Original Article

Ultrastructural Demonstration of Telocytes in Human Postpartum Fallopian Tube

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Abstract

Introduction: Telocytes are an unique type of cells found in the interstitial tissue of various organs including the female reproductive tract. These cells are recently being implicated in various functions, including tissue repair and regeneration. They are associated with nerve endings, but their association with blood vessels and immune cells has not been established in the Fallopian tube unlike the telocytes seen in the uterus. This study aims to look for the association of telocytes with blood vessels and immune cells in the human postpartum Fallopian tube. **Material and Methods:** Ten postpartum Fallopian tube samples from the ampulla were obtained from the patients who underwent lower segment cesarean section with sterilization by the modified Pomeroy's technique. The samples were processed for electron microscopy and studied under a transmission electron microscope. **Results:** The human postpartum Fallopian tube showed increased microvasculature. Telocytes were found to be located in the mucosal and the muscular layers of the human postpartum Fallopian tube, predominantly in the subepithelial layer of the lamina propria. They were seen in association with blood vessels, especially high endothelial venules and immune cells such as mast cell and lymphocytes. **Discussion and Conclusion:** Telocytes seen in association with the blood vessels, especially high endothelial venules and immune cells in the human postpartum Fallopian tube suggest their probable role in the complex interplay in the immune tolerance and immune surveillance of the postpartum Fallopian tube.

Keywords: *Blood vessels, electron microscopy, high endothelial venules, podoms, telopodes*

Introduction

Telocytes are a distinct type of interstitial cells found in many organs. They are characterized by a small cell body and extremely long and thin telopodes.[1] These cells, initially called as interstitial Cajal-like cells (ICLCs), were named "telocytes" by Popescu *et al*. in 2010.[2] These cells were said to be nonmacrophagic phagocytic cells by Díaz-Flores *et al*. in 2014.[3] These cells are difficult to be identified under light microscopy but can be identified by immunohistochemistry using various markers such as c-kit/CD117, Vimentin, CD34, and vascular endothelial growth factor (VEGF).[4] Yet, the golden standard for identifying telocytes is by using the transmission electron microscopy.[1] Although their functions are not clear, they have been implicated in tissue repair or regeneration of organs.[3]

Telocytes have been demonstrated in female reproductive organs, including the uterus and Fallopian tubes. In the uterine myometrium, telocytes establish relationships with capillaries, nerve fibers, and with other interstitial cells such as macrophages, mast cells, lymphocytes, and eosinophils. They are interconnected with each other and with smooth muscle cells through cell-to-cell point contacts or gap junctions. In the Fallopian tube, they are predominantly seen in the lamina propria and in between smooth muscle fibers. They are associated with nerve endings, but their association with blood vessels and immune cells has not been established in the Fallopian tube unlike the telocytes seen in the uterus.[5] The human postpartum Fallopian tube being rich in its microvasculature, this study aims to demonstrate telocytes associated with blood vessels and immune cells in the postpartum Fallopian tube under the transmission electron microscope and to look for its association with blood vessels.

Material and Methods

Ethical approval was obtained from the Institutional Review Board, and informed consent was obtained from all patients who

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participated in the study. Ten postpartum Fallopian tube samples were obtained from patients who underwent lower segment cesarean section with sterilization by the modified Pomeroy's technique. Patients with a previous history of pelvic inflammatory disease and immunocompromised patients were excluded from the study. Tissues were fixed in 3% glutaraldehyde for 3 hrs, postfixed in 1% osmium tetroxide, and dehydrated in ascending grades of ethyl alcohol. After dehydration, clearing was done in propylene oxide and infiltrated with epoxy resin and embedded in the resin mixture. Ultrathin sections (60–90 nm) were cut from the selected areas on an ultramicrotome (Leica Ultracut UCT, UC7) with a diamond knife (Diatome) and sections mounted on the copper grids. Sections were stained with freshly prepared saturated aqueous uranyl acetate for 1 hrs and counterstained with Reynold's lead citrate for 3 min. The grids were examined under the transmission electron microscope (TECNAI T12 SPIRIT) at 60KV.

Results

The ICLCs, called telocytes, were seen located in the mucosal and the muscular layers of the human postpartum Fallopian tube. These cells were found abundantly in the lamina propria, predominantly underlying the basement membrane of the epithelium. The telocytes in the mucosal layer showed a piriform to oval cell bodies with a 1–2 long cytoplasmic process (telopodes) in an ultrathin section. The cell body had a large nucleus with a thin rim of the cytoplasm around it. The nucleus had dense heterochromatin underneath the nuclear membrane. Their thin podomeres and dilated podoms with caveolae and mitochondria were clearly seen. These cells showed numerous microvesicles and exosomes [Figure 1]. Telocytes were also seen to have a triangular body with three thin and long telopodes seen extending from the cell body [Figure 2]. These cells were also seen in association with the blood vessels in the lamina propria [Figure 3]. These cells were seen predominantly in the subepithelial layer between the basement membrane with a migrating immune cell (macrophage) and the high endothelial venules [Figure 3]. The telocytes in the muscular layer showed triangular cell bodies with heterochromatic nuclei and prominent nucleoli. Telocytes were also seen in association with the immune cells such as lymphocytes and mast cells [Figure 4].

Discussion

Telocytes, shortly defined as "cells with telopodes," are a novel interstitial or stromal cell type.[6] These cells have been first discovered in 2005 by Popescu *et al*. They named it as ICLC as these cells had apparent similarity with the gastrointestinal interstitial cells of Cajal, the gut pacemaker cells.[7] These cells have been renamed as telocytes in 2010, as they differ in their electron microscopic, immunochemical, and cell culture behavior from the interstitial cells of Cajal.[8]

Electron microscopically, telocytes are identified by the presence of their long, thin cytoplasmic processes termed as telopodes. Telocytes might contain 1–5 telopodes of length ranging from 10 to 100s of microns. The telopodes are made of alternating thin and dilated segments which are called podomeres and podoms, respectively. The podoms contain numerous caveolae, mitochondria, and rough endoplasmic reticulum. The thickness of telopodes is usually <0.2 μm.[4,8] According to the number of telopodes, telocytes are classified as follows: (1) piriform (one telopode), (2) spindle (two telopodes), (3) triangular (three telopodes), and (4) stellate (more than three telopodes). Immunohistochemically, telocytes are c-Kit/CD117 positive and coexpress CD34+.[4] However, their negativity for CD1a and CD62P help to differentiate them from other immune cells.[9] They can also be identified using vital methylene blue stain based on their typical structure.[10]

The exact role of telocytes is not known. Telocytes were said to be the connecting cells that play a role in paracrine and juxtacrine intercellular modulations.[11] It has been suggested that telocytes could themselves be stem cells,[6] playing a part in tissue regeneration.[12] The exocytotic vesicles were found to possess microRNAs involved in the neoangiogenesis in the infarcted myocardium.[11] Telocytes could also function as mechanical support, resistant, and deformable structures due to the three-dimensional (3D) network properties, possibly controlling the blood vessel closure.[13]

Telomeres establish physical contacts with nerve endings, blood vessels, and different types of progenitor cells. It has been found that the telomeres also have homocellular junction, where the telopodes are connected with one another forming a 3D network or heterocellular junction between telocytes and myocytes or telocytes and immune cells.[7]

The Fallopian tubes provide a special microenvironment for fertilization. In the present study, telocytes in the human postpartum Fallopian tube were demonstrated, mainly in the lamina propria and in between smooth muscle fibers. In the muscular layer, they act as stretch receptors (sensors) or as pacemakers controlling Fallopian tube peristalsis.[5] Their close association with smooth cells indicate the role of telocytes in uterine tube contractility.[14]

While telocytes have been seen associated with blood vessels and immune cells in the uterus, there was no such association observed in the Fallopian tube in humans.[5] In contrary, in the present study, telocytes were seen in association with the blood vessels of the lamina propria of the postpartum Fallopian tube, thereby suggesting their role in the complex interplay between the telocytes and immune cell trafficking through the vessels. It has been suggested that telocytes have angiogenic property as they express VEGF and exocytic vesicles with microRNA for

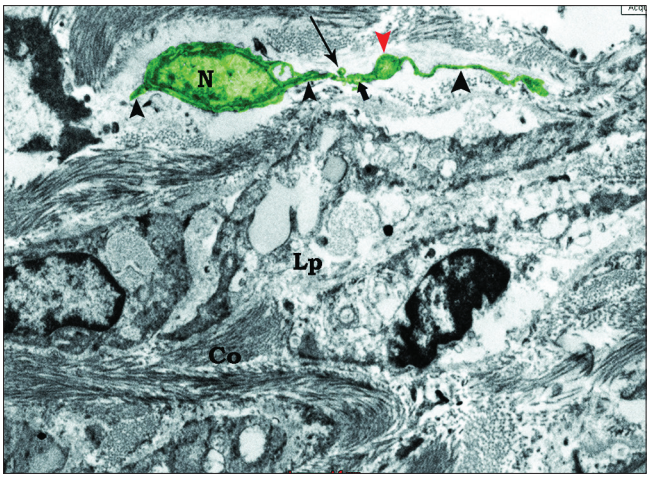

Figure 1: Transmission electron microscopic picture of the lamina propria of the human postpartum Fallopian tube. A telocyte has been highlighted in green. It shows an oval-cell body and nucleus (N) with a thin rim of cytoplasm. Thin cytoplasmic process or podomere (black-arrow heads) are seen extending from the cell body with dilated regions or podoms (red-arrow head) containing microvesicles (Black-short arrow); Co: Collagen bundle, black-slender arrow-exosome

neoangiogenesis.[11] In the postpartum Fallopian tubes, there is an increase in the number of microvasculature, especially the high endothelial venules. The association of telocytes with high endothelial venules in the postpartum Fallopian tube may support its role in neoangiogenesis. It has been suggested that these cells could serve as a sensor of hormone levels, which with the help of its intercellular junctions, perhaps even by paracrine pathway, controls smooth muscle contraction and movement of cilia of the Fallopian tube.[5]

Telocytes have been found to establish contact with the immune cells such as plasma cells and eosinophils.[5] The distance between telocytes and other interstitial cells (macrophages, fibroblasts, and mast cells) in the cardiac tissue is often within the range of tens of nm (10–30 nm) involving in a paracrine and/or juxtacrine secretion through their microvesicles and exosomes playing a vital role in horizontal transfer of macromolecules acting as intercellular signaling among adjacent cells. Their vesicles and exosomes also contain microRNAs, thus involving themselves in modifying their transcriptional activity.[15] In the current study, the telocytes were seen in close association with the mast cells and lymphocytes, thereby suggesting their probable complex interplay in the immune tolerance and immune surveillance of the postpartum Fallopian tube.

Conclusion

Telocytes were seen in association with the blood vessels, especially high endothelial venules, thereby playing a possible role in immune trafficking across them. The association of telocytes with immune cells in the human postpartum Fallopian tube suggests their probable role in the complex interplay in the immune tolerance and immune surveillance of the postpartum Fallopian tube. Thus, these cells may act as a unique tool for clinical diagnostics and new therapeutic strategies in the diseases related to the Fallopian tube.

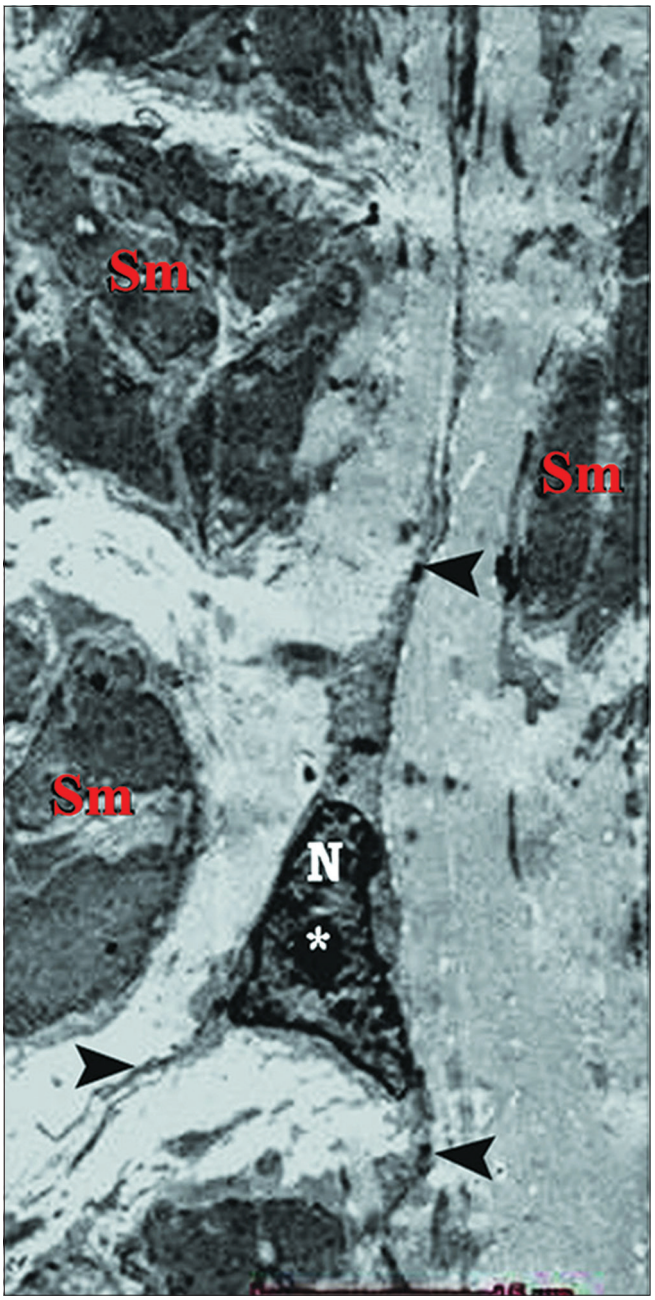

Figure 2: Transmission electron microscopic picture of a telocyte in the muscular layer of the human postpartum Fallopian tube showing a triangular cell body with a heterochromatic nucleus (N) and a prominent nucleolus (*) with a thin rim of cytoplasm around the nucleus. Three long slender telopodes are seen (arrowheads); Sm: Smooth muscle bundle

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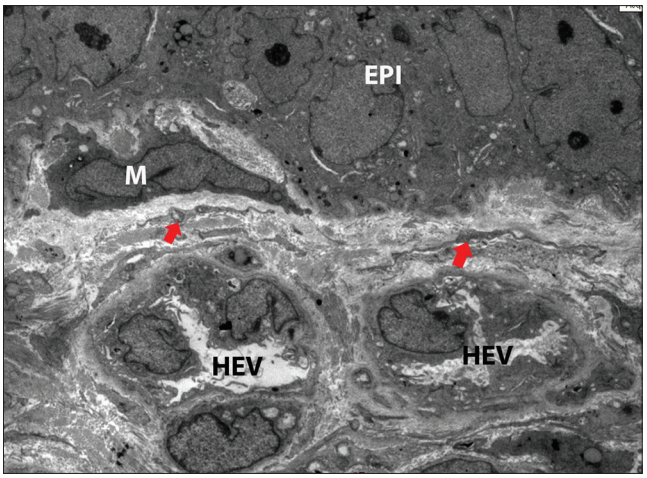

Figure 3: Transmission electron microscopic picture of telopods (red arrows) in the subepithelial layer in association with high endothelial venules in the lamina propria of the human postpartum Fallopian tube. M: Migrating macrophage, EPI: Epithelium, HEV: High endothelial venule

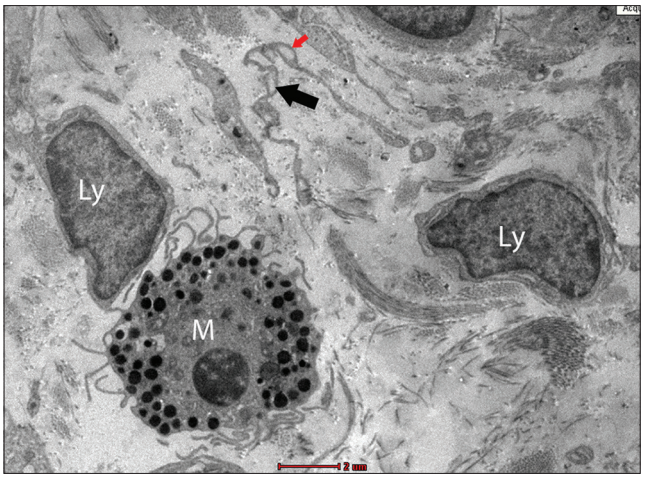

Figure 4: Transmission electron microscopic picture of a telopode (black arrow) is seen in association with mast cell (M) and lymphocytes (Ly) in the lamina propria of the human postpartum Fallopian tube. Red arrow – podom

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Conflicts of interest

There are no conflicts of interest.

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