Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2023**; 50(1): 15
https://doi.org/10.31083/j.ceog5001015

Editorial

Telocytes in the Female Reproductive System: What have We Learned Over the Past Three Years?

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Academic Editor: Michael H. Dahan
Submitted: 10 October 2022 Revised: 18 October 2022 Accepted: 19 October 2022 Published: 12 January 2023

Telocytes, formerly known as interstitial Cajal-like cells, are a specific population of interstitial cells with extremely long cytoplasmic projections (telopodes) found in most organs of the human body, including the female reproductive system. In most papers, telocytes are typically termed "novel" or "recent". Telocytes were first described in 2005. However, considering the modern fast pace of anatomical research, 17 years from an initial discovery is a long time to gain substantive knowledge on a given topic with emerging translation to clinical medicine. Currently, almost 600 papers have been published on telocytes. With many of these papers are basic research on animal models. Telocytes and more specifically female reproductive system telocytes are still at the forefront of interest of many research teams bringing new interesting insight into the normal and pathological processes in which telocytes play a role. Recently there has been an increased interest in telocyte-research which can be documented by more than a hundred PubMed/MEDLINE entries on telocytes over the last two years (2020–2022). Discussing the latest three years in the research of female reproductive system telocytes, Mustafa and Elhanbaly [1] confirmed the estrogen-receptor positivity in rabbit uterine cervical telocytes, whose expression varies in different stages of pregnancy. This finding underlines the notion that telocytes are key regulatory cells of myometrium functioning as steroid hormone sensors. Myometrial telocytes have another recently described function. They interconnect longitudinal and circular muscle layers of uterine myometrium, and probably coordinate myometrial contractions [2]. According to latest scientific research, telocytes play a crucial role also in transport function of uterine tubes. Karasu *et al*. [3] conducted an immunohistochemical study of telocytes in the uterine tubes of patients diagnosed with ectopic pregnancy. The authors detected a higher count of telocytes in the muscle layer of the uterine tube. They correlated this finding with diminished motility, leading to a higher risk for ectopic pregnancy. These results contrast with the majority of the papers on the role of telocytes in the pathogenesis of various disease entities. It is the low count of telocytes or their functional disturbance that is generally associated with the pathogenesis of various diseases. Future research should investigate the possibility that hyperplastic and overactive telocytes can also be damaging. This may underline the long-known fact that "moderation is the key" since the overactivity of any cell population has potentially damaging consequences to normal organ functioning. In 2021, Aleksandrovych *et al*. [4] performed an immunofluorescence study of telocytes in the uterine tube with a similar aim to elucidate their potential role in tubal motility. Their principal finding was that telocytes are important regulators of muscle contractility and ciliary beating, indicating their involvement in the regulation of normal gamete/embryo transfer through the uterine tube necessary for successful natural reproduction. In the same study, the authors observed that the population of tubal telocytes from patients diagnosed with uterine leiomyomas (uterine fibroids) grew by an unknown compensatory mechanism. In 2022, the same research team published a paper on a similar topic investigating telocytes in the uterine tubes of patients with uterine leiomyomas. In this report, they morphologically studied the leiomyoma tissue and correlated the findings. The main conclusion was that while in leiomyomas telocytes are decreased in number, their uterine tube population grows [5]. Another study published by Zhao *et al.* [6] took a molecular biological approach to investigate the role telocytes have in the regeneration and repair of intrauterine adhesions—postoperative or postinfectious scar tissue that can lead to fertility problems, miscarriage and other complications. The authors' results demonstrated that telocytes could activate the Wnt signaling pathway responsible for regulating cell proliferation and differentiation. Thus telocytes were able to stimulate the regeneration and repair of intrauterine adhesions in a paracrine fashion. Another recent study by Maldarine *et al.* [7] experimented with a rodent tumorigenesis model in paraurethral Skene's glands (so called "female prostate") to determine the role of telocytes in this condition. To the best of our knowledge, this is the first published paper on telocytes in this location. The authors used transmission electron microscopy and immunofluorescence for telocyte visualization with results being contradictory. While telocytes may suppress tumorigenesis by maintaining normal tissue homeostasis, their relationship with immune cells can make them

sensitive to pro-inflammatory stimuli. Taking into account their proangiogenic capacity, the authors hypothesized that telocytes could contribute to tumor formation. Telocytes were recently studied in the uterovaginal junction of the chicken [8]. Transitioning back to human studies, Abu-Dief *et al.* [9] researched placental telocytes in preeclampsia and revealed that in patients with preeclampsia, the telocyte population in the chorionic villi, decidua, and myometrium was significantly decreased, potentially contributing to the pathogenesis of this serious condition. The role of telocytes in invasive lobular carcinoma of the mammary gland was presented by Díaz-Flores *et al.* [10] performed an immunohistochemical and electron microscopic study with results indicating that telocytes are a potential source of cancer-associated fibroblasts. Despite the 17 years since their initial description, telocytes are still not unanimously accepted as a unique cell population. This is reflected in the terminology the authors used throughout the manuscript that studied cells were termed ambiguously as CD34+ stromal cells/telocytes.

All these studies indicate that female reproductive system telocytes are an important topic with a great potential for future experiments to demonstrate findings that will be translated into clinical practice. As a Guest Editor of the Special Issue "Telocytes in the Female Reproductive System: Current Knowledge, Challenges and Possible Clinical Applications", I would like to invite all experts in this field to contribute their current research results to this special issue that will broaden our understanding of the role of telocytes in the female reproductive system.

Author Contributions

IV and MK wrote the manuscript. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The authors would like to thank for administrative and technical support provided by the staff at the Institute of Histology and Embryology, Faculty of Medicine, Comenius University Bratislava.

Funding

This research was funded by the Slovak Research and Development Agency, grant number APVV-18-0499.

Conflict of Interest

The authors declare no conflict of interest. Ivan Varga is serving as one of the Editorial Board members/Guest editors of this journal. We declare that Ivan Varga had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Michael H. Dahan.

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