Identification of PDGFRα+ cells in uterine fibroids – link between angiogenesis and uterine telocytes

Veronika Aleksandrovych1, Tomasz Bereza2, Magdalena Ulatowska-Białas3, Artur Pasternak2, Jerzy A. Walocha2, Kazimierz Pityński4, Krzysztof Gil1

1Department of Pathophysiology, Jagiellonian University Medical College, Krakow, Poland
2Department of Anatomy, Jagiellonian University Medical College, Krakow, Poland
3Department of Pathomorphology, Jagiellonian University Medical College, Krakow, Poland
4Department of Gynecology and Oncology, Jagiellonian University Medical College, Krakow, Poland

Submitted: 2 March 2019; Accepted: 14 June 2019
Online publication: 22 July 2019

Arch Med Sci 2022; 18 (5): 1329–1337
DOI: https://doi.org/10.5114/aoms.2019.86795
Copyright © 2019 Termedia & Banach

Abstract

Introduction: Telocytes (TCs), also called interstitial Cajal-like cells (ICLC), CD34+ cells or PDGFRα+ cells (platelet-derived growth factor receptor α positive cells), a new type of cell of mesenchymal origin, were described over one decade ago. The unique nature of these cells still deserves attention from the scientific community. Telocytes make homo- and heterocellular contact with myocytes, immunocytes and nerves, have their own immunohistochemical and secretome profiles and thus might regulate local regenerative processes including angiogenesis and fibrosis. The aim of our study was to observe the missing link between angiogenesis and telocytes in leiomyoma, the most common benign tumors affecting women of reproductive age.

Material and methods: We observed uterine tissue samples from leiomyoma, adjacent myometrium and unchanged tissue from patients with leiomyoma and control subjects using routine histology, histochemistry, immunofluorescence (CD117, CD31, CD34, PDGFRα, tryptase, sFlt-1) and image analysis methods.

Results: The decline of the telocyte density in the foci of fibroids correlated with poor vascularization inside the leiomyoma. Moreover, the expression of sFlt-1 (anti-angiogenic-related factor) significantly increased inside a fibroid. In leiomyoma the decrease of telocyte and blood micro-vessel density was accompanied by prevalence of collagen deposits, unlike the unchanged myometrium.

Conclusions: Our results demonstrate TCs in human uterine fibroids and highlight their possible involvement in the pathogenesis of myometrial pathology in the context of angiogenesis.

Key words: angiogenesis, telocytes, interstitial Cajal-like cells, leiomyoma, hypoxia, CD34.

Introduction

Currently, the most common benign tumor, affecting up to 80% of all women of reproductive age, is still uterine leiomyoma (UL) [1]. This pathologic myometrial formation can be a source of considerable quali-
Telocytes (TCs) are a novel type of interstitial cell population. Telocytes were first described by the Popescu group in 2005 and characterized by a small cell body and extremely long prolongations named telopodes (Tps) with alternating thin segments (podomers) and dilated segments (podoms). Currently, these cells are identified by immunohistochemistry, immunofluorescence and, occasionally, by transmission electron microscopy (TEM). The presence of TCs has been reported in a variety of anatomical units in human and animal bodies. These cells have their own unique morphology, demonstrate specific direct (homocellular and heterocellular junctions) and/or indirect (chemical, paracrine/juxtacrine signaling, microvesicles and exosomes, sex hormones and microRNAs) contact with various surrounding cells, and have gene expression and immunohistochemical profiles [17–22]. Primarily, only eight basic ultrastructural identification criteria were proposed by Huizinga et al. in 1997 and unified as the “gold standard” [23]. Later, the addition of two more precise criteria regarding quantitative estimation of cell organelles and accurate description of cell prolongations by Popescu and his group yielded the “platinum standard” of diagnosis for TCs [20, 21, 24]. The most useful markers for general identification are CD34 and PDGFRα [25, 26].

Dynamics and possible involvement of TCs in pathogenesis were observed in such diseases as systemic sclerosis [27, 28], Crohn’s disease [29], myocardial infarction [30], gallstone disease [18, 31, 32], psoriasis [33], endometriosis and acute salpingitis [34–36], liver fibrosis [37], primary Sjögren’s syndrome [38], keratoconic human cornea [39] and pathologies of the urinary bladder [40, 41]. In addition, a difference in the number of TCs in the myometrium and endometrium during pregnant and nonpregnant states has been described [42–44]. Cretoiu et al. focused on the distribution and role of TCs in the female reproductive system [45, 46].

The interaction of TCs and local angiogenesis in a human leiomyoma has not been clearly verified yet. Several studies have described TCs in UL, while no one has described its interplay with myometrial vascular structure. The aim of our study was to determine the link between myometrial TCs and vascularization in a human leiomyoma, and to clarify their possible role in angiogenesis. We suggest that the interplay of TCs and adjacent cells could reveal new aspects in the pathophysiology of myometrial changes.

**Material and methods**

**Subjects**

Twenty patients with symptomatic intramuscular solid UL (mostly located in the fundus of the uterus) were scheduled for elective surgery (laparoscopic hysterectomy) and selected for the study group (20 women, mean age: 56.8 ±10.0 years). The control group consisted of 15 patients (15 women, mean age: 57.6 ±12.7 years) who underwent elective surgery for other reasons and had no pre- or intraoperative signs of uterine fibroids. Hysterectomy was performed according...
Identification of PDGFRα+ cells in uterine fibroids – link between angiogenesis and uterine telocytes

Arch Med Sci 5, 1st September / 2022 1331

to the standard procedure. Samples of tissue from the foci of fibrosis and adjacent myometrium were taken for further observation from the study group. Samples of unchanged myometrium were also prepared from the control group. All patients were surgically treated at the Institute of Gynecology, Jagiellonian University Medical College in 2018. The study was conducted in accordance with the moral, ethical, regulatory and scientific principles governing clinical research. All surgical samples were retrieved with the approval of the Jagiellonian University Bioethical Committee (protocol number – 122.6120.40.2016) using procedures that conformed to the Declaration of Helsinki guidelines.

Tissue processing

Tissue samples from fresh hysterectomy specimens were collected and rinsed thoroughly with PBS (phosphate-buffered saline, 0.01 M, pH = 7.4), fixed in 4% phosphate-buffered paraformaldehyde, routinely processed and embedded in paraffin. Serial sections were cut and mounted on poly-L-lysine-coated glass slides.

Routine histology

The sections were deparaffinized, rehydrated and stained with either hematoxylin–eosin (H&E) to evaluate the gross tissue organization or Masson’s trichrome staining to detect collagen deposits.

Immunofluorescence

Indirect double immunofluorescence after heat-induced epitope retrieval was used to allow the simultaneous visualization of two antigens. After deparaffinization and rehydration, the slides were incubated for 30 min in PBS with appropriate normal serum at room temperature, followed by overnight incubation at 4°C in a solution of PBS with appropriate normal serum containing primary antibodies. After 5 washes (10 min each) in PBS, the specimens were then incubated for 1 h at room temperature with secondary antibodies diluted in PBS. Finally, the slides were washed in two changes (10 min each) of PBS and cover-slipped with fluorescence mounting medium (Dako, Denmark) and Menzel-Gläser cover glasses. Labeled specimens were analyzed immediately. The primary antisera and secondary antibodies used are listed in Table I.

| Antibody | Catalog number, company, country | Dilution |
|----------|---------------------------------|----------|
| Primary antibodies: | | |
| Polyclonal rabbit anti-c-kit | A4502, Dako, Denmark | 1 : 100 |
| Monoclonal mouse anti-CD34 | M7165, Dako, Denmark | 1 : 100 |
| Polyclonal rabbit anti-CD34 | orb46647, Biorbyt, UK | 1 : 200 |
| Monoclonal mouse anti-CD31 | M082301-2, Dako, Denmark | 1 : 100 |
| Polyclonal goat anti-PDGFR alpha | AF-307-NA, R&D Systems, USA | 1 : 100 |
| Monoclonal mouse anti-tryptase | M7052, Dako, Denmark | 1 : 100 |
| Polyclonal rabbit anti-VEGFR-1 | orb127531, Biorbyt, UK | 1 : 100 |
| Secondary antibodies: | | |
| Alexa Fluor 488 Goat Anti-Mouse | 115-545-146, Jackson ImmunoResearch, USA | 1 : 400 |
| Alexa Fluor 594 Goat Anti-Rabbit | 111-585-144, Jackson ImmunoResearch, USA | 1 : 400 |
| Alexa Fluor 594 Donkey Anti-Goat | 705-585-003, Jackson ImmunoResearch, USA | 1 : 400 |
| Alexa Fluor 488 Rabbit Anti-Mouse | 315-545-045, Jackson ImmunoResearch, USA | 1 : 400 |
| Alexa Fluor 488 Goat Anti-Rabbit | 111-545-144, Jackson ImmunoResearch, USA | 1 : 400 |
| Alexa Fluor 594 Goat Anti-Mouse | 115-585-146, Jackson ImmunoResearch, USA | 1 : 400 |

Microscopic examination of telocytes, collagen deposits and vascular parameters

Slides were examined using an MN800FL epi-fluorescence microscope (OptaTech, Warszawa, Poland) equipped with an Olympus DP74 digital CCD camera. Digital images were collected at either 200×, 400× or 600× magnification. The qualitative analysis of cells was provided in 10 consecutive high-power fields of vision (600×) using the computer-based image analysis system Multiscan 18.03 software (CSS, Warszawa, Poland). All samples were assessed by two independent specialists (each blinded to the other) without any knowledge of the clinical parameters or other prognostic factors to avoid bias.

The use of mast cell tryptase staining enabled c-kit-positive mast cells to be distinguished from c-kit-positive TCs. TCs were considered cells that were c-kit positive and tryptase negative concurrently, with the characteristic morphology in tissue samples. Additionally, cells double positive for CD34...
and PDGFRA with the characteristic morphology and localization were also recognized as TCs. In order to distinguish populations of CD34-positive cells in the myometrial tissue (vessels and telocytes), we used double immunolabelling for CD34/CD31. Double positive structures were marked as vessels, whereas CD43-positive cells with elongated oval-shape body and long extensions were marked as telocytes. The vascular density was evaluated by the analysis of CD31 and sFlt-1 (VEGFR-1) immunopositivity in all myometrial samples. In all sections the immunoreactive cells found were evaluated with respect to the relative frequency (arbitrarily graded as very few = (+), few = +, moderate density = ++, multiple density = +++).

The percentage of collagen deposits and muscle tissue was analyzed in specimens, stained with Masson trichrome. The collagen and muscle fiber volume ratio was determined in ten consecutive fields of view of each sample.

**Results**

The histopathological changes in all uterine samples in this study were determined by hematoxylin–eosin and Masson’s trichrome staining. Leiomyoma was composed of interlacing fascicles of uniform spindle cells. The nuclei were elongated, and the cytoplasm was abundant, eosinophilic and fibrillar. The adjacent myometrium and the foci of fibroids were cytologically identical, but the latter was circumscribed and nodular with denser cellularity (Figure 1). Light microscopy of uterine fibroids, adjacent myometrium and normal myometrium using Masson’s trichrome staining for collagen revealed collagen to be abundant in the fibroid tissue, while the myometrium had sparse, well-aligned collagen bundles adjacent to smooth muscle cells. The study group was characterized by the prevalence of collagen deposits compared with the control group. The amount of muscle fibers was lower compared with the adjacent myometrium. Conversely, the percentage of muscle fibers was higher in the normal myometrium, while collagen was scantily present in this type of tissue. In addition, a more significant difference in contents of both components was revealed in the myometrium, surrounding myometrial fibroids. The prevalence of muscle fibers correlates with poor organization of collagen deposits, which was approximately 2.5 times lower compared with muscles (Table II).

![Figure 1](image-url) Hematoxylin–eosin and Masson’s trichrome-stained sections of human myometrium. The myometrium sections from the control group (A, C) compared with the foci of leiomyoma (B, D). With Masson’s trichrome staining, collagen deposits were blue in color; muscle fibers, red in color. Fragments of disordered smooth muscle cells were separated by abundant extracellular matrix (ECM). Scale magnification bar: 100 μm
Immunofluorescent labeling was performed for the primary identification of TCs on uterine tissue affected and unchanged by UL. We used current, mostly proven markers, including CD34, PDGFRα and the canonic c-kit. Double immunolabeling for c-kit and tryptase was performed for the identification of mast cells and signs of consequent inflammation. In immunostained slides, c-kit and tryptase double-positive mast cells were generally round or oval shaped, with a centrally located nucleus. The c-kit-positive/mast cell tryptase-negative cells were considered TCs (Figure 2). These cells were mostly fusiform in shape with small branches. They have been detected in UL and adjacent myometrium as well as in normal myometrium from healthy uterus.

We also found that double immunopositive cells for CD34 and PDGFRα (putative uterine TCs) are present in leiomyomas, adjacent myometrium and normal myometrium. Mostly they had elongated oval-shaped cellular bodies and were distributed among the intertwined myometrial fibers and in close vicinity to blood vessels. The general pattern of their localization resembled parallel eccentric lines. However, in some parts, they reflected directional smooth muscle bundles. CD34/PDGFRα-positive cells were scantily present in the foci of leiomyoma (Figure 3).

Immunolabeling for CD31 was performed for assessment of vascular density in myometrial tissue from affected and unchanged by leiomyoma samples. The CD31 labeling showed lower expression in the foci of leiomyoma. The normal myometrium as well as adjacent to the pathology had plenty of CD31-positive cells, which mostly formed circular and longitudinal lines (Figure 4). In addition, double immunostaining for CD34/CD31 revealed

| Variable | Affected uterus | Unchanged uterus |
|----------|----------------|-----------------|
| Collagen (%) | 44 ±15 | 18 ±6 | 24 ±10 |
| Muscle fibers (%) | 33 ±13 | 45 ±13 | 43 ±10 |
cells which were only CD34-positive and had long extensions. They were detected between vessels and myometrial fibers, not rare in close vicinity to small vessels. Their expression was higher in the normal myometrium and lower in that affected by myoma. We assume that CD34-positive cells were uterine telocytes (Figure 5).

The opposite tendency was observed in samples labeled by VEGFR-1 (sFlt-1). The expression of this marker was higher in the foci of leiomyoma, while normal and adjacent myometrium had fewer sFlt-1 positive cells (Figure 6).

In all sections the immunoreactive cells found were evaluated with respect to the relative frequency. The subjective qualitative analyses showed the decreasing density of TCs in fibroids compared with both types of unchanged myometrium (adjacent and from healthy uterus). The expression of CD31 was higher in the normal myometrium and significantly lower in the foci of leiomyoma. The opposite effect was typical for sFlt-1 expression. Leiomyoma was characterized by increasing of sFlt-1 expression. Results of semi-quantitative analysis of CD34 immunoreactivity in TCs from human fetal skeletal muscle samples are summarized in Table III.

Discussion

Since TCs were reported for the first time, a number of studies worldwide have described these cells in different organs. Their primary identification is frequently sought. The c-kit receptor was the most attractive target in immunohistochemical observation. However, duplex immunoreactivity gave a reason to discuss a few populations of TCs in the human myometrium and the human small intestine [47–49]. In 2005, Ciontea et al. suggested that at least two subpopulations of TCs could exist in the human myometrium: c-kit-positive and c-kit-negative cells [48]. In addition, consistent with previous studies, Went et al. provided a list of c-kit-negative structures including the endometrium, myometrium and uterine cervix [50]. Moreover, Duquette et al. separately revealed vimentin (+)/c-kit (−) TCs in the human myometrium [47]. Later, in 2014, Yang et al. revealed that TCs were negative for c-kit in the rat oviduct [35]. First, Faussone-Pellegrini et al. concluded in 2011 that CD34-labeling “remains the best available choice for TC identification, possibly in combination with c-kit and vimentin labeling”, as c-kit-negative cells were described not only in the human uterus but also in the animal uterus [51]. Two years later, Vanrucci et al. proposed double immunofluorescent staining for CD34 and PDGFR-α as a specific marker for TCs in the gastrointestinal tract [52], which

Table III. Relative frequency of c-kit-positive/tryptase-negative, CD34-positive and PDGFRα-positive, CD31-positive and sFlt-1-positive cells in different parts of human unchanged uterus and uterus affected by leiomyoma.

| Variable                  | c-kit+/tryptase- | CD34+/PDGFRα+ | CD31 | VEGFR-1 (sFlt-1) |
|---------------------------|-----------------|---------------|------|-----------------|
| Normal uterus:            |                 |               |      |                 |
| Unchanged myometrium     | +++             | +++           | +++  | +               |
| Myomatous uterus:         |                 |               |      |                 |
| Adjacent myometrium      | ++              | ++            | ++   | +               |
| Focus of fibroid          | +               | +             | +    | ++              |
was successful in the heart and other organs [53]. Finally, in 2016, Faussone-Pellegrini et al. emphasized that “CD34 is the most reliable TC marker” [26]. Recently, some authors published the results of TC identification in the uterus based only on c-kit immunolabeling, which, in our opinion, is an omission. Moreover, some of them stressed that leiomyoma does not have any c-kit-positive cells, while an excess number of mast cells, common for the studied pathology, is strongly c-kit-positive. Therefore, we stressed the significance of using double immunofluorescent staining with anti-tryptase antibodies for separating mast cells from TCs. We found CD34- and PDGFR-α-positive cells in myometrial tissue from the foci of fibroids, the surrounding walls of the same uterus and healthy samples without UL. We emphasized that TCs exist in all samples of observed tissue.

Several studies have been devoted to explaining a possible role of new cells in diseases. In addition, all authors identified some quantitative and qualitative features common to TCs in pathological conditions: a reduction in numbers and/or damage of cells (up to absence) as well as shrinkage and shortening of Tps [26, 28, 54, 55]. Most likely, they are more sensitive to local ischemia than other stromal cell types, such as fibroblasts, myofibroblasts and mast cells. Manetti et al. observed the dynamics of TCs in tissues (the gastric wall — submucosa and muscle layers, the myocardium and the lung) from patients affected by systematic sclerosis and suggested that the reduction of TCs can lead to changing of the three-dimensional organization of the extracellular matrix and, as a result, the development of fibrosis [28]. In addition, the similar decline of TCs has been documented in myocardial infarction [30], aging of the human heart [56], liver fibrosis [37], ulcerative colitis [57], Crohn’s disease [29], gallstone disease [19], endometriosis [35], psoriasis [34], renal ischemia/reperfusion injury [40, 41] and different lung diseases [56]. Regardless of location, staging and character of pathology, the reduction of TCs is correlated with subsequent fibrosis, has a cellular origin and is common for many injuries and pathologies [58, 59]. We intend to provide further quantitative analysis of TC number in the foci of myoma and healthy myometrium, although we could hypothesize that the density of TCs declines in leiomyoma.

The interaction between TCs and the pathophysiological mechanisms common for the selected diseases is unclear. From one point of view, the amount of TCs declined under changes in the microenvironment associated with pathology. From the other viewpoint, the decrease of TCs could be a key point in the pathogenesis. These cells reflect damage, or they could be involved in the background of the diseases; the question remains open. We revealed the presence of TCs in uterine fibroids. Before, only comparisons of the density and the distribution in pregnant and nonpregnant uteruses in rats and humans had been provided. TCs constituted approximately 7% of the total cell number in nonpregnant myometrial cell culture and approximately 3% of the entire cell population in the myometrium of adult nonpregnant humans [60, 61]. The TC interstitial system is composed of cells that by either homocellular or heterocellular contact integrate overall information from the vascular, the nervous and the immune systems, the interstitium and stem cells. In the myometrium, TCs can influence the contractile activity of smooth muscle cells. Of note, they differed in telopodal width and podomic thickness with pregnancy states, which may be related to their function [44, 45]. Current studies showed that the podomers are thicker in nonpregnant myometrium than in pregnant myometrium (~82 vs. 75 nm), and the podoms were thicker in pregnant myometrium (~316 vs. 269 nm) [21, 43].

Richter et al. demonstrated that the numbers of TCs and Tps correlate negatively with the amount of mature fibrillar collagens and correlate positively with degraded collagen in the human heart [54]. We observed the same trend, which requires further investigation.

Growth factors have an influence on myometrial cellular transformation and turnover. For instance, PDGF modulates the rate of cell proliferation in myometrium and leiomyoma cells and likely plays a role in smooth muscle cell (SMC) hypertrophy as its expression is increased in the myometrium during gestation. It is upregulated by estrogen in uterine SMC and might interact with other growth factors such as TGF-β and EGF to enhance proliferation [5]. TCs are immunohistochemically positive for platelet-derived growth factor receptor α and β (PDGFR-α and -β) and VEGF. Of note, telocytes might be involved in the regulation of excessive cellular matrix production inside the foci of myoma [62].

Myometrial changes relate to three basic pathophysiological links: fibrosis, angiogenesis and the immune response. Growth factors involved in the pathogenesis of UL have receptors on TCs. Recent data showed that TCs are immunopositive to TGF-β, which is also involved in myocardial physiopathology. We suggest that the same could occur in myometrial contractility. One of the essential elements of leiomyoma is the vascular capsule. Neovascularization correlates with hypoxia and misbalance of vascular and coagulation factors. We observed a decrease of vasculization in the foci of leiomyoma, accompanied by increasing expression of VEGF receptor-1 (sFlt-1). Hypoxia could be a leading factor leading
to this change. However, the common feature for both observed subjects was that in the foci of leiomyoma we saw a decline of telocytes and of vascularization too. Uterine telocytes are sensitive to angiogenic factors (PDGF and VEGF) and ischemia; they declined and even disappeared during fibrosis, observed in close vicinity to blood vessels. They might play a role in the angiogenic response, universal for the human body. In clinical practice it might clarify the pathogenesis of the oxidative response in the myometrium and help in selection of further appropriate therapy as a consequence. We intend to observe this correlation in our future scientific work.

In conclusion, our data demonstrate that TCs are present in human uterine fibroids and highlight their possible involvement in the pathogenesis of myometrial pathology in the context of angiogenesis. Further studies will allow clarification of the details of their putative roles in angiogenesis and the principles of their interaction in the myometrium. We hypothesize that in-depth observation of TCs in the human uterus brings additional value to reproductive medicine.

**Conflict of interest**

The authors declare no conflict of interest.

**References**

1. Stewart EA, Cookson C, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG 2017; 124: 1501-12.
2. McWilliams MM, Chennathukuzhi VM. Recent advances in uterine fibroid etiology. Semin Reprod Med 2017; 35: 181-9.
3. Brosens I. Uterine Leiomyomata: Pathogenesis and Management. Informa Healthcare/Taylor & Francis Abingdon, England 2006.
4. Levy G, Hill M, Beall S, Zakrz SM, Seghers JH, Catherini WH. Leiomyoma: genetics, assisted reproduction, pregnancy and therapeutic advances. J Assist Reprod Genet 2012; 29: 703-12.
5. Aleksandrovych V, Bereza T, Sajewicz M, Walocha JA, Gil K. Uterine fibroid: common features of widespread tumor (Review article). Folia Med Cracov 2015; 55: 61-75.
6. Bulun SE. Uterine fibroids. N Engl J Med 2013; 369: 1344-55.
7. Tal R, Segars J. The role of angiogenic factors in fibroid pathogenesis: potential implications for future therapy. Hum Reprod Update 2014; 20: 194-216.
8. Ciarmela P, Islam S, Reis F, et al. Growth factors and myometrium: biological effects in uterine fibroid and possible clinical implications. Hum Reprod Update 2011; 17: 772-90.
9. Sirin G, Kanaarslan N. Evaluation of the effects of pregabal on chondrocyte proliferation and CHAD, HIF-1alpha, and COL2A1 gene expression. Arch Med Sci 2018; 14: 1340-7.
10. Ishikawa H, Xu L, Sone K, Kobayashi T, Wang G, Shou M. Hypoxia induces hypoxia-inducible factor 1 alpha and potential HIF-responsive gene expression in uterine leiomyoma. Reprod Sci 2019; 26: 428-35.
11. Walocha JA, Litwin JA, Miodoński AJ. Vascular system of intramural leiomyomata revealed by corrosion casting and scanning electron microscopy. Hum Reprod 2003; 18: 1088-93.
12. Fletcher NM, Abusamaan MS, Memaj I, et al. Oxidative stress: a key regulator of leiomyoma cell survival. Fertil Steril 2017; 107: 1387-94.e1.
13. Pei X. Who is hematopoietic stem cell: CD34+ or CD34-? Int J Hematol 1999; 70: 213-5.
14. Hussein MM, Mohktar DM. The roles of telocytes in lung development and angiogenesis: an immunohistochemical, ultrastructural, scanning electron microscopy and morphometrical study. Dev Biol 2018; 443: 137-52.
15. Zheng Y, Wang X. Roles of telocytes in the development of angiogenesis. Adv Exp Med Biol 2016; 913: 253-61.
16. Kuczyńska I, Janas P, Ciuk S, Cholopak W, Klimek-Piotrowska W, Holda MK. A comprehensive guide to telocytes and their great potential in cardiovascular system. Bratisl Lek Listv 2017; 118: 302-9.
17. 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: 729-40.
18. Matyja A, Gil K, Pasternak A, et al. Telocytes: new insight into the pathogenesis of gallstone disease. J Cell Mol Med 2013; 17: 734-42.
19. Cretoiu SM, Popescu LM. Telocytes revisited. Blomol Concepts 2014; 5: 85-69.
20. Popescu LM, Ciontea SM, Cretoiu D. Interstitial Cajal-like cells in human uterine and fallopian tube. Ann N Y Acad Sci 2007; 1101: 139-65.
21. Cretoiu SM, Cretoiu D, Marin A, Radu BM, Popescu LM. Telocytes: ultrastructural, immunohistochemical and electrophysiological characteristics in human myometrium. Reproduction 2013; 145: 357-70.
22. Aleksandrovych V, Walocha JA, Gil K. Telocytes in female reproductive system (human and animal). J Cell Mol Med 2016; 20: 994-1000.
23. Huizinga JD, Thuneberg L, Vanderwinden JM, Rumesen JJ. Interstitial cells of Cajal as targets for pharmacological intervention in gastrointestinal motor disorders. Trends Pharmacol Sci 1997; 18: 393-403.
24. Gherghiceanu M, Popescu LM. Interstitial Cajal-like cells (ICLC) in human resting mammary gland stroma. Transmission electron microscope (TEM) identification. J Cell Mol Med 2005; 9: 893-910.
25. Diaz-Flores L, Gutiérrez R, Díaz-Flores LJr, Gómez MG, Sáez FJ, Madrid JF. Behaviour of telocytes during physiological activation. Semin Cell Dev Biol 2016; 55: 50-61.
26. Faussone-Pellegrini MS, Gherghiceanu M. Telocyte’s contacts. Semin Cell Dev Biol 2016; 55: 3-8.
27. Manetti M, Guiducci S, Ruffo M, et al. Evidence for progressive reduction and loss of telocytes in the dermal cellular network of systemic sclerosis. J Cell Mol Med 2013; 17: 482-96.
28. Manetti M, Rosa I, Messerini L, Guiducci S, Matusic-Cerinic M, Ihiba-Manneschi L. A loss of telocytes accompanies fibrosis of multiple organs in systemic sclerosis. J Cell Mol Med 2014; 18: 253-62.
29. Milia AF, Ruffo M, Manetti M, et al. Telocytes in Crohn’s disease. J Cell Mol Med 2013; 17: 1525-36.
30. Manole CG, Cismasiu V, Gherghiceanu M, Popescu LM. Experimental acute myocardial infarction: telocytes involvement in neo-angiogenesis. J Cell Mol Med 2011; 15: 2284-96.
Identification of PDGFRα+ cells in uterine fibroids – link between angiogenesis and uterine telocytes

31. Pasternak A, Bugajska J, Szura M, et al. Biliary polyunsaturated fatty acids and telocytes in gallstone disease. Cell Transplant 2017; 26: 125-33.
32. Pasternak A, Gil K, Gajda M, Tomaszewski KA, Matyja A, Walocha JA. Interstitial cajal-like cell: a new player in cholelithiasis? Am J Gastroenterol 2014; 109: 603-4.
33. Manole CG, Gherghiceanu M, Simionescu Q. Telocyte dynamics in psoriasis. J Cell Mol Med 2015; 19: 1504-19.
34. Yang J, Chi C, Liu Z, Yang G, Shen ZI, Yang XZ. Ultrastructure damage of oviduct telocytes in rat model of acute salpingitis. J Cell Mol Med 2015; 19: 1720-8.
35. Yang XL, Yang J, Liu Z, Yang G, Shen ZI. Telocytes damage in endometriosis-affected rat oviduct and potential impact on fertility. J Cell Mol Med 2015; 19: 452-62.
36. Aleksandrovych V, Sajewicz M, Walocha JA, Gil K. Tubal telocytes: factor infertility reason? Folia Med Cracov 2016; 56: 17-23.
37. Fu S, Wang F, Cao Y, et al. Telocytes in human liver fibrosis. J Cell Mol Med 2015; 19: 676-83.
38. Alunno A, Ibba-Manneschi L, Bistoni O, et al. Telocytes in minor salivary glands of primary Sjögren’s syndrome: association with the extent of inflammation and ectopic lymphoid neogenesis. J Cell Mol Med 2015; 19: 1689-96.
39. Marini M, Mencucci R, Rosa I, et al. Telocytes in normal and keratoconic human cornea: an immunohistochemical and transmission electron microscopy study. J Cell Mol Med 2012; 16: 3602-11.
40. Gevaert T, De Vos R, Everaerts W, et al. Characterization of upper lamina propria interstitial cells in bladders from patients with neurogenic detrusor overactivity and bladder pain syndrome. J Cell Mol Med 2011; 15: 2586-93.
41. Wolnicki M, Aleksandrovych V, Gil K. Interstitial cells of Cajal and telocytes in the urinary system: facts and distribution. Folia Med Cracov 2016; 56: 81-9.
42. Salama NM. Immunohistochemical characterization of telocytes in rat uterus in different reproductive stages. Egypt J Histol 2013; 36: 185-94.
43. Roaesi I, Radu BM, Cretoiu D, Cretoiu SM. Uterine telocytes: a review of current knowledge. Biol Reprod 2015; 93: 10.
44. Campeanu RA, Radu BM, Cretoiu SM, et al. Near-infrared low-level laser stimulation of telocytes from human myometrium. Lasers Med Sci 2014; 29: 1867-74.
45. Cretoiu SM, Cretoiu D, Popenescu LM. Human myometrium – the ultrastructural 3D network of telocytes. J Cell Mol Med 2012; 16: 2844-9.
46. Cretoiu D, Cretoiu SM. Telocytes in the reproductive organs: current understanding and future challenges. Semin Cell Dev Biol 2016; 55: 40-9.
47. Duquette R, Shmygol A, Vaillant C, et al. Vimentin-positive, c-kit-negative interstitial cells in human and rat uterus: a role in pacemaking? Biol Reprod 2005; 72: 276-83.
48. Ciontea SM, Radu E, Regalia T, et al. C-kit immunopositive interstitial cells (Cajal-type) in human myometrium. J Cell Mol Med 2005; 9: 407-20.
49. Horiguchi K, Keef KD, Ward SM. Distribution of interstitial cells of Cajal in tunica muscularis of the canine rectoanal region. Am J Physiol Gastrointest Liver Physiol 2003; 284: 756-67.
50. Went PT, Dirnhofer S, Bundi M, et al. Prevalence of KIT expression in human tumors. J Clin Oncol 2004; 22: 4514-22.
51. Faussone-Pellegrini MS, Popenescu LM. Telocytes. Biomol Concep 2011; 2: 481-9.