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Telocytes: facts, speculations and myths

(Review article)

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Abstract: Telocyte (TC) is an interstitial cell type with a small cellular body and extremely long tentacle-like extensions. TCs were discovered a decade ago and have specific morphological characteristics, immunohistochemical and secretome profiles, electrophysiological properties, microRNA expression. Moreover, they are different in gene expression from other cells. TCs play an important role in plenty of processes. Apparently, they are involved in homeostasis, remodelling, regeneration, repair, embryogenesis, angiogenesis and even tumorigenesis. "Telocytes need the world", was emphasized by Professor Popescu and it will be actual at any time. This review summarizes particular features of TCs in different organs and systems, emphasizing their involvement in physiological and pathophysiological processes.

Key words: Interstitial Cajal-like cells (ICLC), telocytes, telopodes, fibroblast-like cells, CD34.

History

About one decade ago, there has been discovered a novel cell type with unique morphology and functions. L.M. Popescu's group from Bucharest, Romania, focused on interstitial (stromal) cells in the connective tissue of many organs of humans and laboratory mammals, which named interstitial Cajal-like cells (ICLC) in 2005. A few years later, in 2008, M.S. Faussone-Pellegrini and her team from Florence, Italy, described ICLC in the muscle coat of the human gut and noticed they consistently differed from the canonical gastrointestinal cells of Cajal (ICC) in both ultrastructure and immunophenotype. In 2010 the acronym ICLC was replaced with a more appropriate name one and introduced to scientific world for the first time in the paper "*TELOCYTES – a case of serendipity: the winding way from Interstitial Cells of Cajal (ICC), via Interstitial Cajal-Like Cells (ICLC) to TELOCYTES*" in the Journal of Cellular and Molecular Medicine. From that time, this novel cell type became known as the TCs (using the Greek affix "Telos"). Nowadays, all cell name's synonyms (ICLC, fibroblast-like cells, telocytes) are widely used in publications [1–4].

Morphology of telocytes

The TC has a small, oval-shaped cellular body, containing nucleus, surrounded by a small amount of cytoplasm. The cellular body average dimensions are, as measured on TEM images: 9.39 μm ± 3.26 μm (min = 6.31 μm; max = 16.42 μm). The nucleus occupies about 25% of the cell volume and contains clusters of heterochromatin attached to the nuclear envelope.

The perinuclear cytoplasm is rich in mitochondria (which occupy about 5% of the cell body) particularly in podoms, which contain a small Golgi complex, as well as the elements of rough and smooth endoplasmic reticulum and cytoskeletal elements (thin and intermediate filaments). The cell periphery is represented by the usual plasmalemma, with no (or thin and discontinuous) basal lamina, and some caveolae (about 2–3% of cytoplasmatic volume; ~0.5 caveolae/μm of cell membrane length) [1–7].

Telocytes have a variable number of telopodes (Tps) (very long cellular extensions), which are probably the longest cellular prolongations in the human body. Tps are made by an alternation of dilated portions, named podoms (250–300 nm), containing mitochondria and endoplasmic reticulum and podomers (~80 nm) with thin segments. The podomers are thicker in nonpregnant myometrium than in pregnant one (~82 versus 75 nm), and the podoms were thicker in pregnant myometrium (~316 versus 269 nm) [1, 2, 5]. The shape of the TCs depends on the number of their telopodes (Tps): piriform for one prolongation, spindle for two Tps, triangular for three, stellate, etc. Their spatial appearance is that of a polyhedron with a different number of vertices, depending on their Tps number [8].

Tps form a three-dimensional network that may function as a scaffold to define the correct organization of tissues and organs [9]. Mandache *et al.* mentioned that telopodes develop a wrapping activity gathering masses of amyloid fibrils, partially or totally surrounding them. These cellular 'bags' made by telopodes have sometimes inner cytoplasmic processes with honeycomb-like appearance which fragments in bunches the amyloid fibrils [10].

Huizinga *et al.* proposed eight basic ultrastructural criteria for TC identification in 1997 ("**gold standard**"). Later Popescu and his group added two more criteria and formed "**platinum standard**" of diagnosis for TCs [3, 11, 12].

1. Location: among tubulo-alveolar structures, in the non-epithelial space
2. Close contact with target: nerve bundles, and/or epithelia, and/or smooth muscle cells, and/or capillaries, immunoreactive cells by "stromal synapses"
3. Characteristic cytoplasmic processes
   a. Number: (1–5, frequently: 2–3)
   b. Length: tens to hundreds of μm
   c. Thickness: uneven caliber, <0.5 μm with dilations, but very thin from the emerging point
   d. Aspect: moniliform, usually with mitochondria in dilations
   e. "Ca^{2+} release units": present
   f. Branching: dichotomous pattern
   g. Organization in network: labyrinthine system of overlapping cytoplasmic processes
4. Gap junctions: with smooth muscle cells or with each other
5. Basal lamina: occasionally present
6. Caveolae: 2–4% of cytoplasmic volume; ~0.5 caveolae/μm of cell membrane length
7. Mitochondria: 5–10% of cytoplasmic volume
8. Endoplasmic reticulum: about 1–2% of cytoplasmic volume, either smooth or rough
9. Cytoskeleton: intermediate and thin filaments, as well as microtubules
10. Myosin thick filaments: undetectable

Some characteristics (morphology and density) of telocytes change with aging and some conditions. For instance, amount of TCs is decreasing in liver fibrosis, mirroring the recent findings as described in the colonic wall in ulcerative colitis, the terminal ileum of patients affected by small bowel Crohn's disease, and skin, gastric wall, lung and myocardium in systemic sclerosis [13, 14]. In pregnant uteri endometrial TCs increase, compared with non-pregnant, in spite of a significant decline in the number of myometrial TCs. Postpartum uteri show the highest significant count of myometrial TCs and non-significant difference in endometrial TC count, as compared with the adult non-pregnant group [15, 16]. Alunna *et al.* revealed that telocytes were markedly reduced in minor salivary glands from primary Sjögren's syndrome patients compared to normal and

non-specific chronic sialadenitis of minor salivary glands. Such a decrease was associated with both worsening of glandular inflammation and progression of ectopic lymphoid neogenesis [17]. Li *et al.* mentioned that TCs in vasculature could appear with slightly modified morphology, with more spherical, shorter and thicker prolongations [18].

Cantarero *et al.* have identified in TCs the presence of a single non-motile cilium called primary cilium. Primary cilia contain a 9+0 axoneme, consisting of nine outer doublet microtubules but lacking the central pair of microtubules. Except for nodal cilia, primary cilia are thought to lack axonemal dyneins and be immotile. Primary cilia in TCs might play a role in signalling processes within the vascular niche [19]. Moreover, in arterioles, TCs often send Tps bordering the tunica adventitia, while in venules and capillaries, they were located parallel with the longitudinal axis of the smooth muscle cells of the vessel wall [19]. The density of TCs in blood vessels is different, by region [18].

Distribution of telocytes

Telocytes have been found in a large variety of organs and are distributed in vertebrates (fish, reptiles, birds, mammals, including human) (Table 1) [5, 9, 15].

Table 1. Localization of telocytes in various organs.

Organ	Localization of telocytes
Blood vessels (coronary arteries, internal thoracic arteries and carotid arteries)	on the endothelial surface [19, 20]
Bone marrow	in close spatial relationships with small blood vessels and/or capillaries [20]
Canine dura mater	closed to capillary and surrounded by a great deal of collagen fibers [9]
Duodenum	in the lamina propria, immediately below mucosal crypts [19]
Endocardium	in the subendothelial layer, between the endocardial endothelium and the cardiomyocytes bundles [21–23]
Endometrium	in the human endometrial stroma of the stratum functionalis and in the basal endometrium after menstruation [24–27]
Epicardium	in human subepicardial area, in between collagen fascicles, in the neighbourhood of a cardiomyocyte [28]
Esopagus	in lamina propria of human oesophageal mucosa, submucosa, as well as in muscular layer, in the adventitia [29, 30]
Exocrine pancreas	in close proximity with both secretory acini and exocrine epithelial ducts and regulatory nerves and blood vessel apparatuses [31–34]
Eye	in limbus, sclera and uvea of eye [35]

Organ	Localization of telocytes
Fallopian tube	in mucosa and muscular layer among smooth muscle fibres [3, 11, 36]
Fascia lata	between collagen fibers [37]
Gallbladder	in the muscularis propria and in the bile ducts [38–40]
Heart valves	in the interstitial layer of human cardiac valves in all three valve types (mitral, tricuspid and aortic), in both apex and base of heart valves [41]
Ileum	in the in the muscularis and the lamina propria [42]
Jejunum	in the lamina propria of jejunum just beneath the epithelial layer of the mucosal crypts and in between the smooth muscle cells of muscularis mucosae [43]
Kidney	around renal tubules and vessels in the kidney cortex interstitium (in sub-capsular space) [44–46]
Liver	in the Disse space of the liver [47]
Lungs	in interstitial space of a intralobular bronchiole, in terminal and respiratory bronchioles, in alveolar ducts [48, 49]
Mammary gland	in non-epithelial tissue compartments [50–52]
Meninges and choroid plexus	in the vicinity of putative stem cells [53]
Mesentary	in the vicinity of and intermingled with capillaries, nerve bundles, adipocytes and other interstitial cells, mainly macrophages and fibroblasts [54]
Minor salivary glands	formed an almost continuous layer encircling both the excretory ducts and the secretory units [17]
Myocardium	TCs represent a small fraction of human cardiac interstitial cells [55–60]
Myometrium	in the myometrial interstitium [15, 61, 62]
Neuromuscular spindles	form the innermost and (partially) the outermost layers of the NMS capsule, and the internal capsule [63]
Parotid glands	around ducts of various calibers [64]
Placenta	in the large stem villi, with their long, slender process surrounding the blood vessel wall, or interposed between arterioles and the trophoblast basement membrane in small stem villi [65–67]
Pleura	in human parietal pleura, the sub-mesothelial space contained numerous telocytes [68]
Prostate	in prostatic stroma, especially in the adjacent epithelial area [69]
Pulmonary vein	at the internal limit of the myocardial sleeves, parallel with the long axis of the pulmonary vein [70]

Table 1. Cont.

Organ	Localization of telocytes
Renal pelvis	in the lamina propria [71]
Skeletal muscles	in interstitium: [72, 73]
Skin	in dermis [74]
Spleen	in red pulp [75]
Temporomandibular joint disc	closed to collagen bundles [76]
Testis	in the outer layer around peritubular cells [77]
Thoracic duct	subendothelial region of the wall as well as in intimate association with smooth muscle bundles throughout the media [78]
Trachea	among smooth muscle fibers and endothelium [48, 79]
Trigeminal ganglion	in close vicinity to microvessels and nerve fibers around the neuronal-glial units (NGUs) [80]
Urethra	in the lamina propria [71]
Ureters	in the lamina propria, mainly exist in between smooth muscle bundles [45, 81, 82]
Urinary bladder	in the lamina propria [45, 83]

Vicinity of telocytes and its secretomes

TCs demonstrate specific direct (homocellular and heterocellular junctions) and/or indirect (chemical, paracrine/juxtacrine signalling, microvesicles and exosomes, sex hormone and microRNAs) contacts with various surrounding cells. Homocellular junctions allow TCs to keep an architecture of tissue, generating 3D (three-dimensional) networks. Moreover, they contain elements of the cytoskeleton such as microfilaments, microtubules and vimentin [3]. Connections between TCs-exosomes-intercellular junctions cytoskeleton form the equivalent of a primitive nervous system [84]. In the heart TCs make contacts with different morphology (puncta adhaerentia minima, processus adhaerentes and manubria adhaerentia) [22, 23]. In the TCs the most represented are the nexuses (gap junctions), that are known to allow the exchanges of metabolites and signals [2, 7].

Heterocellular contacts TCs make with a variety of cells: smooth muscle cells, nerves, immunocytes (macrophages, mast cells and lymphocytes), stem cells, melanocytes in the eye [35], erythrocytes in the spleen [75] and with Schwann cells in the heart [23]. Gherhiceanu *et al.* reported that TCs make contact with virtually all types of cells in the human heart. His team suggested that heterocellular contacts occur by means of minute junctions (*point contacts*, *nanocontacts* and *planar contacts*)

and the mean intermembrane distance is within the macromolecular interaction range (10–30 nm) [23]. Moreover, TCs establish close contacts, stromal synapses (connective connections), with tracheal mast cells and in the trigeminal ganglion [79, 80].

Telocytes release at least three types of extracellular vesicles: exosomes (45 ± 8 nm), ectosomes (128 ± 28 nm) and multivesicular cargos (1 ± 0.4 μm) from their Tps and, occasionally, from the cell body [6, 85]. Yang *et al.* observed that the vascular TCs secreted more vesicles and bands in the Tps than the TCs that were located within other structures. The presence of a large number of vesicles appears to be a conserved feature of TCs regardless of their location [77]. These cells secrete interleukins (IL-2, IL-6, IL-10 and IL-13), growth factors (VEGF and EGF), nitric oxide, macrophage inflammatory protein 1α and 2 (MIP-1α and MIP-2), Monocyte Chemoattractant Protein 1 (MCP-1), Growth-Related Oncogene/Keratinocyte-derived Chemokine (GRO-KC). Three major classes of elements in telocyte secretomes include growth factors, chemoattractants, and cytokines/chemokines, indicating that telocytes may regulate stem cell growth and differentiation, microenvironmental formations [86–89]. Yang *et al.* revealed the presence of TCs that were directly connected to Leydig cells, which suggests that TCs are indirectly involved in the secretion of testosterone, rostenedione and dehydropiandrosterone [77].

Telocytes and its genes, proteins and microRNAs

The four different studies were conducted on gene expression profile of TCs in the last two years. Researchers focused on TCs-specific or TCs-dominated gene profiles in chromosome 1, 2, 3, 17 and 18 using global comparison between TCs and other cell types found in the mouse lung tissue [90]. TCs had a strong number of up- and down-regulated genes in all patterns (Table 2). Important to note that amount of down-regulated genes was 2–3 times higher than up-regulated in all observed chromosomes.

Table 2. Number of up-regulated and down-regulated genes in chromosomes of telocytes.

Chromosome	Number of up-regulated genes	Number of down-regulated-genes
1	14	39
2	26	80
3	13	59
4	17	56
17	16	68
18	10	22

(Date: 19.06.2016)

After analysis of up-regulated genes functions in TCs, it had been mostly suggested that these cells are involved in cellular signaling, cell expansion and movement (migration, adhesion, migration and division), embryogenesis, morphogenesis and tissue homoeostasis (including immune homeostasis), tissue remodelling and repair, maintenance of oxidative microenvironment preventing tumorigenesis and anti-inflammatory responses [90–96].

Zheng *et al.* provided the first proteomic analysis on TCs and showed these cells are exactly different from the protein expression point of view. In TCs proteins were mainly located in the cytoplasmic compartment and involved in cell signalling, energy and metabolic pathways. Myosin-14, periplakin and envoplakin, SOD2 (SODM), acid ceramidase were up-regulated in TCs. Several proteins up-regulated in TCs were found among the top 100 vesicular proteins that are present most frequently in mammalian extracellular vesicles proteome [92, 96].

TCs express significant amount of pro-angiogenic microRNAs (miR126, miR130a, let-7-family, miR-10, miR-155, miR-503, miR-126, miR-27b, miR-503, and miR-100), also miR-21, miR-22, miR-29 and miR-199a, both stromal specific and vascular smooth muscle specific (miR-143/145). These cells do not express miR-193 and have lack of expression of cardyomyocyte-specific miRs (miR-1 and miR-133a or miR-208) [2, 60, 97, 98].

Immunohistochemical features

Nowadays immunohistochemistry combined with TEM is the most applicable method to identify TCs (Table 3). Despite the fact that has not yet been found a specific marker for TCs, usually for primary identification scientists use CD34 [99]. Important to note that CD117/c-kit has been excluded for some organs or its parts [99] and differs between TCs populations (possible site dependant) [2, 6, 100]. For instance, rat uterus tissue contains different types of immune positive TCs: c-kit (–)/vimentin (+), c-kit (+)/vimentin (+), c-kit (+)/CD34 (+), while in human dermal tissue TCs were c-kit (–)/CD34 (+)/CD31 (–) [101, 102]. This range might be the basis of region-specific TCs roles [6, 103].

Table 3. Immunohistochemical profile of telocytes.

Positive	Negative
CD34, CD117/c-Kit, plated-derived growth factor receptor alpha and beta (PDGFRα and-β), VEGF, inducible nitric oxide synthase (iNOS), calveolin-1, vimentin, connexin 43, oestrogen and progesterone receptors (PRs), CD44, desmin, nestin, cadherin-11, CD29, CD10	Procollagen 1, CD31/PECAM-1, α-smooth muscle actin (α-SMA), CD11c, CD90/Thy-1, CD68, CD1a, CD62-P, CD45

The best available choice is a combination of four immunohistochemical markers: CD34, c-kit, vimentin and PDGFRα [4, 14, 103]. However, for differential diagnosis between TCs and other cells is often used a double immunolabelling [100, 104]. Compare cardiac TCs with cardiac fibroblasts and pericytes, Bei *et al.* demonstrated that cardiac TCs are CD34/c-kit, CD34/vimentin and CD34/PDGFR-β positive and α-SMA weak positive, while cardiac fibroblasts are only vimentin and PDGFR-β positive and pericytes are CD34 negative, α-SMA and PDGFR-β positive [104, 105]. Endoneurial fibroblasts are CD34 positive [7, 106].

Zhou *et al.* experimentally showed a high expression level for PDGFR-α compare with PDGFR-β in cardiac TCs [102]. The double immunofluorescent staining for CD34 and PDGFR-α is considered to be a specific immunohistochemical marker for TCs in gastrointestinal tract [100, 107].

TCs inconstantly express stem cell markers such as Sca-1 (Stem cell antigen-1) and Oct4 (octamer-binding transcription factor 4) [2]. Chang *et al.* depicted that splenic TCs express nanog (a transcription factor critically involved with self-renewal of undifferentiated embryonic stem cells) and Sca-1, while c-kit negative [44]. Using flow cytometry analysis, Bei *et al.* showed that TCs were homogenously positive for mesenchymal marker CD29 but negative for hematopoietic marker CD45, which is similar to bone marrow-derived mesenchymal stem cells [105]. In addition, as CD34+ cells may lose CD34 expression and acquire other marker expressions "in vivo" and "in vitro" [105, 108]. Petre *et al.* found that TCs in the mammary gland stroma were CD10±/c-kit-/vimentin+ [109, 110].

Electrophysiological characteristics

Recently, studies on the electrophysiological properties of TCs have shown various types of ionic channels in different organs (transient outward and inward currents). In different organs TCs have been shown to possess different types of potassium, chloride and calcium channels.

Lee *et al.* found that TCs in murine detrusor muscle express small-conductance Ca^{2+}-activated K^+ channels, most prominently the SK3 isoform, whereas expression of SK channels was low in smooth muscle cells [111]. It followed that SK channel regulation of bladder excitability was likely mediated through TCs rather than through SMCs. Moreover, SK3 channels have been identified in the myometrium and in the glandular and luminal epithelium of the endometrium [112]. Kim *et al.* showed the presence of calcium-activated potassium channels in stomach [3, 113, 114]. Cretoiu *et al.* suggested that rhythmical intracellular calcium discharges originating in TCs contribute to the pacemaker activity [3].

Sheng *et al.* firstly demonstrated that cardiac atrial and ventricular TCs expressed large conductance Ca^{2+}-activated K^+ current (BK_{Ca}) and inwardly rectifying

K^+ current (IK_{ir}), but not transient outward K^+ current (I_{to}) and ATP-sensitive potassium current (K_{ATP}) [115].

In human myometrium, patch-clamp recordings of TCs 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 [3, 115]. Rosenbaum *et al.* observed small-conductance calcium-activated potassium currents in human myometrium and concluded that its expression is higher in non-pregnant compared to pregnant tissue [116]. A similar situation with SK3 expression in vascular endothelium is found during pregnancy. These are also expressed in TCs and are down-regulated during pregnancy when they reduce contractility [6, 117].

T-type calcium channels are present in TCs from human myometrium, which in pregnancy and labour participate in the generation of endogenous bioelectric signals responsible for the regulation of the surrounding cell behaviour. It might be the missing link for describing the molecular mechanisms by which TCs are involved in mechanical stretching during uterine enlargement in pregnancy. The expression of α-subunit of T-type calcium channels in TCs is less intense in the case of non-pregnant myometrium [6, 118]. Steroid hormones and oxytocin might mediate the higher expression of T-type calcium channels in TCs derived from pregnant myometrium. As TCs have steroid hormone receptors, this might lead to frequent and sustained contractions that are able to trigger birth [6]. In fetal cardiac myocytes, T-type Ca^{2+} channels were suggested to play role in the regulation of cardiomyocyte size [118].

TCs have differences in reactivity to the low-level laser stimulation (LLLS). In pregnant myometrium primary cultures a growth rate of lateral telopodal extension of TCs is higher than in non-pregnant ones. Twenty-five percent of TCs from pregnant uterus present a local thickening of the TP upon LLLS. The local thickening phenomenon was directly correlated with a delayed telopodal response to stimulation [119]. C-kit inhibition by imatinib (receptor antagonist) led to a reduction in both the amplitude and frequency of myometrial contraction in a dosedependent manner. TCs might be players in the coordination of uterine activity in a kit-independent manner [25, 120].

Myometrial TCs have large input resistance, ranging between 1.2 and 12 GΩ. They failed to produce the regular slow waves of depolarization described in classical ICCs, although some irregular excursions of membrane potential ranging from 10 to 35 mV have been observed by Duquette *et al.* TCs did not generate action potentials in response to depolarizing current. Only passive electric potentials were recorded when current pulses were applied [105].

Possible role of TCs

Nowadays, more researchers focus on intercellular communication of TCs and its roles in cells niche. The number of publications is gradually rising, reflecting the importance of these cells. Sometimes at the beginning, data might be slightly speculative, but later they can be empiric proved. Likewise, more attention to attract connection TCs with smooth muscle cells, nerve endings, vessels and stem cells. They play a key role in a variety of pathological processes (myocardial infarction, heart failure, renal ischemia-reperfusion injury, liver fibrosis and others) and adaptive responses [121–125].

TCs might behave as an immune system modulator interrelating immune cells in interstitium context and providing functional support [30]. For instance, TCs are major cell type of the human thoracic duct [78]. The importance of TCs in normal and pathological immune response is faceted, proved by different point of view. Ardeleanu *et al.* proposed that TCs could be the common cells of origin for both perivascular epithelioid cell tumours (PEComas) and gastro-intestinal stromal tumours (GISTs) [34, 121]. Mou *et al.* proposed that stromal cells containing TCs might influence the self-assembly of reconstituted breast cancer tissue [51]. Mandache *et al.* considered that TCs might play an important role in amyloid deposits formation [10]. Important to note, TCs can be a structural and functional unit of main immunological barriers in the human organism. Yang *et al.* suggested that TCs play important roles in the blood-testis barrier [77], whereas Gherghiceanu *et al.* proposed involving TCs in "blood–myocardium barrier" as they the main population in the sub-epithelial layer of endocardium [21].

The tandem telocytes-stem cells has been found in stem-cell niches in various organs (e.g. epicardium, lungs, skeletal muscle, choroid plexus, skin) [35, 122, 123]. Cantarero *et al.* proposed TCs with nerve fibers and blood vessels form such functional unit as "'mesenchymal cell niche" [19], while Luesma *et al.* suggested that there are two different types of stem-cell niches into the eye: epithelial niches (basal cells in cornea and conjunctiva) and stromal niches (iris, corneoscleral junction). The TCs network could even be a scaffold for stem cells migration between different layers of the eye [35]. Moreover, a study, made by Gherghiceanu and Popescu in 2009, has suggested that TCs are involved in mesothelial renewal and might guide the migration of mesenchymal cells into the mesothelial layer of the epicardium [28]. According to Petre *et al.* TCs "could be actors in the mammary stem niche" [43, 109]. Splentic TCs could take part in formation of splenic hematopoietic niche and play important role in transmitting the signals [75]. Alunna *et al.* suggested that a loss of minor salivary glands telocytes might have important pathophysiological implications in primary Sjögren's syndrome [17].

Telocytes are located in the neuromuscular spindles and participate in the control of muscle tone and motor activity. They produce electric slow waves that trigger and

coordinate smooth muscle contractions in the uterus. The decreasing in TCs caused dysregulation of oviduct motility, suggesting that tubal TCs impairment leads to the infertility of tubal origin and even tubal ectopic pregnancy [103, 126, 127]. Matyja *et al.* showed that a reduction in TC number may be a consequence of the toxicity of the supersaturated bile, while some other bile components (glycocholic and taurocholic acids) may exert protective effects on TCs and thus possibly influence the mechanisms regulating gallbladder and extrahepatic bile duct motility [39, 128–130]. Fu *et al.* found that hepatic TCs were significantly decreased by 27%–60% in human liver fibrosis, suggesting that loss of TCs might lead to the altered organization of extracellular matrix [13].

Telocytes have a powerful potential in tissue repair and regeneration (in heart, lung, skeletal muscle, skin, meninges and choroid plexus, eye, liver, uterus and urinary system) [131, 132]. It might be a future target for therapeutic value in preventing of diseases. In conclusion, it is not superfluous to emphasize the importance of new studies, that allow us better understanding the nature of Telocytes.

Conflict of interest

None declared.

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