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Telocytes in the architecture of uterine fibroids

Veronika Aleksandrovych[1], Artur Pasternak[2], Krzysztof Gil[1]

[1]Department of Pathophysiology, Jagiellonian University Medical College, Kraków, Poland
[2]Department of Anatomy, Jagiellonian University Medical College, Kraków, Poland

Corresponding author: Veronika Aleksandrovych, MD
Department of Pathophysiology, Jagiellonian University Medical College
ul. Czysta 18, 31-121 Kraków, Poland
Phone: +48 12 633 39 47; Fax: +48 12 632 90 56; E-mail: v.aleksandrovych@doctoral.uj.edu.pl

Abstract: Knowledge of uterine fibroids has existed since the time of Hippocrates. However, there are still wide gaps in the understanding of its pathogenesis. No single theory explains the background of uterine fibroid pathology, which affects more than 50% of women worldwide. By contrast, a newly depicted cell type called telocytes was only recently identified in the past twenty years. These cells have evoked ambivalent opinions in the scientific community. The unique features of telocytes coupled with experimental evidence by numerous researchers and our hypotheses and conceptions are discussed in this review. We emphasize the main telocyte interactions in the context of the uterine fibroid architecture. This review reveals the pivotal role of telocytes, describing their contacts with smooth muscle cells, fibroblasts, vessels and nerves, inflammatory cells and stem cells. Our data are based on the latest publications and our own results.

Key words: uterine fibroids, extracellular matrix, telocytes, stem cell niche, CD34, telopodes.

Impact statement

This minireview describes the main interactions between the canonic structural components of uterine fibroids and newly revealed cells: telocytes. The latest data allow an evaluation of the importance of the leiomyoma architecture from another point of view. We hope that the facts and questions presented in this article will be discussed and reinforced by subsequent studies.

Structural heterogeneity of leiomyoma

Uterine fibroids, also known as leiomyomas, are the most common benign tumor of the female reproductive system, affecting nearly 50% of women of childbearing age, deteriorating their quality of life and potentially causing infertility [1–3]. An inalienable feature of each uterine leiomyoma (UL) is the excess production of extracellular matrix (ECM), which functions by providing structural support to cells [4, 5]. Despite UL having a monoclonal nature, being derived from a single cell, its phenotype is heterogeneous. Smooth muscle cells (myocytes) and fibroblasts are abundant in each fibroid. Moreover, the relative prevalence of certain histological components is based on the leiomyoma size [6], and the UL cell type is responsible for its growth [7, 8]. Importantly, fibroblasts originating from different parts of the human body exhibit divergent behaviors and are distinct cells [9]. Some mechanisms of cellular differentiation that occur during fibroid development are still unknown [6]. However, findings suggest that the growth rate of leiomyomas is based on vascularization [10, 11], sensitivity to hormonal regulation [12], and age [13]. The cellular heterogeneity of UL stipulates a symptomatic component, providing important data for further therapy [14].

Uterine fibroids contain their own specific vasculature [3, 15, 16]. Large fibroids have a "vascular capsule", while smaller fibroids are usually avascular [17, 18]. The vascular network separates the lesion from the surrounding myometrium. Walocha *et al.* distinguished two types of vascularizations of intramural UL. The first vascularization is characterized by the formation of a dense capsule of peripheral vessels, while the central part of the fibroid is only scantly vascularized. In the second vascularization, foci of an intensive regression of the tumor are separated from the surrounding tissue by strong vascular septa [3, 17]. The vascular density of UL is a constant mark that does not change in response to hormonal therapy [11, 19], while the microvessel density is decreased in UL compared to that in the unaffected myometrium [11, 20–22], leading to the development of interstitial ischemia. Holdsworth-Carson *et al.* showed that the vascular density does not change in seeding fibroids, whereas in large UL, it does change. They suggested that local ischemia is not common for all types of UL [6].

A neurogenic component is invaluable for uterine homeostasis, playing a major role in the pathophysiological mechanisms of chronic pelvic pain and co-occurring in diseases such as endometriosis, adenomyosis, inflammatory pelvic disease or leiomyomata [23, 24]. It is perhaps no secret that abundant nitric oxide-synthesizing nerves play a role in inflammatory reactions and oxidative stress. As a result, these nerves are undoubtedly involved in the pathophysiology of UL [25]. Moreover, fibroids usually have a highly vascularized pseudocapsule characterized by the presence of nerve fibers [26, 27].

Recently, special attention has been paid to the value of stem cells in UL, notably in the context of its pathogenesis and effective therapeutic targeting [28, 29]. The uterus has an enormous capacity for enlargement during pregnancy. Hence, the myometrium contains many stem cells [30]. In the human myometrium, smooth muscle cells and mast cells are sensitive to a putative stem cell factor, and cultured myometrial cells produce this factor as well. This finding seems to be an example of autoregulation of cell differentiation, providing a possible link between the inflammatory process and tissue growth [30, 31]. Overexpression of interleukin-11 and interleukin-13, as well as transforming growth factor β, are common in UL, while expression of interleukin-8 is lower than that in the unaffected myometrium [3].

Overview of telocytes

The history of telocytes (TCs) spans only about twenty years, when they first appeared in the publication "TELOCYTES — a case of serendipity: the winding way from Interstitial Cells of Cajal (ICC), via Interstitial Cajal-Like Cells (ICLC) to TELOCYTES" in 2010 in the Journal of Cellular and Molecular Medicine, authored by Popescu and Faussone-Pellegrini [32–34]. TCs have since been described in more than fifty anatomical units in human and animal bodies (fish, reptiles, birds and mammals) [34]. Despite their mesenchymal origin, TCs are distinct from fibroblasts in regard to their morphological, immunohistochemical and secretome profiles; gene expression; and mRNA levels [35].

Typical telocytes (TCs) have small, oval-shaped cellular bodies containing the nucleus, surrounded by a small amount of cytoplasm. The main morphological feature is the presence of a variable number of cellular extensions, termed telopodes (Tps), which are probably the longest cellular prolongations in the human body. Tps are constructed by alternations of dilated portions, named podoms (250–300 nm), containing mitochondria and the endoplasmic reticulum, along with and podomers (~80 nm) with thin segments [36, 37].

Currently, several types of TCs linked to surrounding cells have been identified. Direct contact allows them to communicate with each other (homocellular) as well as with adjacent non-TC cells (heterocellular). TCs contact smooth muscle cells, nerves, immunocytes (macrophages, mast cells and lymphocytes), stem cells, melanocytes in the eye [38], erythrocytes in the spleen [39] and Schwann cells in the heart [40]. Two types of synapses have been described as unique in the literature and specific for TCs: nanocontacts with cardiomyocytes [40] and stromal synapses (connective tissue connections) with mast cells and tracheal mast cells [41]. The interplay of TCs and the constituents of ULs are no less important in the framework of its pathogenesis (Fig. 1).

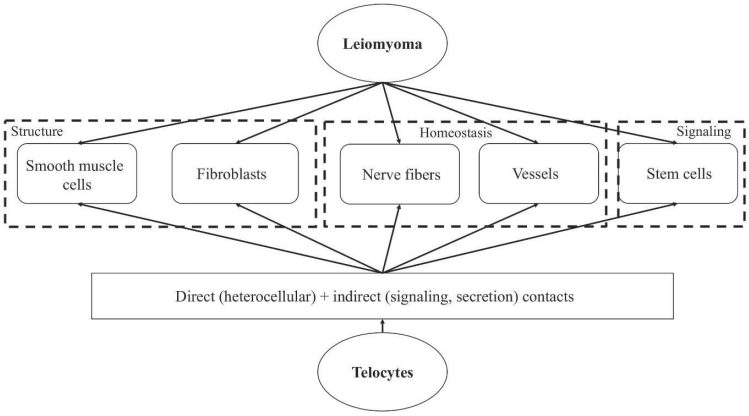

Fig. 1. Interactions between telocytes and different components of uterine fibroid.

The best method for the primary identification of TCs is transmission electron microscopy (TEM) combined with immunolabeling. We have emphasized that CD34 and plated-derived growth factor receptor alpha (PDGFRα) are the most commonly used markers for TC detection among the molecules that exhibit immunopositivity in these cells [33, 34, 37].

Telocytes are involved in the electrophysiological activity of excitable tissue, notably in the myometrium. Potassium, chloride and calcium channels are common for these cells in different organs. The activity of calcium channels in myometrial TCs is under hormonal regulation and changes during pregnancy or therapy with estrogens and oxytocin [42–44].

Dimensional role of telocytes in leiomyoma

When the myometrium is affected by leiomyoma, there is a loss of normal gross tissue organization. The prevalence of collagen in comparison with muscle fibers is sometimes accompanied by dysfunctional uterine spontaneous contractions and responsiveness [45]. Homo- and heterocellular contacts with smooth muscle cells and fibroblasts allow TCs to form networks with a 3-D organization. Sometimes, TCs may even form 2-D networks [46, 47]. The physiological balance between cellular components and the interstitium is destroyed by the prevalence of fibrosis in various diseases (hepatic fibrosis, gallstone disease, systemic sclerosis, primary Sjögren's syndrome, psoriasis, myocardial infarction), notably in uterine leiomyoma [48–54], which is accompanied by the decline, or even disappearance, of TCs in tissues and organs [48]. Ultrastructural alterations of TCs, including swollen mitochondria, cytoplasmic vacuolization and the presence of lipofuscinic bodies, with their reduction in the skin, are common in systemic sclerosis, often correlating with the

subsets and stages of the process. Moreover, the same changes have been described in the gastric wall (submucosa and muscle layers), the myocardium and the lung [49]. Damage to and loss of telocytes might be caused by ischemic injury, as TCs appear to be more sensitive to ischemia than other stromal cell types, such as fibroblasts, myofibroblasts, and mast cells [50]. Ischemia can lead to an alteration of the three-dimensional organization of the extracellular matrix and, as a result, development of fibrosis. The uncontrolled activity of fibroblasts/myofibroblasts might be a consequent of TCs in the foci of leiomyoma.

Another key aspect of UL is the regulation of matrix production. Undoubtedly, this process correlates with local secretion of growth factors [55, 56], some of which are under hormonal regulation, especially by progesterone [57]. Sex steroid receptors are dependent on TC localization. In the human gallbladder, these cells are negative for the progesterone receptor, while in normal cells and those affected by UL in the myometrium, they are strongly positive [58]. Scant data are available on the immunosensitivity of TCs to different growth factors, but VEGF and PDGFR alpha are always expressed in the aforementioned cells. In our opinion, the immunological properties of TCs, along with their local sensitivity to sex steroid hormones and contacts with smooth muscle cells, allow us to predict their intermediate role in the production and regulation of the ECM.

Leiomyoma results in the abnormal orientation of muscle fibers and contractive disturbances [45]. Normally, smooth muscle cells and nerve fibers provide the contractive function of the myometrium. As TCs express K^+ channels and make close contacts with myocytes [44], they also take part in myometrium contraction. However, we still lack much information about the electrical activity of TCs isolated from the human myometrium. Several experiments have found opposite results [45, 59–61]. We know that telopodes in the non-pregnant myometrium are longer, the podomers are thicker and the podoms are thinner compared to those in the pregnant myometrium [32, 33, 43]. These morphological transformations lead to altered exo- and ectosome secretion, as well as excitation of the myometrium, most notably during pregnancy. The fluctuation of sex steroid hormones, as well as additional hormonal therapy, certainly affects myometrial TCs [43, 62]. Similarly, the pathogenesis of leiomyoma partly depends on the hormonal background. The decline or disappearance of TCs in the foci of fibroids might be a factor of local electrophysiological disorder.

Homeostatic role of telocytes in leiomyoma

Vascularization and innervation of fibroids are essential for their expansion, which generally provides a symptomatic component of this pathology, namely, bleeding and pain. The formation of a pseudocapsule, including vessels and nerve fibers, is a specific feature of UL that is hypothetically connected with prognosis [26, 63]. Pro-

angiogenic factors are a top priority among the pathomechanisms of vascular capsule formation. Moreover, some angiogenic factors are overexpressed in UL, including VEGF and basic fibroblast growth factor [63]. Telocytes have been detected in close proximity to blood vessels (on the endothelial surface) [64, 65]. Telocytes are positive for VEGF immunolabeling and secrete this growth factor as well [66], which may induce the proliferation of pulmonary endothelial cells [67]. Moreover, TCs are sensitive to hypoxia and participate in neo-angiogenesis [51]. Estrogens regulate the secretion of VEGF and have receptors on myometrial telocytes [63], suggesting the indirect involvement of myometrial TCs in the formation of the vascular capsule in leiomyoma (Fig. 2).

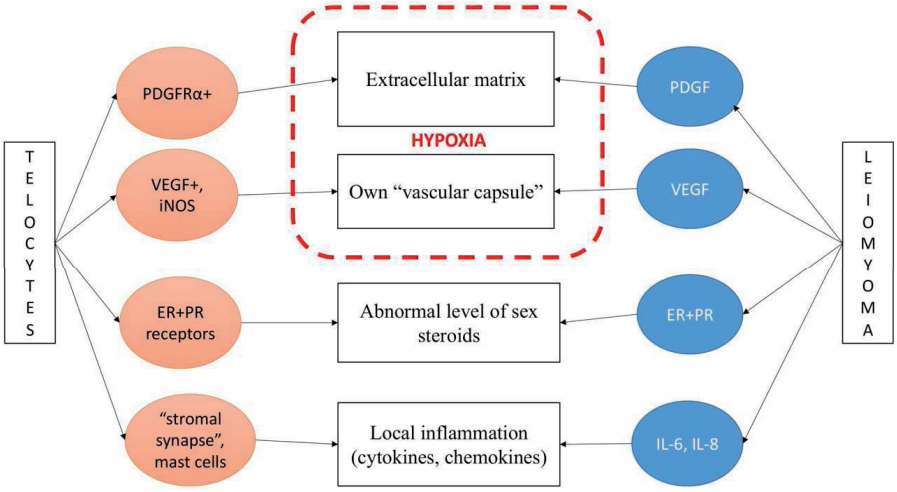

Fig. 2. Interplay of telocytes with main pathogenic factors of leiomyoma.

The density of TCs has been the focus of observations, providing an exciting study in various tissues, including the intestine, ureter, myometrium, myocardium, and fallopian tube. UL is no exception from this list; however, its innervation still has wide gaps, and not enough is known about it. We know that TCs are located close to nerve endings and that some of them make connective structures using Tps between smooth muscle cells and nerves [32, 33, 46, 68]. Interestingly, the appendix has the highest numbers of TCs compared to other parts of the intestine, which is explained by the need for its complex innervation [69]. The opposite situation is common in Crohn's disease, wherein gut dysmotility is accompanied by the decline and disappearance of TCs [70]. Hence, the number of TCs correlates with the function of excitable tissue and its damage. The decline of TCs in UL and their detection in the pseudocapsule might represent the background of pain and electrophysiological disturbance in myometrial tissue.

Importantly, the iNOS/nitric oxide system is fundamental not only in the female reproductive system. Uterine TCs activate peritoneal macrophages and stimulate the production of iNOS [71, 72]. Moreover, these cells are positive for iNOS as well. UL is characterized by a prevalence of NOS-positive nerve fibers. We hypothesized that myometrial TCs participate in this pathophysiological unit of fibroids by regulating iNOS production [71].

Integrative role of telocytes in leiomyoma

Mirancea defined telocytes as "nurse" cells because they collect information from nervous, vascular, and stem cells, as well as from the immune system [68]. Albulescu *et al.* hypothesized that the TC secretome plays a modulatory role in stem cell proliferation and differentiation [66]. Is TC function over-estimated, or it could have value in the pathogenesis of UL?

The reported presence of close contacts between TCs and lymphocytes or plasma cells might indicate an immunomodulatory role for TCs. Mast cell synapses with TCs have been found in the human myometrium. Close contacts with TCs suggest that mast cells might take part in this cellular cross talk. It is possible that mast cells and myometrial TCs assist, or even function, as pacemaker cells in myometrial contractions. In addition, such close cell connections suggest juxtacrine cell-to-cell signaling (chemical synapse), and the (micro) vesicles found in the synaptic cleft may correspond to an exosome-based mechanism [73, 74]. Myometrial mast cells have receptors for stem cell factor (SCF), which is produced by myometrial cells [31]. Therefore, under the control of smooth muscle cells, mast cells secret mediators that affect tissue remodeling and growth. TCs make contacts with smooth muscle cells, as well as with mast cells. TCs can be associated with immunological response in UL, as well as with tissue growth.

The latest area of interest is the relationship between stem cells and TCs. The stem cell niche's involvement with TCs has been described in skeletal muscle, heart, lung and skin [75–79]. This interaction is always discussed in the context of tissue remodeling, regenerative medicine, and targeted therapy. Stem cells unaffected and affected by uterine fibroid myometrium are not similar. The latter possesses mutated MED12 and reduced levels of DNA repair [79, 80]. A trigger factor may affect the microenvironment (niche), consequently causing further UL development. As a component of the stem cell niche, TCs might be involved in this process. We also stress that close vicinity of TCs to blood vessels and its immunosensitive for growth factors' receptors reflect a putative role in the local angiogenesis that might be also important in context of microenvironmental misbalance in the leiomyoma [81].

Conclusions

The variety of heterocellular contacts between telocytes and surrounding cells/anatomical structures in uterine fibroids allows us to focus our attention on its importance. New populations of recently discovered cells might represent novel, missing links in the skeleton of the oldest gynecological pathology. The multifunctional profile of telocytes explains their possible roles and properties.

Author contributions

All of the authors were involved in writing this manuscript. All of the authors reviewed, edited, and approved the final version of the manuscript.

Conflict of interest

None declared.

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