Telocytes in the Female Reproductive System

Subjects: Cell Biology | Obstetrics & Gynaecology
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Telocytes (TCs) have been described in the ovary, uterine tubes, uterus, vagina, mammary gland, and placenta. Their morphological features, immunophenotype, physiological functions, and roles in disease have been thoroughly documented in both animal models and human subjects. TCs, with their extremely long cytoplasmic processes called telopodes, play a pivotal role in the morphological and functional interconnection of all the components of the interstitial compartment, but also with constituents of the parenchyma.

Keywords: telocytes ; female reproductive system ; ovaries

1. Introduction

The female reproductive organs form a highly complex and intricately connected system with many peculiarities unlike any other when considering other organ systems of the mammalian body. The most astonishing feature of the female reproductive system (FRS) is its capability to induce immune tolerance towards the hemiallogenic embryo. Although this characteristic has been evolutionarily conserved for tens of millions of years, which still can not be fully understood, despite the fact that over the last few decades, the knowledge of the morphology, physiology, and pathophysiology of the FRS has been growing exponentially [1][2]. The FRS's main task is to ensure the successful development of an embryo/fetus with the ultimate goal of species preservation. In order to fulfill this goal, all the organs belonging to the FRS must work in highly regulated cooperation and synchrony [3]. If any of the components fail to operate properly, various pathological conditions may occur. One of the most significant, which has become a global problem, especially in developed countries, is female-factor infertility [4]. Another clinically important issue is the proneness of some FRS organs to cancerogenesis [5]. The most challenging aspect is that the exact mechanisms by which many of these conditions occur are largely unknown. However, there is one cell population that may be a game-changer in understanding the intricate functioning of the system as a whole—telocytes (TCs) [6].

2. General Information on Telocytes—Morphology and Physiological Functions

The history of TCs can be dated back to the works of Santiago Ramón y Cajal, published at the turn of the 19th and 20th century, who discovered a new cell population of "interstitial neurons" in the gut [7]. A century later, research teams had been studying these cells, now known as interstitial cells of Cajal (ICCs), a designation honoring the Nobel laureate, even though these "interstitial neurons" were, in fact, gut pacemakers, not genuine neurons [8]. In an attempt to find similar cells in other organs, Romanian morphologists under the guidance of prof. Laurentiu M. Popescu discovered a unique yet completely unrecognized cell population. First known as interstitial Cajal-like cells (ICLCs), these cells were later renamed TCs for the sake of simplicity and to emphasize their individuality [9].

The shortest and most pertinent definition is that TCs are cells with telopodes. Telopodes represent the most striking morphological feature of these cells—cytoplasmic projections of extraordinary proportions. Their length is surpassed only by that of nerve cell axons [10]. The most thoroughly studied aspect of TCs is their specific morphology. TCs have a small cell body of different shapes. The most commonly described are spindle-shaped, star-shaped, triangular, or piriform TCs [11]. Telopodes, on the other hand, are exquisite in proportions. They can extend from tens to hundreds of micrometers, but are only a fraction of a micrometer wide, making them difficult to study using standard light microscopy. Therefore, the gold standard of TC study is transmission electron microscopy [12]. The length is not the only peculiarity of telopodes. Another important feature of these projections is their moniliform appearance, with alternating thin (podomers) and thick (podoms) segments. Their main function is the formation of homocellular and heterocellular junctions with other components of the stromal compartment, but also functional parenchymal structures such as epithelial cells. In this manner, TCs connect themselves with basically the whole cellular microenvironment of a given organ [13]. This arrangement suggests that telocytes are involved in structural organization, intercellular signaling, microenvironmental

maintenance, mechanotransduction, and immune surveillance [14]. Specifically, in the FRS, TCs also serve as hormonal sensors that regulate hormone-dependent physiological and pathological processes [15]. Finally, yet importantly, TCs were also described in close relation to stem cells, which implies their possible importance in tissue regeneration and repair [16]. Apart from direct contact via cell junctions of different types, TCs are also a source of various extracellular vesicles, like exosomes, ectosomes, and multivesicular cargos. These structures contain different molecules that mediate the TC′s influence on its surroundings in a paracrine way [17]. Most of the aforementioned characteristics are universal for TCs in humans, as well as other animal species, irrespective of the particular organ or organ system. Nevertheless, slight differences have been described in the literature. These TC peculiarities, specifically concerning the FRS, are covered in the next sections.

3. Morphological and Functional Specifics of Female Reproductive System (FRS) Telocytes

Without overstating, it can be said that TCs have been described in almost every organ one can think of. Except of the FRS, TCs have been discovered in the intestine [18], lungs [19], skeletal muscle [20], skin [21], ureter [22], heart [23], testes [24], prostate [25], eye [26], and even in remarkable locations such as a cow´s teat [27]. TCs in the FRS are quite alike to TCs in other organs, but there are several morphological and functional characteristics that make them distinct. The first unique trait of FRS TCs, in general, is their immunohistochemical profile (details are covered in the next section). For instance, they are positive for estrogen and progesterone nuclear receptors (ER and PR), implying their role in the regulation of hormone-mediated processes occurring in FRS organs. The other significant individuality is that TCs dynamically change their morphology and function based on the current period of the female reproductive cycle, whether it is the menstrual or estrous cycle, and also change noticeably during pregnancy. According to observations by Vannnucchi and Faussone-Pellegrini, such changes may seem to indicate that these are separate populations of TCs, each active in different stages of female reproduction. However, their positivity for both steroid hormone receptors suggests that they are the same, yet morphologically and functionally different [28].

Ovarian TCs are among the least studied compared to other organs of the FRS. Liu et al. studied telocytes in mice ovarian stroma. Using a combination of different methods, including immunofluorescence, immunohistochemistry, flow cytometry, and electron microscopy, the authors identified cells with a small body, long dichotomously branching telopodes with a typical moniliform alternating pattern of podomers and podoms. From the functional perspective, the most probable is their participation in microenvironmental maintenance [29]. Mazzoni et al. studied TCs in the stroma of piscine gonads. In the ovaries, TCs established homo- and heterocellular contacts with all interstitial components, e.g., fibroblasts, theca cells, and blood vessels. The authors hypothesized that TCs might contribute to tissue remodeling of the ovary [30]. Mokhtar also described TCs in fish ovarian stroma making close contacts with immune cells, blood vessels, and atretic follicles, comprising around 8% of the total cellular makeup of the stromal compartment. They were also shown to shed extracellular vesicles in close vicinity to blood capillaries. From the functional perspective, TCs were hypothesized to regulate tissue regeneration during the spawning season [31]. A more recent 2020 paper studying the process of follicular atresia in fish arrived at a conclusion that TCs cooperate with other cell populations, like rodlet cells (special cells present in some epithelia in fish with secretory, sensory, and immune functions), immune cells, and follicular cells in this physiological process by reorganizing the extracellular matrix (ECM) [32].

Tubal TCs, on the other hand, are among the best studied in the FRS. They were first scrutinized shortly after the first description of ICLCs by the Romanian team in 2005. Popescu et al. used a wide spectrum of methods in order to thoroughly examine these cells, but most importantly, they extended the “gold standard” of ultrastructural criteria for their identification, originally derived from the ultrastructural study of ICCs. They established the “platinum standard” that incorporated all typical features of the “characteristic cytoplasmic processes”, not yet known as telopodes, including their length, thickness, branching pattern, and organization. The authors also proposed several hypothetical physiological functions based on their morphological specifics–intercellular signaling, paracrine regulation of their surroundings, pacemaking, and mediation of neurotransmission. Interestingly, the authors also considered the possibility that they can act as further-differentiating progenitor cells or cells capable of phenotypic switch [33]. In a later study, Popescu et al. investigated the topographical representation of TCs in individual histological layers of the uterine tube. Their density was highest in the lamina propria right under the epithelial lining, progressively decreasing towards the more superficial layers of the tubal wall [34]. Eventually, after discovering that they also express ER and PR, Cretoiu et al. discussed that TCs might regulate the hormone-dependent physiology of the uterine tube, e.g., its motility, expanding the palette of probable functions [35].

Uterine TCs display several characteristics similar to those found in the uterine tube. They also express ER and PR, implying that TCs serve as hormone sensors and thus regulate hormone-dependent changes associated with the

endometrial cycle, pregnancy-related changes, and motility [36][37]. Salama performed original research in female rats divided into four groups based on the reproductive state: immature, adult non-pregnant, adult pregnant, and postpartum rats. The author found TCs in the endometrium and myometrium of all groups, but with quantitative differences. The least numerous population was found in the myometrium and endometrium of immature rats, with a significant increase in non-pregnant adult rats. The pregnant group had a high count of TCs in the endometrium and a low count in the myometrium. The myometrium of the postpartum group contained an abundance of TCs. From these results, it could be inferred that TCs are important during the reproductive period and can adapt according to different functional demands. The high count in the endometrium during pregnancy could indicate that TCs contribute to pregnancy-associated endometrial changes, e.g., decidual reaction. On the other hand, the diminished number of myometrial TCs during pregnancy may prevent pathological contractility and preterm parturition [38]. A recent experimental in vitro study of TCs showed that endometrial TCs influence various physiological characteristics of endometrial stromal cells (ESC). The regulation of ESC proliferation, adhesion, and motility indicate that TCs have a role in the crosstalk between different signaling pathways important for the microenvironmental upkeep of the endometrium [39]. Myometrial TCs were also experimentally demonstrated to express voltage-gated calcium channels, suggesting that TC-mediated calcium fluctuation may determine the proper coordination of myometrial contractility [40]. Jiang et al. studied the immunomodulatory capability of uterine TCs, in terms of their capacity to influence macrophages. TCs were observed to directly activate these innate immune cells through the mitochondrial signaling pathway. Even though the experiment was performed on peritoneal macrophages, the results may suggest that similar processes also occur in the uterine microenvironment [41].

The knowledge of TCs in the vagina is very limited. The only experimental paper studying TCs via immunohistochemical methods was authored by Shafik et al. back in 2005, who concluded that they regulate smooth muscle activity by slow wave initiation [42].

Classifying the placenta as a part of the FRS can be problematic, because it is a temporary or transient organ developing during pregnancy, and on top of that, it is jointly formed by both the maternal and embryonic contribution. Nevertheless, placental TCs as a part of the FRS will be will described. Placental TCs can be discussed from two perspectives. First is their role in early changes that result from the trophoblast-endometrium interplay during embryo implantation, while the second focuses on TCs role in the mature placenta. In the early stages, the endometrium undergoes decidual changes, while at the same time, the immune response has to be adequately regulated in order to mitigate the recognition of the hemiallogenic embryo as non-self by the immune system. The participation of TCs in these processes can be deduced from the results of the already mentioned Jiang et al. study examining TC influence on immune cells [41]. Focusing on the direct observation of TCs in the chorionic villi of the mature placenta, Nizyaeva et al. studied their ultrastructural individualities in human specimens harvested upon delivery between week 36–39 of gestation. The TC population was found to be heterogeneous with several distinct morphological types. Based on their ultrastructural specifics, the authors concluded that placental TCs contribute to trophoblast differentiation and regulation of the growth of chorionic villi. Placental TCs were also observed in close vicinity to Hofbauer cells (special macrophages of the chorionic villi), providing an insight into the potential immunomodulatory activity of placental TCs [43].

In a like manner, TCs in the mammary gland are often discussed separately, since the mammary gland belongs, from the embryological perspective, to skin derivatives. In spite of that, the mammary gland TCs within the scope of FRS will be discussed, considering the fact that it is closely connected to reproduction. The electron microscopic identification of TCs in the mammary gland stroma was carried out by Gherghiceanu et al., who hypothesized that TCs are crucial in three-dimensional (3-D) organization and functional integration of stromal components of the mammary gland [44]. Petre et al. found TCs in stem cell niches of the mammary gland, indicating that they might be important in morphological and functional changes related to early development, and pregnancy-associated growth and differentiation [45]. In a 2020 original paper, Sanches et al. examined the mammary gland of the Mongolian gerbil with a goal to perform an ultrastructural and immunohistochemical study of TCs during lactation and post-lactational involution. The authors observed that their function was closely associated with matrix metalloproteinase 9 (MMP-9) and vascular endothelial growth factor (VEGF), suggesting their capacity for ECM remodeling and angiogenesis regulation, respectively [46].

4. Immunophenotype of FRS Telocytes

Besides electron microscopic features, immunophenotypic traits are the most cited TC characteristics by which they can be distinguished. Unfortunately, as of today, no research endeavors have been successful in determining a unique and specific marker that would unambiguously differentiate TC from other populations of interstitial cells. Nevertheless, there are several immunohistochemical markers that can be considered reliable in TC identification. The most suitable approach is the combination of markers as a part of double immunohistochemistry, immunocytochemistry, immunofluorescence. These can also be used in tandem with other methods of TC detection. However, it is extremely important to note that

there are organ-to-organ differences in the expression of these markers, which makes the straightforward detection of TCs even more challenging than the fact that there is no TC-specific marker.

The handful of studies that at the disposal showed that ovarian TCs express CD 34, platelet-derived growth factor receptor (PDGFR) α/β, vimentin [29], MMP-2 and MMP-9 [30], desmin, CD 117 (c-kit), and S-100 protein [31].

Regarding the immunophenotype of TCs in the uterine tube, Cretoiu published a comprehensive review on different aspects of tubal TCs, including the most typical markers detectable via immunohistochemistry or immunofluorescence. A marker that displayed the strongest positivity was CD 117, followed by CD 34. The former was located mostly on the cell body, while the latter was found predominantly on telopodes. S-100 positivity was also demonstrated with variations found in different histological layers of the uterine tube. The expression of other markers, namely NK-1, nestin, and vimentin, was either weak or inconsistent. Finally, yet importantly, tubal TCs expressed ER and PR, but also atypical markers caveolin-1 and caveolin-2 [34][47].

Similar to those in the uterine tubes, uterine TCs are also thoroughly studied from various angles, including the expression of immunohistochemical markers. There is a substantial overlap with other organs of the FRS, especially the uterine tube, but as always, previous experimental works found several organ-specific markers. The immunophenotypic details of the uterine TCs were elucidated only one year after their initial discovery, indicating that uterine TCs are among the best documented overall, not only in the FRS. They express CD 117, CD 34, vimentin [48], ER, and PR [36]. The own previous experiments also demonstrated that uterine TCs are CD 117 positive in different histological layers of both the uterine body and cervix, with the strongest positivity found in the myometrium [49]. Apart from these typical markers, Hatta et al. and Rosenbaum et al. demonstrated that uterine TCs are positive for connexin 43 and SK3 channels, respectively [47][50] [51]. T-type Ca2+ channels and PDGFR α are markers that can also be found in uterine TCs. To mitigate the no-single-specific-marker problem, the best course of action is the marker combination in terms of double immunohistochemistry. The most reliable merger seems to be CD 34/PDGFR α [52].

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