial smooth muscle contractions [11]. Furthermore, uterine telocytes have been reported to express mibefradil-sensitive T-type calcium channels

that is responsive to near-infrared low-level laser stimulation [50] that may be important in bioelectric signaling for modulating cellular behaviors during pregnancy and labor [45]. Furthermore, telocytes expressing calcium-activated chloride channels and inwardly rectifying chloride channels in gastrointestinal tract have been identified to mediate gut motility [51, 52]. Moreover, transient outward potassium current that mediated pacemaker-like activity was noted in gastrointestinal telocytes [13]. In addition, ionic currents were previously reported in telocytes whereby small conductance potassium SK3 channels in human myometrium [12] and in murine bladder [53] may be key to regulating muscular excitability and contractility. In addition, calcium-activated potassium channels in guinea pigs that regulate repolarization of stomach [54] and hyperpolarization-activated cyclic nucleotide-gated (HCN) channel of murine gastric antrum were identified [14].

We recently presented evidence of human ventricular and atrial telocytes that express large conductance Ca^{2+}-activated K^+ current (BK_{Ca}) and inwardly rectifying K^+ current (IK_{ir}) currents (Fig. 16.3) in a TGF-beta1-dependent manner indicating their importance in cardiac electrophysiology or electrotonic interactions in cardiac fibrosis [32]. We recorded and characterized ion currents in single telocytes with long telopodes using conventional whole-cell voltage clamp setup. Paxilline (a specific BK_{Ca} inhibitor)-sensitive and naringenin-responsive (a specific BK_{Ca} opener) currents were detected, confirming the presence of BK_{Ca} currents in atrial and ventricular telocytes. Furthermore, it was found that 4-aminopyridine-insensitive

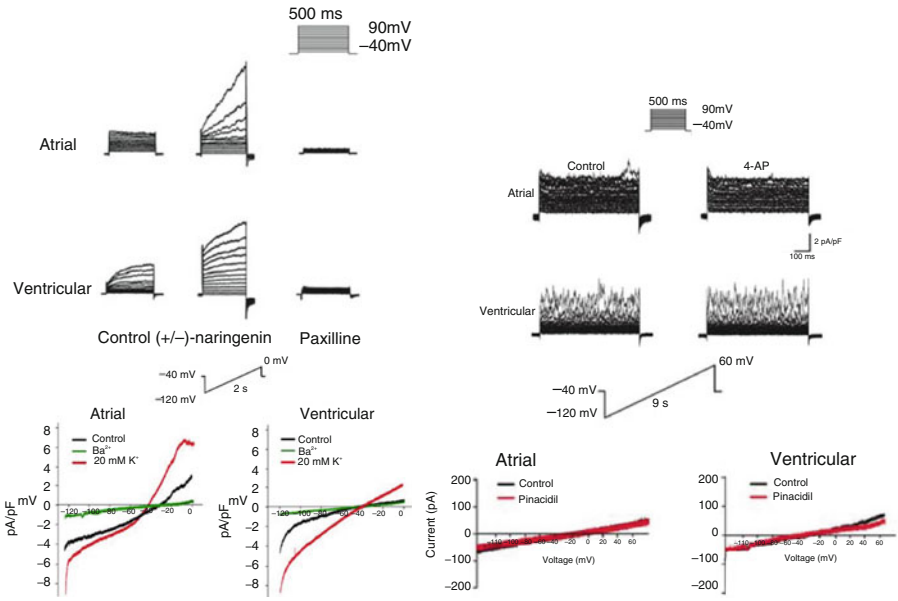

Fig. 16.3 Patch-clamp electrophysiology of atrial and ventricular telocytes. Both outward and inward potassium currents consistent with BKca and IKir were detected in the voltage-clamped cells (Images adapted from Sheng et al. [32])

and pinacidil (K_{ATP}-specific channel enhancer)-unresponsive currents were present, indicating the respective absence of transient outward currents (I_{to}) and ATP-sensitive K current (K_{ATP}) in myocardial telocytes. Nevertheless, inwardly rectifying K^+ currents that were attenuated by Ba^{2+} ion coupled with strongly spiking current amplitude in the presence of 20 mM K^+ bath solution were elicited in depolarizing telocytes, indicating the presence of IK_{ir} inward currents. The close proximity of telocytes to cardiac fibroblasts and cardiomyocytes suggests a probable role in facilitating mechano-electrical coupling of the heart. Consistently, calcium-releasing stores, such as caveolae, sarcoplasmic reticulum, and mitochondria that are typical of voltage-responsive cells, are present in telocytes [31]. Nevertheless, it is unclear if cellular resistance and capacitance of telocytes and resting membrane potentials would be sufficient to depolarize the heterocellularly coupled cardiomyocytes.

Human atrial fibroblasts are known to express a range of potassium channels that are important in proliferation and myofibroblast transformation Importantly, it is currently unclear the implications of greater potassium channel responsiveness observed in the atrial telocytes as compared to ventricular telocytes when stimulated with TGF-β1, a major mediator of myocardial fibrosis [32]. Although such dichotomy of cellular physiology coincided with the more robust fibrotic response of atrial fibroblasts as compared to ventricular fibroblasts in myocardial fibrosis [55, 56], it is unclear if the differential expression of such ion channels in atrial and ventricular telocytes has functional significance in cellular proliferation and overall interstitial conductivity or fibrotic response.

Telocytes are increasingly being recognized to carry ionic currents that may have important implications in behavioral response of local tissue niche. It is unclear if telocytes may exhibit regional-specific property in different organs. Experimental evidence supports the presence of functionally competent BK_{Ca} and IK_{ir} channels, but not I_{to} and K_{ATP} channels, in cardiac atrial and ventricular telocytes. It is unknown if telocytes could assume a different phenotype in different conditions such as those observed conversion of fibroblasts to myofibroblasts that may affect different cellular physiologies (e.g., smooth muscle actin expression [32]) that exerts distinct impact on the myocardial milieu.

16.3 Conclusion

There are mounting evidence that support functional present of a wide array of ion channels in telocytes found in various tissues. These channels are reported to contribute to telocyte electrophysiology but may also have other bioelectrical and mechanical significance in the tissue niche. Illustrating how these diverse ion channels contribute to function already well recognized in telocytes in mechanical supporting, topographical nursing, long-range sensing, microvesicle releasing, repair signaling, cytokine secreting, and immune system modulating would unveil a comprehensive road map of bioelectric traffic crisscrossing the intercellular highways of networked interstitial sphere in communicating with the parenchyma to sustain tissue homeostasis.

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References

1. Levin M. Endogenous bioelectrical networks store non-genetic patterning information during development and regeneration. J Physiol. 2014;592(Pt 11):2295–305.
2. Levin M. Molecular bioelectricity in developmental biology: new tools and recent discoveries: control of cell behavior and pattern formation by transmembrane potential gradients. Bioessays. 2012;34(3):205–17.
3. Edelstein L, Smythies J. The role of telocytes in morphogenetic bioelectrical signaling: once more unto the breach. Front Mol Neurosci. 2014;7:41.
4. Camelliti P, Green CR, LeGrice I, et al. Fibroblast network in rabbit sinoatrial node: structural and functional identification of homogeneous and heterogeneous cell coupling. Circ Res. 2004;94(6):828–35.
5. Gaudesius G, Miragoli M, Thomas SP, et al. Coupling of cardiac electrical activity over extended distances by fibroblasts of cardiac origin. Circ Res. 2003;93(5):421–8.
6. Sachse FB, Moreno AP, Abildskov JA. Electrophysiological modeling of fibroblasts and their interaction with myocytes. Ann Biomed Eng. 2008;36(1):41–56.
7. Popescu LM, Gherghiceanu M, Manole CG, et al. Cardiac renewing: interstitial Cajal-like cells nurse cardiomyocyte progenitors in epicardial stem cell niches. J Cell Mol Med. 2009;13(5):866–86.
8. Kostin S. Myocardial telocytes: a specific new cellular entity. J Cell Mol Med. 2010;14(7):1917–21.
9. Gherghiceanu M, Manole CG, Popescu LM. Telocytes in endocardium: electron microscope evidence. J Cell Mol Med. 2010;14(9):2330–4.
10. Kostin S, Popescu LM. A distinct type of cell in myocardium: interstitial Cajal-like cells (ICLCs). J Cell Mol Med. 2009;13(2):295–308.
11. Cretoiu SM, Cretoiu D, Marin A, et al. Telocytes: ultrastructural, immunohistochemical and electrophysiological characteristics in human myometrium. Reproduction. 2013;145(4):357–70.
12. Rosenbaum ST, Svalo J, Nielsen K, et al. Immunolocalization and expression of small-conductance calcium-activated potassium channels in human myometrium. J Cell Mol Med. 2012;16(12):3001–8.
13. Parsons SP, Huizinga JD. Transient outward potassium current in ICC. Am J Physiol Gastrointest Liver Physiol. 2010;298(3):G456–66.
14. Si X, Huang L, Gong Y, et al. Role of calcium in activation of hyperpolarization-activated cyclic nucleotide-gated channels caused by cholecystokinin octapeptide in interstitial cells of cajal. Digestion. 2012;85(4):266–75.
15. Zheng Y, Cretoiu D, Yan G, et al. Comparative proteomic analysis of human lung telocytes with fibroblasts. J Cell Mol Med. 2014;18(4):568–89.
16. Popescu LM, Manole CG, Gherghiceanu M, et al. Telocytes in human epicardium. J Cell Mol Med. 2010;14(8):2085–93.
17. Parajuli SP, Soder RP, Hristov KL, et al. Pharmacological activation of small conductance calcium-activated potassium channels with naphtho[1,2-d]thiazol-2-ylamine decreases guinea pig detrusor smooth muscle excitability and contractility. J Pharmacol Exp Ther. 2012;340(1):114–23.
18. Zheng Y, Li H, Manole CG, et al. Telocytes in trachea and lungs. J Cell Mol Med. 2011;15(10):2262–8.
19. Popescu LM, Manole E, Serboiu CS, et al. Identification of telocytes in skeletal muscle interstitium: implication for muscle regeneration. J Cell Mol Med. 2011;15(6):1379–92.

20. Zheng Y, Bai C, Wang X. Telocyte morphologies and potential roles in diseases. J Cell Physiol. 2012;227(6):2311–7.
21. Nguyen BL, Fishbein MC, Chen LS, et al. Histopathological substrate for chronic atrial fibrillation in humans. Heart Rhythm. 2009;6(4):454–60.
22. Mandache E, Gherghiceanu M, Macarie C, et al. Telocytes in human isolated atrial amyloidosis: ultrastructural remodelling. J Cell Mol Med. 2010;14(12):2739–47.
23. Hinescu ME, Popescu LM. Interstitial Cajal-like cells (ICLC) in human atrial myocardium. J Cell Mol Med. 2005;9(4):972–5.
24. Hinescu ME, Gherghiceanu M, Mandache E, et al. Interstitial Cajal-like cells (ICLC) in atrial myocardium: ultrastructural and immunohistochemical characterization. J Cell Mol Med. 2006;10(1):243–57.
25. Gherghiceanu M, Popescu LM. Heterocellular communication in the heart: electron tomography of telocyte-myocyte junctions. J Cell Mol Med. 2011;15(4):1005–11.
26. Bani D, Formigli L, Gherghiceanu M, et al. Telocytes as supporting cells for myocardial tissue organization in developing and adult heart. J Cell Mol Med. 2010;14(10):2531–8.
27. Popescu LM, Faussone-Pellegrini MS. TELOCYTES – a case of serendipity: the winding way from Interstitial Cells of Cajal (ICC), via Interstitial Cajal-Like Cells (ICLC) to TELOCYTES. J Cell Mol Med. 2010;14(4):729–40.
28. Gherghiceanu M, Popescu LM. Cardiac telocytes – their junctions and functional implications. Cell Tissue Res. 2012;348(2):265–79.
29. Gittenberger-de Groot AC, Winter EM, Poelmann RE. Epicardium-derived cells (EPDCs) in development, cardiac disease and repair of ischemia. J Cell Mol Med. 2010;14(5):1056–60.
30. Nielsen MS, Axelsen LN, Sorgen PL, et al. Gap junctions. Compr Physiol. 2012;2(3):1981–2035.
31. Smythies J, Edelstein L. Telocytes, exosomes, gap junctions and the cytoskeleton: the makings of a primitive nervous system? Front Cell Neurosci. 2014;7:278.
32. Sheng J, Shim W, Lu J, et al. Electrophysiology of human cardiac atrial and ventricular telocytes. J Cell Mol Med. 2014;18(2):355–62.
33. Cretoiu SM, Radu BM, Banciu A, et al. Isolated human uterine telocytes: immunocytochemistry and electrophysiology of T-type calcium channels. Histochem Cell Biol. 2015;143(1):83–94.
34. Mou Y, Wang Y, Li J, et al. Immunohistochemical characterization and functional identification of mammary gland telocytes in the self-assembly of reconstituted breast cancer tissue in vitro. J Cell Mol Med. 2013;17(1):65–75.
35. Xiao J, Wang F, Liu Z, et al. Telocytes in liver: electron microscopic and immunofluorescent evidence. J Cell Mol Med. 2013;17(12):1537–42.
36. Miao Q, Shim W, Tee N, et al. iPSC-derived human mesenchymal stem cells improve myocardial strain of infarcted myocardium. J Cell Mol Med. 2014;18(8):1644–54.
37. Ja KM, Miao Q, Zhen Tee NG, et al. iPSC-derived human cardiac progenitor cells improve ventricular remodelling via angiogenesis and interstitial networking of infarcted myocardium. J Cell Mol Med. 2015;20(2):323–32.
38. Zhao B, Liao Z, Chen S, et al. Intramyocardial transplantation of cardiac telocytes decreases myocardial infarction and improves post-infarcted cardiac function in rats. J Cell Mol Med. 2014;18(15):780–89.
39. Zhao B, Chen S, Liu J, et al. Cardiac telocytes were decreased during myocardial infarction and their therapeutic effects for ischaemic heart in rat. J Cell Mol Med. 2013;17(1):123–33.
40. Richter M, Kostin S. The failing human heart is characterized by decreased numbers of telocytes as result of apoptosis and altered extracellular matrix composition. J Cell Mol Med. 2015;19(11):2597–606.
41. Weber KT, Sun Y, Bhattacharya SK, et al. Myofibroblast-mediated mechanisms of pathological remodelling of the heart. Nat Rev Cardiol. 2013;10(1):15–26.
42. Popescu LM, Gherghiceanu M, Hinescu ME, et al. Insights into the interstitium of ventricular myocardium: interstitial Cajal-like cells (ICLC). J Cell Mol Med. 2006;10(2):429–58.
43. Fertig ET, Gherghiceanu M, Popescu LM. Extracellular vesicles release by cardiac telocytes: electron microscopy and electron tomography. J Cell Mol Med. 2014;18(10):1938–43.
44. Popescu LM, Fertig ET, Gherghiceanu M. Reaching out: junctions between cardiac telocytes and cardiac stem cells in culture. J Cell Mol Med. 2015;20(2):370–80.

45. Cretoiu D, Hummel E, Zimmermann H, et al. Human cardiac telocytes: 3D imaging by FIB-SEM tomography. J Cell Mol Med. 2014;18(11):2157–64.
46. Kohl P, Gourdie RG. Fibroblast-myocyte electrotonic coupling: does it occur in native cardiac tissue? J Mol Cell Cardiol. 2014;70:37–46.
47. Wang X, Veruki ML, Bukoreshtliev NV, et al. Animal cells connected by nanotubes can be electrically coupled through interposed gap-junction channels. Proc Natl Acad Sci U S A. 2010;107(40):17194–9.
48. He K, Shi X, Zhang X, et al. Long-distance intercellular connectivity between cardiomyocytes and cardiofibroblasts mediated by membrane nanotubes. Cardiovasc Res. 2011;92(1):39–47.
49. Miragoli M, Gaudesius G, Rohr S. Electrotonic modulation of cardiac impulse conduction by myofibroblasts. Circ Res. 2006;98(6):801–10.
50. Campeanu RA, Radu BM, Cretoiu SM, et al. Near-infrared low-level laser stimulation of telocytes from human myometrium. Lasers Med Sci. 2014;29(6):1867–74.
51. Zhu Y, Mucci A, Huizinga JD. Inwardly rectifying chloride channel activity in intestinal pacemaker cells. Am J Physiol Gastrointest Liver Physiol. 2005;288(4):G809–21.
52. Zhu MH, Sung IK, Zheng H, et al. Muscarinic activation of Ca2+-activated Cl- current in interstitial cells of Cajal. J Physiol. 2011;589(Pt 18):4565–82.
53. Lee H, Koh BH, Peri LE, et al. Functional expression of SK channels in murine detrusor PDGFR+ cells. J Physiol. 2013;591(Pt 2):503–13.
54. Kim YC, Suzuki H, Xu WX, et al. Ca2+ -activated K+ current in freshly isolated c-Kit positive cells in guinea-pig stomach. J Korean Med Sci. 2009;24(3):384–91.
55. Hanna N, Cardin S, Leung TK, et al. Differences in atrial versus ventricular remodeling in dogs with ventricular tachypacing-induced congestive heart failure. Cardiovasc Res. 2004;63(2):236–44.
56. Burstein B, Libby E, Calderone A, et al. Differential behaviors of atrial versus ventricular fibroblasts: a potential role for platelet-derived growth factor in atrial-ventricular remodeling differences. Circulation. 2008;117(13):1630–41.

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