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OPINION PAPER

Recently discovered interstitial cells termed telocytes: distinguishing cell-biological and histological facts from fictions

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Historical introduction

The discovery of cells that connect neurons and smooth muscle cells in the digestive tube dates back to the end of the nineteenth century. Santiago Ramón y Cajal, a Spanish histologist, 1906 Nobel Prize winner and one of the founding fathers of modern neuroscience (De Carlos and Borrell 2007), discovered a peculiar cell population in the wall of the gut. He found these 'enigmatic' cells embedded in the loose connective tissue of the *tunica muscularis* between nerve ganglia and smooth muscle cells. Ramón y Cajal considered them primitive interstitial neurons as it was possible to visualize them by methods typically used in neurohistology, such as silver impregnation or methylene blue staining (Popescu and Faussone-Pellegrini 2010). Despite this discovery, the exact structure and function of the cells remained questionable for more than half a century. Eventually, advancements in transmission electron microscopy enabled the detection of cells that closely resembled what Cajal had described. In his honour, the term 'interstitial cells of Cajal' (ICCs) was introduced when it became evident that the cells were not neurons (Faussone Pellegrini et al. 1977; Thuneberg 1982).

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Interstitial cells of Cajal and the motility of the gut

ICCs in the wall of the gut have spindle-shaped bodies and long, branching cytoplasmic processes, through which they form unique three-dimensional networks. Many of their ultrastructural morphological features, like their discontinuous basal lamina, direct contact with smooth muscle cells via gap junctions and their close relation to nerve endings, indicate that they represent specialized muscle cells (alternatively, muscle-like cells). On the other hand, some ultrastructural features bear closer resemblance to those of common connective tissue fibroblasts (Komuro et al. 1996). ICCs are considered important regulatory elements of gastrointestinal motility, especially in the generation and propagation of slow electric waves, which regulate the contractile activity of smooth muscle and enable neurotransmission between neurons and smooth muscle cells (Burns 2007).

Based on their localization and possible function, at least three different types of ICCs exist within the muscle layer of the gastrointestinal tract, as critically reviewed by Mostafa et al. (2010). The authors concluded that while some of the ICCs may act as pacemaker cells, others mediate both inhibitory and excitatory motor transmission (or the transmission of mechanoreceptive information from the muscle layer). The third distinct population of ICCs was described to play a role in conducting electrical information from the first population of ICCs. Decrease in the number of ICCs was described in almost all gastrointestinal motility disorders, including Hirschsprung's disease, intestinal neuronal dysplasia type B, chronic idiopathic constipation, gastroparesis, idiopathic inflammatory bowel disease, pyloric stenosis, achalasia and chronic idiopathic intestinal pseudo-obstruction (Rolle et al. 2007; Chen et al. 2016; Gfroerer and Rolle 2013). In spite of that, few research papers have been published on the effects of reduced numbers of specific subtypes of ICCs on impaired motility of the gastrointestinal tract or in relation to the severity of clinical signs and symptoms of the diseases. Thus, a

causal relationship between the absence of ICCs and the development of gut motility disorders has not been established.

The majority of morphological findings, which describe the distribution of ICCs in the affected parts of the gastrointestinal tract, are controversial. For instance, in the case of *morbus Hirschsprung*, some authors described reduced number of ICCs with disrupted connections in the aganglionic part of the intestine (Yamataka et al. 1995; Vanderwinden et al. 1996). On the other hand, other studies demonstrated normal or only slightly reduced numbers of c-kit-positive ICCs in the aganglionic part of the intestine in patients with *morbus Hirschsprung* (Horisawa et al. 1998; Newman et al. 2003). This discrepancy can be partially explained by the fact that c-kit is not specific for the determination of the true functional state of ICCs as it does not play a pivotal role in the pacemaker activity of ICCs. A recent study suggested that a novel marker anoctamin 1 should be used for the evaluation of ICCs in *morbus Hirschsprung* patients because it is more specific and functionally important (Coyle et al. 2016). Nevertheless, immunohistochemical identification using c-kit remains one of the most commonly used techniques to visualize ICCs in tissue samples. C-kit (CD117) is a transmembrane receptor tyrosine kinase; in the wall of gut, it is exclusively expressed on the surface of ICCs and mast cells. Therefore, monoclonal antibodies against the c-kit receptor have facilitated the routine identification of ICCs in histological specimens (Gfroerer and Rolle 2013; Komuro and Zhou 1996). ICCs also react with antibodies against vimentin, whereas smooth muscle cells are vimentin-negative (Burns 2007; Rumessen & Thuneberg 1996).

Interstitial Cajal-like cells and telocytes

Over the last couple of years, similar cells have been found in a number of organs in the human body. These so-called 'interstitial Cajal-like cells' (ICLCs) have been described in the urinary bladder, prostate, penis, mammary gland, uterus, vagina, placenta, exocrine part of the pancreas, heart, blood vessels and many other organs (reviewed by Crețoiu and Popescu 2014; Aleksandrovych et al. 2017). The discovery of these cells outside the gut wall is attributed to the Romania-based research team led by Professor Laurentiu M. Popescu (1944–2015). In 2005, he observed ICLCs for the first time in the exocrine part of the pancreas via transmission electron microscopy and immunohistochemical visualization using anti-c-kit (Popescu et al. 2005). In that study, the authors observed that ICLCs use a system of cytoplasmic projections to make contacts with blood capillaries, the serous acini of the pancreas, stellate cells (a morphological counterpart to liver Ito cells) and nerve fibres. Over the next five years after this groundbreaking discovery, scientists detected and described ICLCs in many different organs in humans and laboratory animals. Professor Popescu understood his scientific success as a case of serendipity. This belief served as the inspiration for rather unconventional title of his first detailed review paper about ICLCs, 'TELOCYTES - a case of serendipity: the winding way from Interstitial Cells of Cajal, via Interstitial Cajal-Like Cells (ICLC) to TELOCYTES' (Popescu and Faussone-Pellegrini 2010). We venture that from the histological point of view, it is a revolutionary, though rather controversial, publication. As of 2018, it had been cited, depending on the source database, more than 300 times.

Other researchers and pioneers in the field found the name 'interstitial Cajal-like cells' too long and impractical, so Popescu and Faussone-Pellegrini proposed the new term 'telocytes' (Popescu and Faussone-Pellegrini 2010); according to Aristotle, '*telos*' was an individual's greatest potential. In an interview, Professor Popescu was asked how he came up with the name. His remarkable answer revealed a deep passion of the scientist for culture: 'The idea to call the newly discovered cells telocytes came to me during a break at the Vienna State Opera' (Manole and Crețoiu 2015). Oddly, the revolutionary discovery of 2005 and the intense research of the following years were not enough for telocytes to be included in the official, widely accepted histological nomenclature *Terminologia Histologica* (FIPAT 2008), despite the fact that it contains all terms associated with cells, tissues and organs at the microscopic level (Varga et al. 2018). The logical question, and one of the most common, is how is it possible that telocytes were not discovered earlier? The answer is hidden in their specific morphology – their small, inconspicuous bodies and the diameter (0.2 μm) of their cytoplasmic processes is near the resolving power of a light microscope, so they are perfectly camouflaged and almost impossible to distinguish from other structures using common histological staining techniques.

Telocyte morphology – Myth or reality?

Importantly, ICLCs/telocytes were discovered only 13 years ago, a very short time from a scientific point of view. This may be the reason why telocytes are not referenced in textbooks or in the internationally accepted nomenclature. Another important reason is that telocytes are a highly controversial topic, research into which frequently produces more questions than answers. Therefore, telocytes are not yet widely accepted as a distinct cell population. The main objective of this review is to address the most common, intriguing and debatable questions about telocytes´ morphology, which can be summarized into four classical issues. Finally, we also want to underline that despite their enigmatic and controversial nature, telocytes were featured in many prestigious journals. One example for all is this year's paper published in Nature focused on the role of telocytes during the regeneration of the epithelial lining of the small intestine (Shoshkes-Carmel et al. 2018).

Question 1. Are telocytes truly an individual/unique/new cell population?

The number of scientific works on ICLCs/telocytes grows yearly and telocytes were identified in almost all organs and tissues of the human body. The number of ICLC/telocyte papers published annually between 2005 and 2018 is summarized in Fig. 1. However, many researchers do not recognize telocytes as an individual cell population. For example, Spanish pathologists Díaz-Flores et al. describe telocytes only as 'CD34-positive stromal cells' that serve as progenitor/stem cells during the processes of regeneration and reparation (Díaz-Flores et al. 2015, 2016a, b). These cells maintain their CD34 expression even after activation. Some of them can be also positive for smooth muscle actin (SMA) and act as a source cell population for the differentiation of fibroblasts and myofibroblasts, which repair damaged sites via granulation tissue and fibrosis. Ivey and Tallquist (2016), cell biologists from the University of Hawaii, also view the terms 'telocytes' and 'fibroblasts' as merely synonyms that can be used interchangeably. Moreover, Romanian scientists from Carol Davila University in Bucharest, the 'home' university of telocyte discovery, reported that at least one subpopulation of telocytes in the myocardium can be derived from endothelial cells (Rusu et al. 2017). The authors even conceded that cells previously described as telocytes in electron micrographs of the myocardium might actually represent endothelial cells.

At the same time, there is roughly an equal number of publications that describe telocytes as an individual cell population based on their morphology both in vitro and in vivo. Telocytes have small inconspicuous cell bodies in vitro with very long cytoplasmic processes, which can be several tens of micrometres long. Therefore, Bei et al. (2015) distinguish them from fibroblasts, the cell bodies of which are spindle-shaped with much shorter cytoplasmic processes. However, we dispute some of the conclusions of this study. The extremely long cytoplasmic processes described by Bei et al. (2015) in vitro cannot be considered a unique feature of telocytes, since all dying cell populations in metabolic crisis form similar cytoplasmic extensions. We have observed this phenomenon repeatedly in fibroblasts and somatic stem cells after long-term cultivation in our laboratories (Fig. 2). Thus, we want to point out that extremely long cytoplasmic processes are characteristic not only for telocytes, as other cell populations can also display this morphological feature.

Another practice that jeopardizes the full acceptance of telocytes as a morphologically distinct cell population is the repeated use of the same electron micrographs in different articles (as in Kostin 2010 and Kostin 2016). Important is the need to accumulate new evidence and corroborate findings rather than relying on limited data. Finally, yet importantly, we must call attention to the common practice of artificially modifying the colours of electron micrographs. The structures (the cell bodies and, especially, the cytoplasmic processes) that supposedly belong to telocytes are often digitally coloured to distinguish them from their surroundings (for example Ceafalan et al. 2012; Li et al. 2014; Cretoiu et al. 2012). Although this may seem a suitable technique for didactic purposes, such an approach produces a bias that makes it impossible for a reader to make an objective and independent description of a given electron micrograph (the difficulty in distinguishing the processes of different cells due to pseudocolouring). In other hand, many authors published also original electron micrographs; without artificial digital colouring and we can corroborate that transmission electron microscopy is still the gold standard for identification of telocytes.

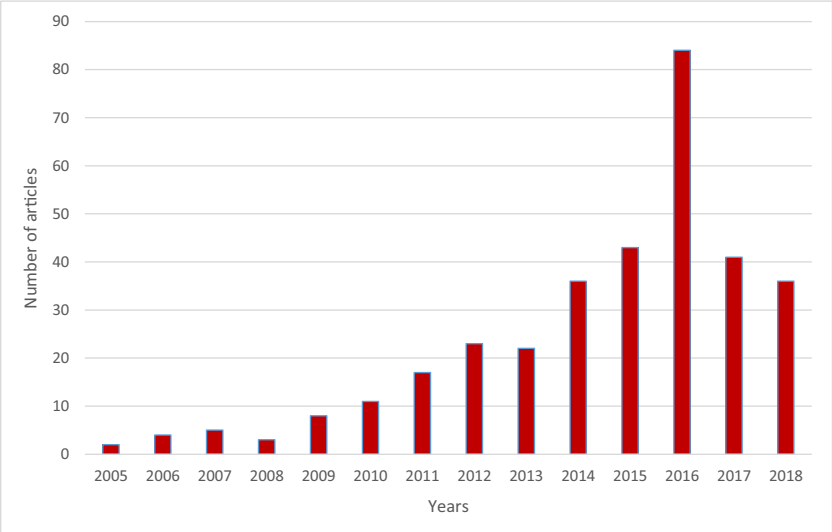

Fig. 1 Number of scientific articles published per year (until August 2018) on the topic of telocytes or ICLCs based on searches through www.pubmed.com (National Center for Biotechnology Information, U.S. National Library of Medicine)

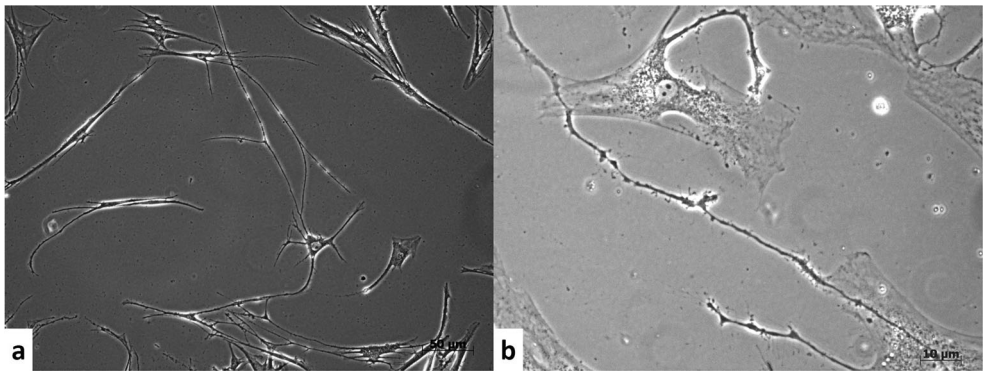

Fig. 2 Extremely long cytoplasmic projections of long-term cultured fibroblasts (**a**) and adipose tissue-derived stem cells (**b**), which resemble the morphological description of telocytes (images obtained by inverted microscopy, Scale bars in Figures = 50 µm, respectively 10 µm)

Question 2. What is the typical ultrastructural morphology of telocytes?

As noted by Ramón y Cajal himself, 'the original' ICCs in the gut can be visualized by staining with methylene blue and via silver salt impregnation (Popescu and Faussone-Pellegrini 2010), although the results are often controversial. On the other hand, ICLCs/telocytes cannot be reliably distinguished from other interstitial cells using only common histological techniques. We feel that it is not possible, based on the photomicrographs presented in various publications (as in Gherghiceanu and Popescu 2005) to reliably confirm that ICLCs are distinct from nerve fibres or artefacts.

Telocytes are typically described as cells with small bodies and two to four very long cytoplasmic processes (Fig. 3). Some authors consider them the second longest processes in the human body after neuronal axons, with lengths of up to hundreds of micrometers (Cretoiu et al. 2012). The cell body is usually described as either pear-shaped, spindle-shaped, triangular or even stellate, depending on the number of processes (Kucybala et al. 2017). In contrast to their remarkable length, telocyte processes are only approximately 0.2 µm thick, which makes them undetectable using only a light microscope. Therefore, as we mentioned before, the exact identification of telocytes requires transmission electron microscopy (Fig. 4). In 2005, Romanian morphologists Gherghiceanu and Popescu (2005) came up with a 'recommended criteria' for the identification of telocytes via transmission electron microscopy, based on their observations of these cells in the mammary gland. Given that telocytes from different organs are morphologically similar, the criteria can be used as a blueprint for the description of telocytes regardless of their location. The criteria include:

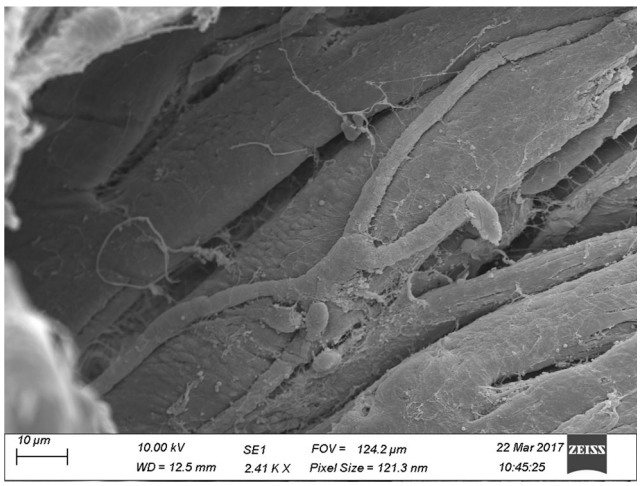

Fig. 3 Telocyte-like cell from the human myocardium with a small cell body and four long cytoplasmic processes (image obtained by scanning electron microscopy, Scale bar in Figure = 10 µm)

- location: in the connective tissue among tubuloalveolar glands, but not directly within epithelial cells;
- caveolae: approximately 2.5% of the cytoplasmic volume;
- mitochondria: approximately 5%–10% of the cytoplasmic volume;
- endoplasmic reticulum: 1%–2% of the cytoplasmic volume, predominantly smooth, but rough can also be present;
- cytoskeleton: intermediate filaments, microfilaments and microtubules;
- thick myosin filaments: undetectable;
- basal lamina: occasionally present;
- 'gap junction' type of intercellular connections: present at the point of contact with smooth muscle cells (not in mammary gland);
- other junctions: with immunologically active cells, blood capillaries, nerve fibres, epithelial cells and smooth muscle cells; and
- cell morphology: usually 2–3 cytoplasmic projections, ranging from several tens to hundreds of micrometres in length, used to form three-dimensional networks.

However, a thorough comparison of the ultrastructural morphology of ICLCs/telocytes with connective tissue **fibroblasts** draws into question if the differences are that striking. The plane of a histological section is often an important factor that determines the observable amount of perinuclear

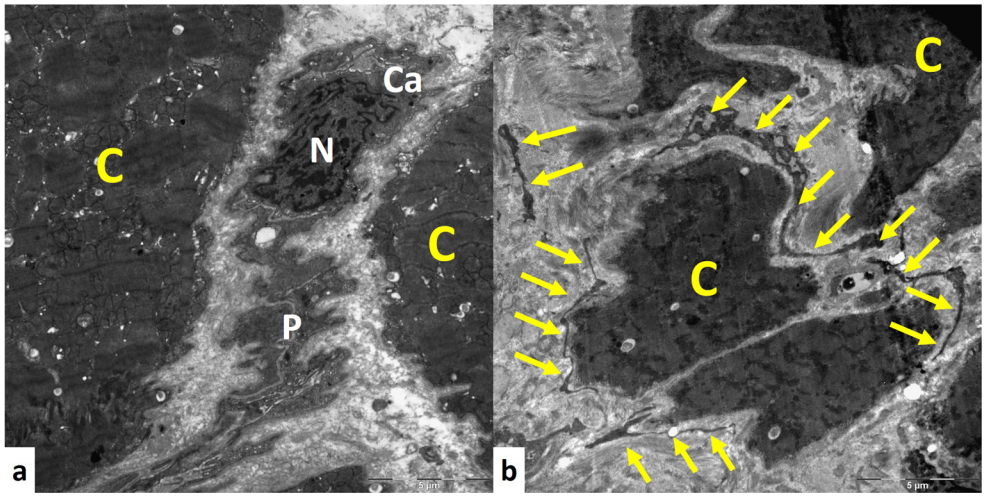

Fig. 4 Human myocardium with (probably) telocytes. **a**) Telocyte-like cell inside the interstitial connective tissue between two cardiac muscle cells (C), with mostly euchromatic nucleus (N), cytoplasm filled with caveolae (Ca), Orig. Magn. 4,400x **b**) Cellular structures (marked with arrows) resembling cytoplasmic processes of telocytes (or endothelial cell in longitudinal section?) within the interstitial connective tissue between cardiac muscle cells (C) Orig. Magn. 4,000x (image obtained by transmission electron microscopy, Scale bars in Figures = 5 μm)

cytoplasm in a given specimen. Moreover, fibroblasts are a dynamic cell population with different functional states. Active forms of fibroblasts display vigorous proteosynthetic activity, which is apparent in their great abundance of different cell organelles. However, after a particular task is completed, fibroblasts can smoothly change their functional state to non-active fibrocyte form, with a corresponding adjustment of their cell organelle spectra, until they differentiate into an inactive form with only a few organelles. Another confusing cells may be **blood and lymphatic endothelial cells**, which are localized in the connective tissue of all organs of the human body – in a longitudinal section their extremely flattened cell body may resemble "a long projection" of telocytes.

Fertig et al. (2014) used transmission electron microscopy to confirm that, during in vitro cultivation, cardiac telocytes release extracellular vesicles, including relatively large multivesicular cargo containing tightly packed, endomembrane-bound vesicles. However, this feature is not telocyte-specific; we described similar multivesicular cargo during the in vitro cultivation of dental pulp-derived **mesenchymal stem cells** in our previous paper (Varga et al. 2011).

Question 3. Is it possible to identify telocytes using monoclonal antibodies?

It is possible to identify telocytes with monoclonal antibodies, but not unambiguously. Many known antigens are provably expressed by telocytes, but none of them are "telocyte-specific". After analysis of the literature in the PubMed database (July 2018), we ascertained that five antigens are the most frequently mentioned as immunohistochemical markers of telocytes or ICLCs:

- CD34–111 entries in PubMed,
- transmembrane receptor tyrosine kinase c-kit (CD117) – 99 entries in PubMed,
- vimentin – 61 entries in PubMed,
- PDGFR-β – 26 entries in PubMed, and
- smooth muscle actin (SMA) – 19 entries in PubMed.

We know that telocyte-specific marker does not exist. But in many laboratories, double immune-histochemical staining is not applicable due to financial and technical problems. These are the reasons why we discuss the most often mentioned antigens associated with telocytes, separately.

CD34 is the characteristic antigen of haematopoietic stem cells, but it is also expressed in a wide variety of cells, including endothelial cells (Pusztaszeri et al. 2006), mast cells (Drew et al. 2005), some dendritic cells (Blanchet et al. 2011) and mesenchymal stem cells (Togarrati et al. 2017). **Vimentin** is a cytoskeletal type III intermediate filament protein that is expressed in cells of mesenchymal origin. Since telocytes are vimentin-positive, their embryonic origin must be mesenchymal. Vimentin plays an important role in anchoring organelles in the cytoplasm. It can be found in most cells of mesenchymal origin, such as fibroblasts (Cheng et al. 2016), endothelial cells (Boraas and Ahsan 2016), dendritic cells (Nagy et al. 2016) and smooth muscle cells in the walls of blood vessels (Ikawati et al. 2018). **PDGFR-β** is a beta-type platelet-derived growth factor receptor with a cardinal role in the formation of blood vessels during embryogenesis. Only two years ago, researchers found that PDGFR-β is also expressed in fibroblasts associated with carcinomas (Kartha et al. 2016). **SMA** is expressed mainly in smooth muscle cells in blood vessel walls and hollow organs like the uterine myometrium (Shynlova et al. 2005). Aside from this typical expression in smooth muscle cells, SMA expression has also been

demonstrated by immunohistochemical techniques in other cells with contractile ability, like myoepithelial cells in exocrine glands (Sato et al. 2003), pericytes (Yonenaga et al. 2005) and myofibroblasts (Cheriyan et al. 2013).

These four antigens have been used extensively by scientists to localize and describe telocytes in different organs. However, we are sceptical about the precision, interpretation and reproducibility of such experiments. After detailed analysis of a research paper published by Rusu et al. (2017), we have concluded that it is challenging to find genuine differences between telocytes, endothelial cells and pericytes in the myocardium. In this study, the authors used antibodies against CD34 and SMA to detect myocardial telocytes. The problem is that endothelial cells and pericytes also expressed CD34 and SMA, respectively. From a morphological point of view, all of these cells can appear similar depending on the specific planes of the histological section. A similar situation occurs with an antibody (clone D2–4) against podoplanin, another possible marker of telocytes, as podoplanin is also expressed by endothelial cells in lymphatic capillaries. Manta et al. emphasized that in histological sections, the processes of telocytes can be easily confused with longitudinally oriented endothelial cells (Manta et al. 2018).

Last but not least, we consider **c-kit (CD117),** which appears to be the most suitable marker for the identification of telocytes (Fig. 5). The proto-oncogene c-kit plays an important role in the growth and differentiation of cells. Aside from telocytes, this transmembrane receptor tyrosine kinase is expressed in mesenchymal stem cells, haematopoietic stem cells, mast cells, melanocytes, ICCs and in multiple types of cancer cells, such as gastrointestinal stromal tumours (Gibson and Cooper 2002). The morphological and topographical differences between the majority of these c-kit-positive cells are well known, so the cells should not be mistaken for each other. According to our previous results, immunohistochemical staining for c-kit appears to be the most suitable method for the detection and description of telocytes in the female genital tract (Urban et al. 2016; Klein et al. 2017).

Telocytes are typically described to be located in close proximity to fibroblasts, pericytes and nerve cells. Therefore, it is advantageous to be familiar with the antigens that are typically expressed in these cell populations. Telocyte, fibroblast, pericyte and neuron positivity for the five antigens commonly used to detect telocytes was summarized and compared by Kucybala et al. (2017). Detailed immunohistochemical profiling revealed that telocytes are positive for approximately ten additional antigens as well as the five most frequently used antigens (Aleksandrovych et al. 2017). Bei et al. (2015) described differences in the immunophenotypes of telocytes and fibroblasts in vitro. After CD34/c-kit, CD34/vimentin and CD34/platelet-derived growth factor β (PDGFR-β) double immunofluorescence staining, telocytes were positive for all three combinations, whereas fibroblasts were positive only for vimentin and PDGFR-β. Interestingly, the authors noted that the immunophenotype of telocytes is variable and dynamic, as not all telocytes were double positive for CD34/c-kit. This is another important fact that prevents an accurate identification of telocytes.

Question 4. Are telocytes described exclusively in humans?

The simple answer is no. To date, telocytes have been described in all classes of vertebrates, but also in many other animal species from different taxa. For instance, Soliman and Emeish studied the distribution of telocytes in the gills of carp species *Cyprinus carpio* in connection to the levels of water salinity (Soliman and Emeish 2017). Ghose et al. (2008) discovered telocytes in the postcaval vein of the frog *Rana tigrina* and demonstrated that telocytes are responsible for the rhythmic contraction of this vein, independent of the electrical conduction system of the heart. Telocytes have also been detected by electron microscopy in tissues of various reptile species, including the male and female reproductive systems of the Chinese softshell turtle (*Pelodiscus sinensis)* (Ullah et al. 2014; Yang et al. 2015a) and in the pancreas and gastric mucosa of the Chinese giant salamander (*Andrias davidianus)* (Zhang et al. 2016a, b). Telocytes are also located in the walls of the gut and uterine tubes of some bird species (Yang et al. 2015b; Yang et al. 2017). Telocytes in mammals have also

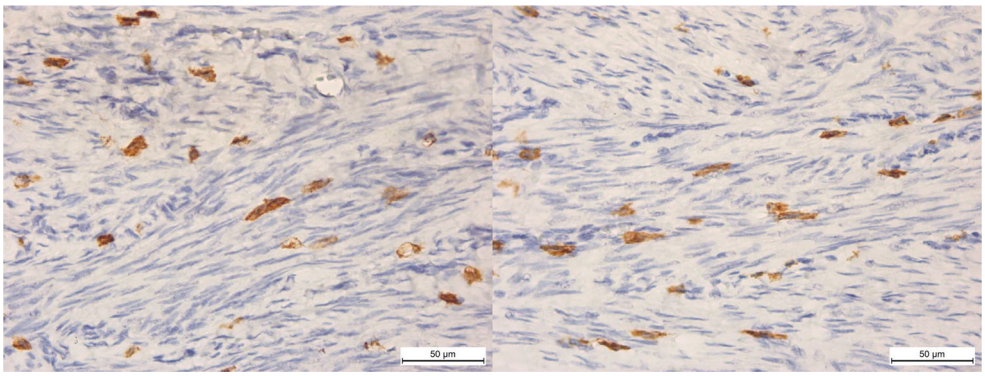

Fig. 5 c-kit (CD117)-positive cells, probably telocytes, from the human uterus. Cells are localized among smooth muscle cells of the myometrium (stained with anti-c-kit antibodies and the brown chromogen diaminobenzidine; Scale bars in Figures = 50 µm)

been intensely studied. They have been detected in livestock, such as sheep (Abd-Elhafeez et al. 2017), in pets, like dogs (Xu et al. 2016), and in laboratory animals, like guinea pigs (Nguyen et al. 2011), rats (Hatta et al. 2012) and mice (Ye et al. 2017). Moreover, telocytes have been found also in invertebrates; in 2017, the presence of telocytes was confirmed in leeches *(Hirudo medicinalis)* (Pulze et al. 2017).

Conclusion and further perspectives

The current state of knowledge indicates that telocytes (probably) form three-dimensional networks in various organs. However, the morphological differences between telocytes, pericytes, fibroblasts / fibrocytes or blood and lymphatic endothelial cells are not so remarkable. Final resolution of the status of telocytes as an individual cell population will be important for morphologists, who still hesitate to include telocytes in histology and cellular biology textbooks, and also waver over their incorporation into the histological nomenclature *Terminologia Histologia* (FIPAT 2008). In any case, future morphological and functional studies of telocytes in vivo will help to find the answers to the questions about this (possibly) new and distinct cell population.

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Compliance with ethical standards

All procedures performed in studies involving human participants (electron and light microscopic observation of surgically obtained tissues) were in accordance with the ethical standards of the institutional ethical committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflicts of interest.

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