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Review

Telocytes: a brief review for the obstetrics/gynecology clinician

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Summary

Telocytes (TCs) are unique interstitial cells with a wide array of intercellular communication tools. They appear to be an integral part of interstitium of different organs, including the female genital organs. Immunohistochemistry of these cells shows that organ-specific phenotypes exist, and electronic microscopy proved occurrence of morphologically different types of TCs within one organ expecting variety functions. Ongoing research is starting to uncover possible roles of TCs in these organs like mechanical support of tissues, regulation of morphogenesis, regeneration of tissues, and maintaining of homeostasis through impact on neural, vascular and endocrine processes. Disturbation in their number or function leads to disruption of hormonal control and is related to cancer progression. This review offers an overview of available data as well as popular theories.

Key words: Telocytes; Communication; Homeostasis; Reproductive tract.

Introduction

Telocytes (TCs) are a recently discovered phenotype of interstitial cells of mesenchymal origin. Although they have been known since 2005 as interstitial Cajal-like cells [1], they were finally recognized as a separate cell type only in 2010, based on their specific morphological and structural features, as well as their proteomic profile [2, 3]. Structurally, they are characterized by a small cell body (9–15 microns) with a small volume of cytoplasm and 1–5 slender cell extensions. These cell extensions are called telopodes, and they are disproportionally long compared to the cell body, with a length of up to 100 microns, with a moniliform shape and a thickness varying between 20–300 nanometers. The thin parts of the telopodes are called podomers and contain microfilaments, microtubules, and the intermediary filament protein vimentin. Dilated parts of the telopodes contain mitochondria, endoplasmic reticulum, and caveolae and are called podoms [4].

Identification of TCs

The gold standard for the identification of TCs is transmission electron microscopy. However, this method is time-consuming and costly. Immunohistochemistry offers a more convenient identification method; however, no single pathognomonic marker has yet been identified. Positivity to these markers varies, and it is also assumed that various organ specific phenotypes of TCs exist [5]. Currently, the most reliable test to identify TCs is considered to be double positivity for CD34/PDGFR-α (platelet-derived growth factor receptor α) and CD34/vimentin, making immunolabelling a viable tool in the identification of TCs [4]. Table 1 offers an overview of usable immunomarkers for identifying TCs in the reproductive system, including placenta.

Function of TCs

TCs seem to form a functional network connecting TCs with other TCs or different structures – secretory ducts, nerve fibers, mast cells, fibroblasts, pericytes, endothelial cells, collagen fibers or vessels. This contact is possible either directly through nano junctions, which can be homo or heterocellular, or indirectly – utilizing extracellular vesicles (EV) [6, 7].

Interstitial cells are responsible for morphogenesis and homeostasis of tissues and organs. TCs belong to this heterogeneous group of cells, and it is clear that they play an important role in the intracellular signaling system. Although the exact function of their network remains unclear, their means of communication suggests that they could play an integral role in neural, vascular, and endocrinological processes. Some authors theorize that TCs are vital in defending, remodeling, and regeneration of tissue [8, 9]. It is also quite probable that TCs are responsible for mechanical support, spatial relationships with different cell types, and modulation of intestinal motility [10].

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Table 1. — *Monoclonal antibodies used in identification of human telocytes in the reproductive system (summary from cited works).*

Endometrium	CD34 (+), vimentin (+), connexin 43 (+)
Myometrium	CD34 (+)/PDGFRα (+), α-smooth muscle actin (-)
Fallopian tube	c-kit (CD117) (+), CD34 (+), vimentin (+), α-smooth muscle actin (+)
Ovary (mouse)	CD34 (+)/PDGFRα (+), CD34 (+)/PDGFRβ (+), CD34 (+)/vimentin (+)
Mammary gland	c-kit (CD117) (+), CD34 (+), vimentin (+)
Placenta	vimentin (+), c-kit (CD117) (+), CD34 (+), VEGF (+), caveolin-1 (+), iNOS (+), α-smooth muscle actin (+), neuron-specific enolase (+), nestin (+)

Table 2. — *Putative functions of telocytes in reproductive system (summary from cited works).*

Uterus	Mechanoreceptors – recording pressure in myometrium; Managing contractibility of myometrium – during labor, during menstrual bleeding, during postpartal involution of the uterus; Hormonal receptors – cooperating on hormonal signaling, providing tools for hormonal control; Endometrium – structural support, regeneration after menstrual bleeding; Leiomyomas – putative active role in their creation/growth
Fallopian tube	Motility –TCs are vital for normal tubal function, or are a marker of their functionality; Hormonal receptors – cooperating on hormonal sign--ling, providing tools for hormonal control
Ovary	Functionality – possible marker for ovarian functionality (premature ovarian failure); Participating in normal follicular development, ovulation, luteinization, formation, and maintenance of the corpus luteum
Mammary gland	Involvement in mammary gland homeostasis and development; Facilitating cancer progression, inhibiting apoptosis of cancer cells
Placenta	Involvement in trophoblast differentiation; Regulation of villous growth; Regulation of the depth of villous invasion in myometrium

Uterus

The uterus is a functionally unique organ. It is capable of contractions of varying intensity – weak contractions to shed the endometrial lining during menstrual bleeding and strong contractions during labor. The elasticity of its smooth muscle cells also allows the uterus to significantly grow in size and volume during pregnancy and to retract to almost original size afterwards. While the hormonal and biochemical interactions are largely understood, some aspects – organ wide coordination of muscle cells, outside interference to modulate these contractions – still remain unclear [11].

TCs were first identified in the uterus in 2005 [12]. They were identified in the endometrial stroma of the *stratum functionalis*, as well as in the basal endometrium after menstruation [13]. TCs were observed to follow the shape of the neighboring epithelial architecture. Given their location and what is known about their capabilities, it's possible they provide structural support for endometrial glands, forming a functional unit [13]. Endometrial TCs express connexin 43, a gap junction protein which is linked with maturation of decidua and the decrease of which is connected with recurrent pregnancy loss [14].

TCs were also identified in myometrium of both pregnant and non-pregnant women, forming a 3D supportive network [15]. Numerous extracellular vesicles (EVs) were observed, suggesting an active role of TCs in this location. Interestingly, no significant differences in EVs released from TCs in pregnant or non-pregnant myometrium were observed [16]. Immature uteri contain only a small number of TCs when compared to adult, non-pregnant uteri. Pregnant uteri show a further increase in endometrial TCs and a significant decrease in myometrial TCs. The telopodes of TCs of a pregnant uterus were shorter and thicker when compared to telopodes of samples from non-pregnant uteri. The highest count of myometrial TCs was observed in postpartum uteri [17]. These observations further support the functional importance of uterine TCs, enabling us to hypothesize that the concentration of TCs is in direct correlation with the contractibility of the uterus. This thesis was further supported by demonstration of the presence of small-conductance calcium-activated potassium channels in the TCs of non-pregnant myometrium, in contrast to their absence in the TCs of pregnant myometrium [18]. These channels were shown to participate in myometrial relaxation in vitro [19].

If we accept the possibility of a TCs network functioning as a "primitive nervous system", we might be a step closer to defining the functional aspect of a pacemaker of uterine contractions. An inward hyperpolarizing current with a Ca^{2+} dependent component was observed in TCs from human non-pregnant myometrium, which also suggest their involvement in the excitability of myometrium [16]. It was also confirmed that TCs stain positive for the presence of estrogen receptor α and progesterone receptor A, intensely on the nuclear level and weaker in the cytoplasm [20]. A recent study also discovered a higher number of TCs in uterine leiomyomas in comparison to adjacent and even normal (distant) myometrium. TCs isolated in leiomyomas were showing signs of increased cellular activity – elongated telopodes, a large number of mitochondria and dilated endoplasmic reticulum cisternae, which would indicate their active role in the creation or growth of leiomyomas [21].

Fallopian tubes

TCs were identified in fallopian tubes, predominantly in the *lamina propria* and in between smooth muscular fibres

of the *tunica muscularis externa*. The concentration of TCs in the wall of the fallopian tubes decreases from the subepithelial area to the serosa. In contrast to TCs in the uterus, local TCs showed positivity to α-smooth muscle actin. TCs located in the fallopian tube tissue are positive for the presence of estrogen receptor α and progesterone receptor A on the TCs, even at the nuclear level [20]. Several disorders connected to damage or dysfunction of the fallopian tubes are also characterized by a reduction or complete loss of TCs.

Yang *et al.* observed in an animal model a significant reduction or complete loss of TCs in fallopian tubes with acute salpingitis. Remaining TCs were also damaged, with ultrastructural abnormalities, such as loss of organelles, swollen nucleus, mitochondria and endoplasmic reticulum dilatation, dissolution of telopodes, and loss of intracellular junctions [22].

A complete loss of TCs in fallopian tubes was also observed in an animal experiment, in which mice were infected with *Chlamydia muridarum*. This led to tubal dysfunction, due to a blocking of the propulsive contractions needed for egg transportation. The experiment also showed that it was not the effect of the infection that led to the disruption of TCs, but the upregulation of nitric oxide synthase 2, as part of the inflammatory response [23].

A very similar observation was made with fallopian tubes affected by endometriosis. Again, a reduction or complete disappearance of TCs was observed, along with signs of ultrastructural damage in the persisting TCs [24]. A reduction of the numbers of TCs or impairment of their functions may very well be a factor in infertility.

Ovary

TCs in ovaries have not attracted much attention yet. Save for two animal experiments, there are no available papers on this topic. Liu *et al.*, however, did prove the presence of TCs in ovarian stromal tissue and also made an interesting discovery. When they induced premature ovarian failure using cyclophosphamide, they also observed a significant reduction in the number of TCs in the ovarian tissue [25]. It is, of course, not yet clear if the reduction in the number of TCs is just a byproduct of generalized atrophy of ovarian tissue (and a possible marker of this disorder), or if ovarian function is actually dependent of their presence.

Abd-Elkareem *et al.* confirmed the presence of progesterone receptor A on ovarian TCs using immunostaining, with moderate cytoplasmic and negative nuclear activity. His experiment also showed that progesterone receptor A, while not exclusively located only on TCs, is vital for normal follicular development, ovulation, luteinization, and the formation and maintenance of the corpus luteum [26].

Mammary gland

TCs in mammary gland were first mentioned in 2005 (then called interstitial Cajal-like cells). They were found in the stroma of the gland, in contact with plasma cells, lymphocytes, fibroblasts, mast cells, and macrophages [27]. It is well documented that mammary stroma having TCs play an important role in breast homeostasis [28]. In case of this specific organ, research is attempting to identify the role of TCs in cancerogenesis, in accordance with tissue organization field theory. According to this theory, the reasons for the creation of cancer are disorders of the cellular microenvironment [29]. When examining tissue samples from patients with mammary carcinoma, Mihalcea *et al.* observed a significant reduction in the heterocellular junctions in affected tissue [30].

Mou *et al.* observed in an *in vitro* experiment on reconstituted breast cancer tissue that TCs were in close contact with cancer cells; they hypothesized that TCs are participating in the creation of the nest structures of cancer cells, a typical structure for the spread of cancer [31]. Furthermore, when comparing cultures with cancer cells alone to cultures with cancer cells and stromal cells, including TCs, they observed a higher apoptosis rate in the first group, leading them to believe that TCs also positively affect the survival of cancer cells [31].

Placenta

The presence of TCs in placental tissue is unique, since placenta is a non-innervated organ. Their presence was confirmed in 2007, specifically in the extraembryonic mesoderm of the villi from human term placenta. Utilizing gap junctions, the TCs formed a network with smooth muscle cells, blood vessels, and myofibroblasts [32]. Given this strategic placement of TCs and the lack of innervation, it is easy to assume that TCs are relevant in cellular signaling and blood flow regulation [33].

The placenta is the place where the physiological exchange between mother and fetus occurs. In a sense, the placenta functions as the lungs, gastrointestinal tract, kidneys, liver, and endocrine organs for the fetus [34]. A guarded balance between proliferation, differentiation, and apoptosis in the placenta is vital for its normal functioning. Pathology of the placenta usually translates into ramifications for the development of the fetus. In pregnancies complicated by preeclampsia, a reduction of utero-placental perfusion is observed, leading to chronic hypoxia of the fetus in late pregnancy. Placental ischemia may trigger the release of placental factors that are responsible for cellular and molecular changes, causing damage or destruction to TCs [33]. The loss of heterocellular contacts provided by TCs can lead to the loss of the hypothetical regulatory function of these cells, negatively affecting the contraction/relaxation of the chorionic villi, which will result in a decrease of the contact surface of the villi with maternal blood and potentially leading to intrauterine growth retardation of the fetus [35].

A more recently published study by Nizyaeva *et al.* de-

scribed three types of TCs in placenta, based on their ultrastructural differences. Type I TCs were identified in immature intermediate villi, forming a network in the whole villus, and are characterized by polygonal cell form, irregular nucleus, and with thin surrounding cytoplasm. Type II TCs were found in mature intermediate villi as spindle-shaped cells, under the basal membrane of the syncytiotrophoblast, with an oval nucleus and forming a continuous layer beneath the said membrane. Type III TCs are located deeper in the villous stroma, with a stellate cell shape and displaying a larger number of telopodes than type II TCs [36]. The authors also observed that when compared to TCs in the intestinal tract (the place of their first discovery and with the best described cell characteristics), placenta TCs display a low content of cell organelles, in particular mitochondria. And finally, they hypothesized that it is possible for TCs to transform from type I into types II and III and finally, into fibroblast-like and myofibroblast-like cells, during differentiation of villous stroma. This process – fibrosis of the stroma – is physiological in normal placental maturation but is more pronounced in placental pathology, leading to placental insufficiency and intrauterine growth retardation [36].

Table 2 offers a list of possible roles that TCs have in reproductive organs and the placenta. Most of these functions are, of course, based on hypothesis and by extrapolation of functions of TCs located in different organs.

Conclusion

While it awaits to be seen if TC functions can be confirmed or if the knowledge can be translated into useful clinical information, it is difficult not to understand the enthusiasm that surrounds these unique cells.

References

[1] Gherghiceanu M., Popescu L.M.: "Interstitial Cajal-like cells (ICLC) in human resting mammary gland stroma. Transmission electron microscope (TEM) identification". *J. Cell. Mol. Med*., 2005, *4*, 893.

[2] Zheng M., Sun X., Zhang M., Qian M., Zheng Y., Li M., *et al.*: "Variations of chromosomes 2 and 3 gene expression profiles among pulmonary telocytes, pneumocytes, airway cells, mesenchymal stem cells and lymphocytes". *J. Cell. Mol. Med*., 2014, *10*, 2044.

[3] Zheng Y., Cretoiu D., Yan G., Cretiou S.M., Popescu L.M., Wang X.: "Comparative proteomic analysis of human lung telocytes with fibroblasts". *J. Cell. Mol. Med.*, 2014, *4*, 568.

[4] Cretiou S.M., Popescu L.M.: "Telocytes revisited". *Biomol Concepts*, 2014, *5,* 353.

[5] Faussone-Pellegrini M.S., Gherghiceanu M.: "Telocyte's contacts". *Semin. Cell. Dev. Biol.*, 2016, *55*, 3.

[6] Bosco C., Diaz E., Gutiérrez R., González J., Pérez J.: "Ganglionar nervous cells and telocytes in the pancreas of Octodon degus: extra and intrapancreatic ganglionar cells and telocytes in the degus". *Auton. Neurosci.,* 2013, *2,* 224.

[7] Nicolescu M.I.: "Telocytes in Exocrine Glands Stroma". *Adv. Exp. Med. Biol*., 2016, *913,* 163.

[8] Xiao J., Wang F., Liu Z., Yang C.: "Telocytes in liver: electron microscopic and immunofluorescent evidence". *J. Cell. Mol. Med.*, 2013, *12,* 1537.

[9] Zhao B., Chen S., Liu J., Yuan Z., Qi X., Qin J., *et al.*: "Cardiac telocytes were decreased during myocardial infarction and their therapeutic effects for ischaemic heart in rat". *J. Cell. Mol. Med.,* 2013, *1,* 123.

[10] Milia A.F., Ruffo M., Manetti M., Rosa I., Conte D., Fazi M. *et al.*: "Telocytes in Crohn's disease". *J. Cell. Mol. Med*., 2013, *12,* 1525.

[11] Young R.C.: "Mechanotransduction mechanisms for coordinating uterine contractions in human labor". *Reproduction,* 2016, *2,* 51.

[12] Ciontea S.M., Radu E., Regalia T., Ceafalan L., Cretiou D., Gherghiceanu M., *et al.*: "C-kit immunopositive interstitial cells (Cajal-type) in human myometrium". *J. Cell. Mol. Med.,* 2005, *2,* 407.

[13] Hatta K., Huang M.L., Weisel R.D., Li R.K.: "Culture of rat endometrial telocytes". *J. Cell. Mol. Med.,* 2012, *7,* 1392.

[14] Nair R.R., Jain M., Singh K.: "Reduced expression of gap junction gene connexin 43 in recurrent early pregnancy loss patients". *Placenta,* 2011, *8,* 619.

[15] Cretoiu S.M., Cretoiu D., Popescu L.M.: "Human myometrium - the ultrastructural 3D network of telocytes". *J. Cell. Mol. Med.,* 2012, *11,* 2844.

[16] Cretoiu S.M., Cretoiu D., Marin A., Radu B.M., Popescu L.M.: "Telocytes: ultrastructural, immunohistochemical and electrophysiological characteristics in human myometrium". *Reproduction,* 2013, *4,* 357.

[17] Roatesi I., Radu B.M., Cretiou D., Crretiou S.M.: "Uterine Telocytes: A Review of Current Knowledge". *Biol. Reprod.,* 2015, *1,* 10.

[18] Rosenbaum S.T., Svalo J., Nielsen K., Larsen T., Jorgensen J.C., Bouchelouche P.: "Immunolocalization and expression of small-conductance calcium-activated potassium channels in human myometrium". *J. Cell. Mol. Med.,* 2012, *12,* 3001.

[19] Rosenbaum S.T., Larsen T., Joergensen J.C., Bouchelouche P.N.: "Relaxant effect of a novel calcium-activated potassium channel modulator on human myometrial spontaneous contractility in vitro". *Acta Physiol.,* 2012, *2*, 247.

[20] Cretoiu S.M., Cretoiu D., Simionescu A., Popescu L.M.: "Telocytes in Human Fallopian Tube and Uterus Express Estrogen and Progesterone Receptors". *In* Kahn S.M., (ed). *Sex Steroids.* Rijeka: InTech, 2012, 91.

[21] Othman E.R., Elgamal D.A., Refaiy A.M., Abdelaal I.I., Abdel-Mola A.F., Al-Hendy A.: "Identification and potential role of telocytes in human uterine leiomyoma". *Contraception Reprod. Med.,* 2016, *1,* 12.

[22] Yang J., Chi C., Liu Z., Yang G., Shen Z.J., Yang X.J.: "Ultrastructure damage of oviduct telocytes in rat model of acute salpingitis". *J. Cell. Mol. Med.,* 2015, *7,* 1720.

[23] Dixon R.E., Hwang S.J., Hennig G.W., Ransey K.H., Schripsema J.H., Sanders K.M., Ward S.M.: "Chlamydia Infection Causes Loss of Pacemaker Cells and Inhibits Oocyte Transport in the Mouse Oviduct". *Biol. Reprod.,* 2009, *4,* 665.

[24] Yang X.J., Yang J., Liu Z., Yang G., Shen Z.J.: "Telocytes damage in endometriosis-affected rat oviduct and potential impact on fertility". *J. Cell. Mol. Med.,* 2015, *2*, 452.

[25] Liu T., Wang S., Li Q., Huang Y., Chen C., Zheng J.: "Telocytes as potential targets in a cyclophosphamide-induced animal model of premature ovarian failure". *Mol. Med. Rep.,* 2016, *3,* 2415.

[26] Abd-Elkareem M.: "Cell-specific immuno-localization of progesterone receptor alpha in the rabbit ovary during pregnancy and after parturition". *Anim. Reprod. Sci.,* 2017, *180,* 100.

[27] Popescu L.M., Andrei F., Hinescu M.E.: "Snapshots of mammary gland interstitial cells: methylene-blue vital staining and c-kit immunopositivity". *J. Cell. Mol. Med.,* 2005, *2,* 476.

[28] Kim J.B., Stein R., O'Hare M.J.: "Tumour-stromal interactions in breast cancer: the role of stroma in tumourigenesis". *Tumour Biol.,* 2005, *4,* 173.

[29] Soto A.M., Sonnenschein C.: "The tissue organization field theory of cancer: a testable replacement for the somatic mutation theory". *BioEssays,* 2011, *5,* 332.

[30] Mihalcea C.E., Morosanu A.M., Murarasu D., Puiu L., Cinca S., Voinea S.C., *et al.*: "Particular molecular and ultrastructural aspects in invasive mammary carcinoma". *Rom. J. Morphol. Embryol.,* 2015*, 4,* 1371.
[31] Mou Y., Wang Y., Li J., Lu S., Duan C., Du Z., *et al.*: "Immunohistochemical characterization and functional identification of mammary gland telocytes in the self-assembly of reconstituted breast cancer tissue in vitro". *J. Cell. Mol. Med.*, 2013, *1,* 65.
[32] Suciu L., Popescu L.M., Gherghiceanu M.: "Human placenta: de visu demonstration of interstitial Cajal-like cells". *J. Cell. Mol. Med.,* 2007, *3,* 590.
[33] Bosco C., Diaz E., Gutiérrez R., Gonzáles J., Parra-Cordero M., Rodrigo R., *et al.*: "A putative role for telocytes in placental barrier impairment during preeclampsia". *Med. Hypotheses*, 2015, *1,* 72.
[34] Cross J.C.: "Placental function in development and disease". *Reprod. Fertil. Dev.,* 2006, *1,* 71.
[35] Bosco C.B., Diaz E.G., Gutiierrez R.R., Gonzáles J.M., Parra-Cordero M., Rodrigo R.S., *et al.*: "Placental Hypoxia Developed During Preeclampsia Induces Telocytes Apoptosis in Chorionic Villi Affecting The Maternal-Fetus Metabolic Exchange". *Curr. Stem Cell Res. Ther.,* 2016, *5,* 420.
[36] Nizyaeva N.V., Sukhacheva T.V., Kulikova G.V., Nagovitsyna M.N., Poltavtseva R.A., Kan N.E., *et al.*: "Ultrastructural Characteristics of Placental Telocytes". *Bull. Exp. Biol. Med.,* 2017, *5,* 693.

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