Chapter 19
Electrophysiological Features of Telocytes

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Abstract Telocytes (TCs) are interstitial cells described in multiple structures, including the gastrointestinal tract, respiratory tract, urinary tract, uterus, and heart. Several studies have indicated the possibility that TCs are involved in the pacemaker potential in these organs. It is supposed that TCs are interacting with the neighboring muscular cells and their network contributes to the initiation and propagation of the electrical potentials. In order to understand the contribution of TCs to various excitability mechanisms, it is necessary to analyze the plasma membrane proteins (e.g., ion channels) functionally expressed in these cells. So far, potassium, calcium, and chloride currents, but not sodium currents, have been described in TCs in primary cell culture from different tissues. Moreover, TCs have been described as sensors for mechanical stimuli (e.g., contraction, extension, etc.). In conclusion, TCs might play an essential role in gastrointestinal peristalsis, in respiration, in pregnant uterus contraction, or in miction, but further highlighting studies are necessary to understand the molecular mechanisms and the cell-cell interactions by which TCs contribute to the tissue excitability and pacemaker potentials initiation/propagation.

19.1 Introduction

Telocytes (TCs) have been described in a variety of tissues/organs, including the gastrointestinal tract (colon, small intestine, etc.), urinary tract (urethra, prostate, etc.), respiratory tract (lungs, trachea, esophagus, etc.), skeletal muscle, heart, liver,

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X. Wang, D. Cretoiu (eds.), *Telocytes*, Advances in Experimental Medicine and Biology, 913, DOI 10.1007/978-981-10-1061-3_19

kidney, skin, eye, etc. [1–16]. Extensive immunohistochemical and electron microscopy studies have been conducted on TCs, but their unique features and dynamic changes in cell culture limited the in vitro electrophysiological analysis [17, 18]. In the last years, several patch-clamp studies have been done on TCs in order to identify the ion channels functionally expressed in these cells and to understand their possible contribution to pacemaker potentials. In this chapter will be presented the most recent in vitro electrophysiological studies conducted on TCs from different tissues and the current conclusions based on these studies. At the end of the chapter are discussed some open questions concerning the role played by TCs in the various organs.

19.2 Which Ion Channels Are Functionally Expressed in Telocytes?

Interstitial cells (IC), interstitial cells of Cajal (ICC), interstitial Cajal-like cells (ICLC), and telocytes (TC) were studied in terms of ion channels in a manner which highlights the functions of these cells (Table 19.1). Their distribution in different tissues influenced the evaluation of potential roles played by these cells. It can be assumed that the existence of long extensions, the cell motility, and the ability to develop gap junctions with neighboring cells influence the type of ion channels expressed and their degree of activation and local functions.

19.2.1 Potassium Currents

Voltage-sensitive potassium channels $K_v7.5$ are involved in the excitation of the interstitial cells of Cajal (ICC) associated with the myenteric plexus but not with those associated with the submuscular plexus of the colon [19]. Immunohistochemical and qRT-PCR characterization revealed the presence of $K_v7.5$ channels in the colonic ICC. Carbachol, a muscarinic acetylcholine receptor agonist, inhibited the potassium currents, indicating a cholinergic-dependent activation of the voltage-sensitive potassium channels. Moreover, XE991, a specific Kv7 channel blocker, was able to abolish completely the potassium currents [19]. These currents are very similar to the inwardly rectifying maxi-chloride currents that were previously described in the ICC associated with the mouse myenteric plexus from the small intestine [29]. Generally, the M-current is carried through heteromeric Kv7.2 and Kv7.3, Kv7.3 and Kv7.5, or Kv7.4 and Kv7.5, but in the case of colonic ICC, the current seems to be carried exclusively through homomeric Kv7.5 channels [19, 30–32]. By contrast to the myocytes, the ICC in the prostate are characterized by the absence of sensitive outward potassium currents [20]. Hyperpolarization-activated cyclic nucleotide currents (HCN) have been also described in mouse colonic ICC, but only HCN1 and HCN3 channel transcripts were detected [24].

Table 19.1 Ion channels functionally expressed described in TCs or ICC with a role in cellular excitability

Ion channels	Isoform	Patch-clamp evidence	Pharmacology	IHC/IF evidence	qRT-PCR evidence	Cellular description	Anatomical localization	Species	Reference
Outward rectifying K^+ channels	Kv7.5	Yes	XE991 (20 μM) Carbachol (1 μM)	Yes	Yes	ICC	Colonic intramuscular	Balb/c mice	[19]
	–	Yes	CsCl (130 mM or 15 mM) pipette	No	No	ICC	Prostate	Guinea pig	[20]
	Kv4.3	No	4-aminopyridine (4-AP; 5 mM)	No	No	TC	Atrial and ventricular	Human	[21]
	–	Yes	No	No	No	Vimentin(+)	Myometrium	Human	[22]
						c-KIT(−)			
						ICC-like			
Inwardly rectifying K^+ channels	Kir2.1	Yes	Ba^{2+} (0.5 mM)	No	No	TC	Atrial and ventricular	Human	[21]
ATP-sensitive K^+ channels (K_{ATP})	–	No	Pinacidil (30 μM)	No	No	TC	Atrial and ventricular	Human	[21]
Ca^{2+}-activated K^+ channels	Kv1.1	Yes	Paxilline (100 μM) Na-ringenin (10 μM)	No	Yes	TC	Atrial and ventricular	Human	[21]
	SK3	No	No	Yes	Yes	CD34(+) ICC-like	Myometrium	Human	[23]

(continued)

Table 19.1 (continued)

Ion channels	Isoform	Patch-clamp evidence	Pharmacology	IHC/IF evidence	qRT-PCR evidence	Cellular description	Anatomical localization	Species	Reference
Hyperpolarization-activated cyclic nucleotide (HCN) channels	HCN1 HCN3	Yes	CsCl (5 mM) ZD7288 (10 μM) Zatebradine (10 μM) Clonidine (100 μM) Genistein (10 μM)	No	Yes	ICC	Mid colon	CD1 mice	[24]
	–	Yes	CsCl (5 μM) ZD7288 (5 μM)	No	No	ICC	Gastric antrum	Balb/c mice	[25]
L-type Ca^{2+} channels	–	Yes	Nifedipine (1 μM) Bay K 8644 (1 μM) Ba^{2+} (1.8 mM) ext	No	No	IC	Urinary bladder	Guinea pig	[26]
	–	Yes	Nifedipine (1 μM) Ba^{2+} (5 mM) ext	No	No	IC	Prostate	Guinea pig	[20]
	–	Yes	No	No	No	TC	Myometrium	Human	[27]
T-type Ca^{2+} channels	–	No	Ni^{2+} (100 μM)	No	No	ICC	Urinary bladder	Guinea pig	[26]
	–	Yes	Ni^{2+} (10 μM)	No	No	IC	Prostate	Guinea pig	[20]
	Cav3.1 Cav3.2	Yes	Mibefradil (1 μM)	Yes	No	TC	Myometrium	Human	[27]
	–	Yes	Mibefradil (1 μM)	No	No	TC	Myometrium	Human	[28]
Ca^{2+}-activated Cl^- channels		Yes	Niflumic acid (10 μM)	No	No	IC	Prostate	Guinea pig	[20]
	–	Yes	$CdCl_2$ (50μM) CsCl (85 mM ext; insensitive)	No	No	TC	Myometrium	Human	[9]

ICC's presence was previously described in the atrial and ventricular myocardium [33, 34]. In order to understand the role played by TCs in heart contractility, a detailed analysis of the existing potassium currents was done. In atrial and ventricular TCs have been evidenced large conductance Ca^{2+}-activated potassium currents (BK_{Ca}) and inwardly rectifying potassium currents (Kir), by applying paxilline and naringenin, or Ba^{2+}, respectively. However, in these cells neither potassium outward currents nor the ATP-sensitive potassium currents have been identified by applying 4-aminopyridine, or pinacidil, respectively [21]. The presence of small-conductance calcium-activated potassium channels (SK_{Ca}) was also confirmed in human uterine TCs; their mRNA levels were significantly lower in pregnant myometrium compared to nonpregnant myometrium; and SK activators were suggested to reduce contractility in human myometrium [23].

19.2.2 Calcium Currents

Voltage-gated L-type calcium channels were evidenced in the urinary bladder based on nifedipine and Bay K 8644 response [26], prostate based on nifedipine response [20], and myometrium [27] based on TCs. These channels have different roles in other cell types. Voltage-gated L-type calcium channels are involved in heart automaticity [35–38]. TCs were identified in the heart [39], and it is possible that these cells possess such properties. Changes in urinary bladder function are made by streptozotocin-induced diabetes [40] and hypercholesterolemia [41] via voltage-gated L-type calcium channels. This may correlate with the involvement of these channels in cellular electrical automatism, in a manner relatively independent of tissue. TCs have the ability to achieve gap junctions with surrounding cells, and linking these issues may explain the existence of this automatism on the tissue. Androgens induce intracellular calcium increase via voltage-gated L-type calcium channels in prostate cancer cells [42]. This could explain the involvement of these channels in cell growth and multiplication. By extension, it is important to verify if these channels are involved in the cellular growth and multiplication in physiological conditions.

Voltage-gated L-type calcium channels are involved in augmentation of spontaneous uterine contractility in pregnant rat modulated by protease-activated receptor 2 [43]. This modulation of rhythmic contractions can be extrapolated that is important at TC level and not just at tissue and organ levels, due to long cell extensions that are influenced by mechanical forces and due to gap junctions of TCs. Voltage-gated L-type calcium channels are modulated by alpha5beta1 integrin-fibronectin interactions, with a role in myogenic tone and vascular wall remodeling [44]. Modulation of L-type Ca^{2+} channels by hypoxia [45] can create a logical link in the pathophysiological mechanism, explaining the importance of these channels at TC in the muscle tissue under the influence promoting automatism, but also on the tissue by integrating interactions between TCs and muscle cells, and achieving feed-

back loops that include various other factors such as the vascular factors and humoral factors consecutively.

Voltage-gated T-type calcium channels (Cav3.1 and Cav3.2 subunits) were evidenced in the urinary bladder [26], prostate [20], and myometrium [27] on cultured TC and tissue strips. These channels play various roles in the smooth muscle wall of the blood vessels. Cav3.1 has a role on the blood vessel relaxation in an NO-dependent manner [46] and can induce myogenic constriction in the mesenteric vessels [47] and hypoxia-dependent pulmonary vasoconstriction [48]. These dual behaviors and the dependence on hypoxia may be extrapolated to myometrium, emphasizing the role of TC in uterus development and growth under hypoxic conditions, or even in birth control. Cav3.2 has a role in the relaxation of coronary vascular smooth muscles [49] and augmented contractility during oxidative stress [50]. Cav3.2 functions of myometrium TCs may be involved in fetal growth vascular adaptation.

Intracellular Ca^{2+} concentration is an important excitability regulator in ICC, and besides the L-type and T-type calcium channels, the sodium-calcium exchanger (NCX3) contributes to the calcium homeostasis in the rat bladder [51].

19.2.3 Chloride Currents

Human myometrial TCs have been described to present calcium-dependent hyperpolarization-activated chloride inward currents [9]. Ca^{2+}-activated Cl^- channels on ICC were highlighted indirectly by chloride concentration modulation [52] and subsequently by response to $CdCl_2$ and CsCl [9] and response to niflumic acid [20].

19.2.4 Sodium Currents

Electrophysiological studies on the human myometrium failed to prove the presence of Na^+ currents in TCs [9, 22].

19.3 Are Telocytes Involved in the Pacemaker Activity?

Different types of cells, including ICC/TCs, can induce these changes through intracellular mediators, dynamic changes of ionic concentrations, or other local stimulating factors and can contribute to the existence of spontaneous electrical activity in various areas associated with initiation/propagation of pacemaker activities (Table 19.2).

Table 19.2 Spontaneous electrical activity[a] (pacemaker potentials) in ICC and TC

Anatomical localization	Cellular type	Recording technique	Pharmacology	Molecular mechanisms involved	Species	Reference
Urinary bladder	ICC	Patch clamp	Carbachol (10 nM) Atropine (1 μM) Nifedipine (1 μM) ATP (5 μM)	Muscarinic receptors L-type Ca^{2+} channels	Balb/c mice	[53]
	ICC	Patch clamp	Carbamylcholine (1 μM; 10 μM) Atropine (1 μM) 4-DAMP (1 μM)	M2 and M3 cholinergic receptors	Sprague-Dawley rats	[54]
Intestine (embryonic)	c-KIT(+) ICC	Calcium imaging	Nifedipine (1 μM)	L-type Ca^{2+} channels	ICR mice	[55]
Small intestine	ICC	Patch clamp Calcium imaging	Y25130 (10 μM) YRS39604 (10 μM) SB269970 (10 μM) DIDS (10 μM) Thapsigargin (5 μM) PD98059 (10 μM) SB203580 (10 μM) JNK II inhibitor (10 μM)	Serotonin (5-HT_3, 5-HT_4, 5-HT_7) receptors Cl^- channel Ca^{2+} ATPase (endoplasmic reticulum) Mitogen-activated protein kinases (p42/44; p38; c-jun NH_2-terminal kinase)	Balb/c mice	[56]
	ICC	Patch clamp	Histamine (10, 50 and 100 μM) 2-Pyridylethylamine (2-PEA; 50 μM) Cetirizine (100 μM) Dimaprit (50 μM) R-alpha-methylhistamine (R-alpha-MeHa; 50 μM) 4-methylhistamine (4-MH; 50 μM) U-73122 (5 μM) 5-fluoro-2-indolyl des-chlorohalopemide (FIPI; 1 μM) KT5720 (1 μM) Pyr3 (2 μM)	Histamine (H_1, H_2, H_3, H_4) receptors Ca^{2+} ATPase (endoplasmic reticulum) Phospholipase A Phospholipase C Phospholipase D TRPC3	Balb/c mice	[57]

(continued)

Table 19.2 (continued)

Anatomical localization	Cellular type	Recording technique	Pharmacology	Molecular mechanisms involved	Species	Reference
Urethra	ICC	Calcium imaging	H-89 (10 μM) Forskolin (10 μM) 8-Bromo-cAMP (1 mM)	Protein kinase A (PKA)	New Zealand white rabbits	[58]
	ICC	Calcium imaging	KB-R 7943 (3 μM)	NCX	New Zealand white rabbits	[59]
			SEA-0400 (1 μM) Caffeine (1 mM)	NCX		
			Tetracaine (100 μM)	RyR		
			2-APB (100 μM) U73122 (10 μM)	IP3R		
Fallopian tube	ICC-like/TC	Field potentials	–	–	Human	[60]
Myometrium	ICC-like/TC	Field potentials	–	–	Human	[61]

[a]Only the papers describing the electrical activity recorded on cell cultures were considered and not those dedicated to electrical recordings on strips of tissue

19.3.1 Role of Telocytes in the Pacemaker Activity of Internal Cavitary Organs

ICC-like cells isolated from the urethra [58, 59], bladder [62], prostate [63], *corpus cavernosum* [64], small intestine [56], embryonic intestine [55], Fallopian tube [60], and myometrium [61] present rhythmic firing activities acting also as neuromodulators [65]. These cells which act as pacemakers can modulate the activities of muscular, nervous, or secretory systems. In ICC from the guinea pig prostate, the spontaneous transient depolarizations are initiated with the opening of a small number of Ca^{2+}-activated Cl^- channels followed by a small membrane depolarization which triggers the calcium influx through T-type calcium channels, and furthermore the summation of calcium transients would manifest in the pacemaker potential that opens L-type calcium channels in ICC and their neighboring smooth muscle cells [20].

Patch-clamp experiments using cultured ICC from Balb/C mice urinary bladder revealed that these cells act as pacemaker, presenting individual spikes and bursting potentials similar to those observed in intact bladder tissues [53]. These spontaneous electrical potentials were inhibited by nifedipine (L-type voltage-gated calcium channel blocker) suggesting the involvement of these types of calcium channels [53]. Another study conducted on the rat bladder shows that spontaneous calcium activity is not influenced by L-type Ca^{2+} channels but rather by the T-type calcium channels [66]. The carbachol-induced calcium oscillations were blocked by atropine (a muscarinic receptor antagonist) [53, 54]. These findings suggested the possible role of voltage-gated calcium channels and muscarinic receptors in generating the pacemaker behavior in bladder ICC.

Although, electrophysiological recordings on TCs from human myometrium failed to prove the presence of Na^+ currents [9, 22], studies on transgenic mice have proved that longitudinal contractions of the uterus depend on a KIT signaling pathway of ICC-like cells [67]. On the other hand, the spontaneous electrical activity recorded on the ICC urinary bladder, small intestine, or urethra is based on intracellular calcium changes [53–59].

Calcium imaging on urethra ICC suggests that PKA, RyR, IP3R, and NCX are involved in ICC pacemaker activity [58, 59, 65]. The pacemaker activity in small intestine ICC is modulated through 5-HT_3 and 5-HT_4 receptors, chloride channels, Ca^{2+}-ATPase from the endoplasmic reticulum, phospholipase A, phospholipase C, phospholipase D, and TRPC3 [56, 57]. Calcium imaging studies on embryonic mouse intestinal ICC showed the role of L-type voltage-gated calcium channels in rhythmic electric activities [55]. These results revealed that the pacemaker mechanism is more complex and needs to be studied in an integrated manner. Calcium imaging studies on embryonic mouse intestinal ICC showed the role of L-type voltage-gated calcium channels in rhythmic electric activities [55]. In human myometrium and Fallopian tubes, Cajal-like cells/TC present spontaneous electric activity without a rhythmical pattern [60, 61].

ICC have been proposed to be the pacemaker cells in the gastrointestinal tract. In the small intestine, ICC associated with the myenteric plexus are generating slow waves that contribute to the rhythmic muscle contractions in the proximal intestine

[68]. In the colon, ICC associated with the submuscular plexus contribute to slow waves in canine, rat, mouse, and human [69–73], while ICC associated with the myenteric plexus do not contribute to slow waves in rat and mouse but generate rhythmic transient depolarizations of low and variable frequency as a result of L-type calcium channels activation [72, 73]. In the colon, ICC associated with myenteric plexus and intramuscular plexus are cooperating for the generation of pacemaker activity, and their excitability is regulated by the cholinergic inhibition of $K_v7.5$ channels [19]. Hyperpolarization-activated cyclic nucleotide currents from mouse colonic ICC are tonically activated by basal cAMP production and participate in the regulation of the pacemaker activity [24].

19.3.2 Role of Telocytes in the Pacemaker Activity of the Heart

Cav3.1 plays a role in sinoatrial node automaticity [74] and atrioventricular node automaticity [75]. Extrapolation of Cav3.1 involvement in TC automatism or in tissues containing TC automatism requires further investigations. Cardiac TCs have been suggested to be implicated in cardiac rhythm and atrial fibrillation [76, 77].

Sodium-calcium exchanger is involved in the pacemaker activity of the sinoatrial node [78] and in the overactive bladder in transgenic mice overexpressing NCX1.3 [79]. It is assumed that the activity of NCX on TC is modulated by ionic concentrations, by gap junctions, and telepods length that can develop the pacemaker functionality of a tissue rather than of individual and independent cells.

Ca^{2+}-activated Cl^- channels are found in many cell types and have different roles, among them being cardiac rhythmic depolarization, modulation of smooth muscle contraction, and taste receptor modulation. Their role is unknown in TCs, but the ability of these cells to have long extensions, gap junctions, and an increased dynamic of telepods apparently without stimulus creates opportunities for studying TC behavior under the influence of Ca^{2+}-activated Cl^- channels. TC feature to have a rhythmic electrical activity could be attributed to these channels. In vivo gap junctions between TC and adjacent cells could explain TC calcium dynamics changes in the presence of neighboring muscle cells and also the lack of in vivo electric automatism in the absence of gap junctions. Further studies are needed to assess the role of Ca^{2+}-activated Cl^- channels in TCs and their possible modulatory effect on chemoreceptors.

19.4 What's Next?

19.4.1 TCs Are Sensitive to Stimuli That Modulate Membrane Fluidity

It was evidenced that TC uterine motility can be modulated by mechanical stimuli via optical tweezer [28]. Blocking the voltage-gated T-type calcium channels, which

have a degree of mechanosensitivity, decreases this optical modulation by means of mechanical forces. Channels that have a degree of mechanosensitivity are sensitive to external mechanical stimulation but also to changes in membrane fluidity. Imatinib, a tyrosine kinase inhibitor that can be used in treating patients with chronic myeloid leukemia, may alter membrane fluidity through alteration of lipid metabolism [80]. Imatinib can decrease spontaneous contractile activity in guinea pig models and in human nonpregnant myometrium [81, 82]. Moreover, any change in the concentration of steroid hormones can cause changes in membrane fluidity and influence the functionality of mechanosensitive-like ion channels.

Future studies should focus on cell-cell communication and to explore the influence exerted on TC function by the surrounding myocytes through various factors that might affect membrane fluidity. Our hypothesis is that TCs could be involved in the stimulation of muscle development where mechanical stress is elevated (e.g., uterine musculature). Besides the uterus, TCs may represent a mechanical sensor that contributes to the pacemaker activity in the heart, gastrointestinal tract, or urinary tract.

19.4.2 Hormonal Regulation of TCs: Role in Birth Delivery

We hypothesize the TCs involvement in a feedback loop control of uterus that triggers the contraction initiation in birth delivery. The plasticity of the uterine musculature in pregnancy [83] might be under the influence of TCs that can modulate the activity of the surrounding myocytes. Rhythmic muscular activities are associated to significant vascular changes in the uterus involving endocrine and humoral factors release that could be detected by TCs.

The increase in placental volume and the level of secreted steroid hormones can modulate the cellular membrane fluidity [84, 85] and subsequently the activity of TCs, the function of myocytes, the frequency and force of contractions, and finally the endocrine feedback loop leading to fetal expulsion. These hypotheses should be tested in future studies on the interactions of TCs with surrounding cells in a such manner that can integrate mechanical and hormonal modulation with the therapeutic purpose of preventing the premature birth.

19.4.3 Integrating Information About TCs

There is a lack of comprehensive knowledge on the ion channels functionally expressed in TCs due to the variety of experimental approaches, including species, age differences, and methodology of analysis (in vitro and in vivo studies, staining on living and fixed tissue, presence or absence of neighboring cells, etc.). An important limitation in clinical studies is represented by the reduced number of samples from patients.

The studies conducted so far led to the hypothesis that TCs play a role in intercellular communication. However, the role of TCs in tissue excitability and pacemaker activity is still unclear. Therefore, it is imperative to connect all the information available on TCs and to understand their physiological role and their involvement in a variety of pathological conditions (e.g., psoriasis, myocardial infarction, focal lymphocytic sialadenitis, preeclampsia, ulcerative colitis, etc.) [86–90]. In conclusion, it is a great challenge to explain how TCs with distinct protein expression profiles (e.g., ion channels) from different tissues are correlated with similar functions, morphology, and dynamics of these cells.

Acknowledgments We are grateful for the financial support received through the program Partnerships in priority areas – PN II, UEFISCDI, Project No. 82/2012. B M Radu has a PhD fellowship from the Italian Ministry of Research (MIUR). DD Banciu is financed by the Sectoral Operational Programme Human Resources Development (SOPHRD), the European Social Fund, and the Romanian Government under the contract number POSDRU/159/1.5/S/141531.

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