Scanning Electron Microscopic Study of the Human Uterine Tube Epithelial Lining: Surgical Biopsy Samples and Epithelial Cell Culture

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Received August 24, 2022
Accepted November 16, 2022

Summary

This article summarizes the importance of the exact morphology of human uterine/fallopian tube epithelium at the scanning electron microscopy (SEM) level for the clinical outcome even nowadays. Visual referential micrographs from SEM reflect two ways to view human epithelial cell lining surfaces: the surface epithelial uterine tube from surgical tissue biopsy and human fallopian tube epithelial cells (HFTEC) culture monolayer surface. One colorized image visualizes ciliated cells, distinguishes them from non-ciliated cells, and provides an educational benefit. A detailed description of the ultrastructure in referential and pathologic human uterine tube epithelium is important in defining the morphological basis of high-grade carcinomas, in the mechanism of pathophysiology, and in discussing options for its prevention. Cell cultures of human fallopian tube epithelial cells offer new approaches in simulating the mechanisms of cancer genesis or may help to elucidate the genetic basis of several diagnoses. New technical approaches in SEM provide higher resolution and detailed surface images. The SEM modality is still one of the current options in diagnostics and may be useful for advancing human reproductive organ cancer research.

Keywords

Uterine/Fallopian tube epithelium • Ultrastructure • Scanning electron microscopy • Fallopian tube epithelial cell *in vitro* culture

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Introduction

The human uterine tube represents, under physiological conditions, the most suitable place for fertilization of the oocyte by sperm to form a zygote, the transport of the zygote, and, gradually, the early embryo into the uterine cavity [1]. The uterine tube is lined by a simple columnar epithelium consisting of several cell types. Based on the official morphological nomenclature *Terminologia Histologica* [2], four cell types contribute to uterine tube epithelial lining as follows: ciliated cells (*epitheliocytus ciliatus*), secretory cells (*exocrinocytus tubarius*), peg cells (*epitheliocytus tubarius angustus*), and basal cells (*epitheliocytus tubarius basalis*). Some authors describe only 2 cell types (ciliated and non-ciliated cells), considering peg cells as a subtype of the non-ciliated cell population [3,4]. Paik *et al.* [5] report peg cells as an individual type of secretory non-ciliated cells with a stem cell role. Varga *et al.* [6] suggest reclassifying basal cells in terminology due to their findings based on immunohistochemistry to T-lymphocytes. Basal cells do not reach the surface of the lining; therefore, a description of the epithelial surface ultrastructure cannot reflect them at all [7]. The proportion of ciliated cells is highest in the infundibulum and ampulla, decreasing along the length of the uterine tube. The tubal mucosa typically consists of secretory and ciliated cells that alternate with each other, generally less than 10 cells of one cell type or the other. An increased number of secretory cells indicates a risk of serous ovarian malignancies [8].

Scanning electron microscopy (SEM) in human morphology is standardly used to observe cell surface specializations (presence of cilia, microvilli, or excreting cell membrane-bound vesicles) of the cell lining of the

inner lumen in high levels of magnification. Few authors have accurately described the surface of uterine tube epithelium using SEM in referential samples during the menstrual cycle focusing on the ampullary topographic region [9-13]. The surface of the fertile female uterine tube *ampulla* epithelium in the postmenstrual period shows multiple interruptions of ciliation by fields of non-ciliated flat cells with indistinct cell borders. The preovulatory epithelium (proliferative phase) displays swellings of non-ciliated polyhedral cells. The original distribution of ciliated and non-ciliated cells is preserved, but groups of non-ciliated cells bulge up to the level of the cilia tips. After reaching the level of ciliary tips, the surface has a more uniform appearance. The midcycle (ovulatory) epithelium resembles the morphology of the preceding period with a peak in secretion production, or at some time during ovulation, the non-ciliated cells exhibit disrupted membranes after expelling their secretion. The premenstrual period reflects the decrease of non-ciliated cells well below the ciliary tips level, and again they are flattened with distinct boundaries (clear boundaries are a unique feature for identifying the premenstrual/luteal phase from the postmenstrual phase); ciliated cells may occasionally cluster in elongated fields called tracts or build up small ciliated clumps. The surface epithelium of the uterine tubes at menopause is quite similar to the luteal phase of the samples of fertile patients. Mucosal folds with tracts of ciliated cells (which become a prominent feature) alternate with stretched clumps of ciliated cells. [11]

Material and Methods

Samples from human uterine tubes of women in menopause obtained during the salpingectomy and hysterectomy (approved by the Ethics Committee of the Faculty of Medicine of the Comenius University and the University Hospital Bratislava, approval number EK 051/2019) were evaluated in biopsy as normal/referential. Solid tissue samples were fixed with a 3 % glutaraldehyde buffered solution for 4 hours at room temperature. The samples were then rinsed three times in phosphate-buffered solution and then fixed in osmium tetroxide solution for 2 hours at the 4 °C temperature. After rinsing in demineralized water, the samples were dehydrated in a series of graded ethanol to 100 % ethanol, at which time they were critical point dried at the liquid CO_2 (Leica EM CPD 300 Manual). Finally, they were mounted on aluminium specimen stubs with carbon adhesive tapes, sputter coated with a 15 nm layer of gold/palladium (Leica EM ACE 200). Commercially available cell cultures of normal human fallopian tube epithelial cells (HFTEC, Lifeline Cell Technology) from the 5th passage adhered to glass wafers were gently washed from the culture medium with 3 % glutaraldehyde buffered fixative solution for 30 minutes at room temperature. The samples were then rinsed three times in a phosphate-buffered solution and fixed in an osmium tetroxide solution for 1 hour at the 4 °C temperature. After rinsing in demineralized water, the samples were dehydrated in a series of graded ethanol to 100 % ethanol, followed by critical point drying, sputter coated with a 7 nm layer. All samples were examined with a ZEISS type EVO LS 15 scanning electron microscope. Colorization of selected structures in micrographs for educational purposes by Photoshop application (Adobe Photoshop CS6).

Results

Human uterine tube tissue biopsy samples from menopausal women shows ciliated and non-ciliated cells epithelial, with a majority of non-ciliated ones. The cell boundaries are clear, the non-ciliated cells almost reaching the level of the cilia tips, but they vary in size. Ciliated cells organize in small clumps, and cilia beat in multiple directions. (Figs. 1-4). The cell borders of non-ciliated secretory cells are distinct, there are microvilli on the surface. The non-ciliated cells vary in size, and few secretory cells enlarge to form "dome-like" cells and exhibit delicate "microplicae-like" structures on the surface of non-ciliated cells (Fig. 2). Colorized image of the human uterine tube epithelial lining in menopause demonstrates cilia of ciliated cells what gives the evident visual effect of the ratio between ciliated and non-ciliated cells (Fig. 4).

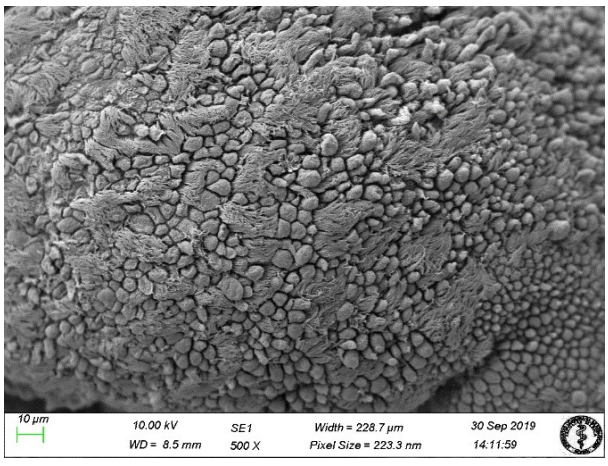

Fig. 1. Human uterine tube mucosa in menopause. Magn. 500x

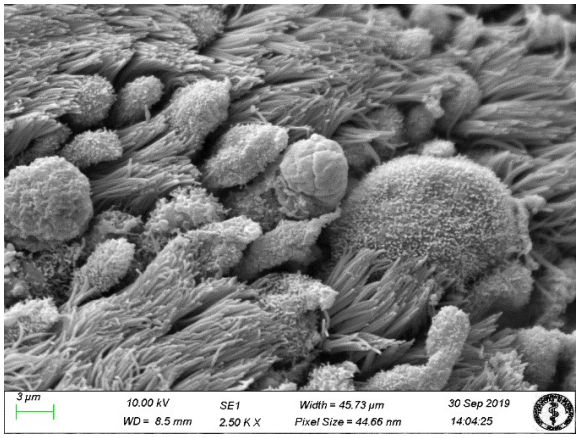

Fig. 2. Detail of the epithelial lining of the human uterine tube mucosa in menopause. A "dome-like" secretory cell and "microplicae-like" structures on the surface of the non-ciliated cell. Magn. 2500x.

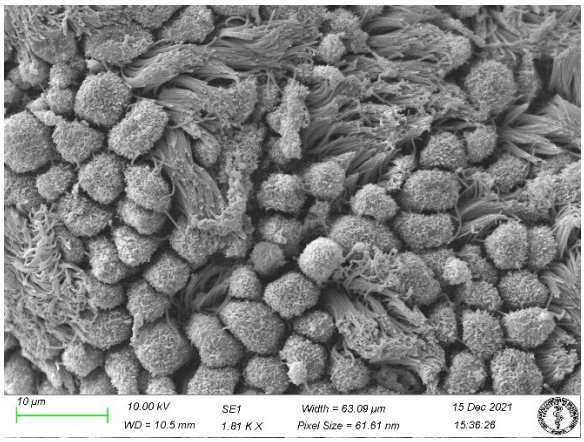

Fig. 3. Detail of the epithelial lining of the human uterine tube mucosa in menopause. Magn. 1810x

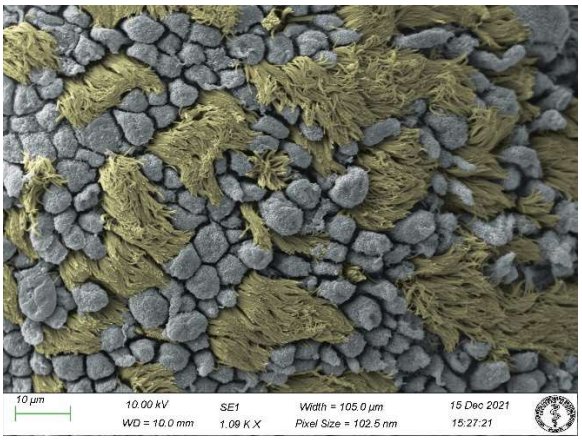

Fig. 4. Colorized image of the human uterine tube epithelial lining in menopause. The yellow color demonstrates the cilia of ciliated cells. Magn. 1090x.

Human fallopian tube epithelial cells (HFTEC) from in vitro cell culture are spread in the monolayer. Cells of elongated to polygonal shape adhered to glass wafer exhibit cilia growth in the central cellular portion (Figs. 5-7). Several cells show elongated shapes (Fig. 6). Cell boundaries are artificially disconnected due dehydration process (Figs. 5, 6). Cilia cover most of the cells' surface, and the nuclei are bulging centrally (Figs. 6, 7).

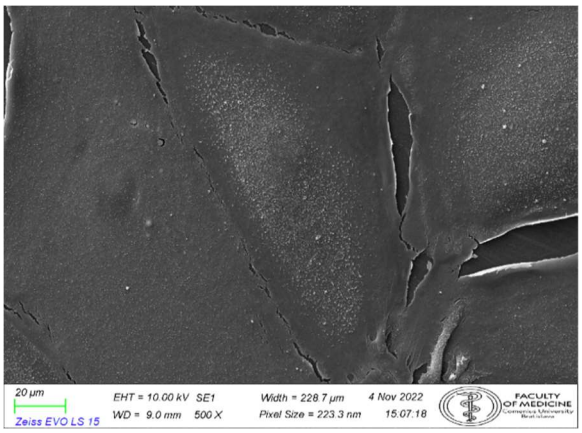

Fig. 5. *In vitro* cell culture **-** Small magnification of human fallopian tube epithelial cells (HFTEC) surface in the monolayer. Slight contamination on the surface. Magn. 500x.

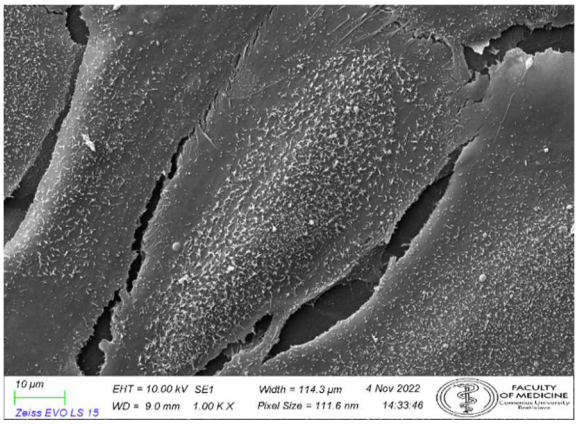

Fig. 6. Middle magnification of HFTEC in the monolayer. Magn. 1000x.

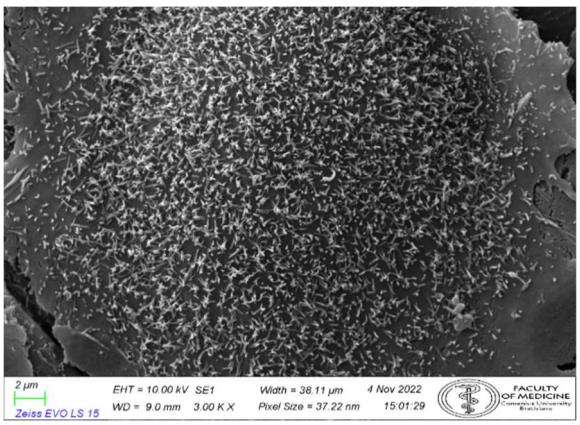

Fig. 7. High magnification of HFTEC. Cilia cover most of the cells' surface. Magn. 3000x.

Discussion

In this study, we described the normal ultrastructure of the surface of human tubal epithelial cells from two sources – surgical biopsies and *in vitro* cell culture. In terms of ciliary cells attenuation within the epithelium, significant morphological changes were evident with aging and were studied in postmenopausal women. Senile epithelium comprises more non-ciliated cells, often transformed into dome-shaped giant cells [11]. Our images from the samples of the menopausal women demonstrate similar findings, the ratio between the amount of non-ciliated cells and ciliated one's increases (Fig. 1-4). Dome-shaped cells were prominent on the epithelial surface and sometimes were present delicate "microplicae-like" structures (Fig. 2). Observations of the uterine tube lining by Makabe *et al.* [14] showed a dramatic decrease in the number of ciliated cells, and they refer to "microplicae-like" structures on the surface epithelium. Similar findings are reported by Correr *et al.* [15], who describe the gradual shortening of microvilli, deciliation, and gradual formation of "microplicae-like" structures. Regressive changes represent an important adaptation of the uterine tube epithelium induced by the physiological process of aging in menopause. By comparing epithelial morphology in oestrogen-treated patients, Donnez *et al.* [16] confirmed that oestrogen therapy significantly reduces the depletion of ciliary cells and maintains the height of the uterine tube epithelium.

Examination of infertility at the level of uterine tube ultrastructure showed extensive changes in the epithelium morphology. Uterine tubes affected by *hydrosalphinx* displayed epithelial cells desquamation, a reduced population of ciliated cells in thin-walled samples, or depleted areas on highly compounded adherent folds, creating "pseudoglandular bridges" [17]. Pregnancy rates were significantly lower in the presence of hydrosalpinx, and retrospective analyses even assessed that hydrosalpinx, present during *in vitro* embryo transfer, has negative consequences on pregnancy, implantation, live birth, and early pregnancy loss. Salpingectomy is strongly recommended before *in vitro* fertilization [18,19]. Regarding therapeutic and diagnostic methods of assisted reproduction, e.g., catheterization, Kitamura *et al.* [20] examined the ultrastructure of the uterine tube using electron microscopy. They concluded that there was no evidence of severe epithelial damage following the use of a transcervical catheter. In contrast to mild catheterization, ligation causes irreversible ultrastructural changes, and re-fertilization of the ligated uterine tube requires the removal of the affected portion [21]. Samples infected with the pathogen *Mycoplasma hominis* showed extensive cilia swelling in an SEM study by Mårdh *et al.* [22]. A new study published by Baczynska *et al.* [23] confirms cilia swelling but not in samples infected with *M. hominis*, but with *Myocoplasma genitalium*. Tissues infected with *Chlamydia trachomatis* and observed in SEM displayed a local toxic effect on the ciliated epithelium and disruptions of secretory cell membranes. *Neisseria ghonorrhoeae* strongly degenerates the epithelium of the uterine tube after 5 days of infection, and the bacteria mostly attach to microvilli of non-ciliated cells. Ciliated cells peeled off from the epithelium. Ling *et al.* [24] investigated the mechanism of fibrosis of the uterine tube wall caused by *Chlamydia trachomatis* and suggested that fibrocytes causing fibrosis is induced by epithelial cells. Ezzati *et al.* [25] summarized the impact of microorganisms on the uterine tube. They elucidated the pathological mechanisms of endometriosis or smoking on tubal fertility, and Lyons *et al.* [26] focused on the role of ciliary beating in similar conditions. Age remained a significant risk factor for serous neoplasia after age adjustment. In addition, a dramatic increase in secretory cells was observed in high-risk carcinoma patients. Secretory cell expansion could potentially serve as a sensitive biomarker for early serous carcinogenesis in the uterine/fallopian tube. The findings support a relationship between serous neoplasia and an increase of secretory cells to ciliated cells [8]. Structural differences in the uterine tube epithelium correlate with the incidence of high-grade serous ovarian carcinomas (HGSOCs) and play an essential role in their mechanism [19, 27, 28]. Labidi-Galy *et al.* [29] detected genes in serous tubal intraepithelial carcinomas (STICs) and elucidated the risk of HGSOC precursors at the molecular level. Coen *et al.* [28] characterized genes responsible for regulating cilia motility which may participate in cancer development. Lim and Oliva [27] pointed out that high-grade ovarian serous carcinomas may be derived from the uterine tube and standard screening methods (such as CA125 biomarkers or routine imaging methods focusing on the ovary) are insufficient for early detection of HGSOCs. Low-grade serous carcinomas may arise directly from the ovarian surface epithelium, as previously thought. It is also possible that normal tubal epithelium may be dislodged and implanted into the ovary at the time of ovulation or during inflammatory tubal processes, where it subsequently undergoes malignant transformation [30].

Lim and Oliva [27] recommend salpingectomy for cancer prevention in risk patients. According to the correlation between serous tubal intraepithelial carcinomas and HGSOCs, Yamamoto *et al.* [31] examined transformed fallopian tube stem cells (regarding the same alteration in HGSOC) to analyse their gene expression and described the biomarkers in comparison with STICs and normal tubal epithelium. In contrast to SEM observations of the human uterine tube, findings in rat experimental animals reveal an increasing ratio between ciliated and non-ciliated cells followed by depletion of secretion, reaching menopause [32] which is in contrast to the finding in humans. The rat model does not seem to be a referential model to study the clinical outcomes of human fertility.

Human tubal epithelial cells for co-culture in in vitro fertilisation procedure were established by Walker *et al.* [33] and Aldarmahi [34]. Comer *et al.* [35] identified immunocytochemical markers to differ between ciliated and non-ciliated cells. They confirmed by SEM observation that estrogen induces differentiation to a ciliated epithelial cell phenotype. Chang *et al.* [36] describe the morphology of tubal epithelial cells in culture at the light microscopic level. The human fallopian tube epithelial cells (HFTEC) culture exhibited a cuboidal cell shape and maintained a constant proliferation rate up to nine passages. Our cell culture samples in SEM (Figs. 5-7) revealed a monolayer of the flat cells of the polygonal to the elongated shape. The cell nucleus bulges centrally, and most cells display cilia on the surface (Fig. 6). Cell linages of HFTEC may provide a new model for studying the tubal regeneration and malignant transformation of the tubal epithelium [36]. For routine clinical practice, the educational purpose of understanding the referential ultrastructure or even pathologically altered one is still important. Bringing new insights into the surface morphology of reference specimens, Polák *et al.* [37] created an atlas of the ultrastructure of human organs with colourful visual images. Colorizing becomes beneficial, and even complicated ultrastructure is transformed into an understandable image. Our colorized image (Fig. 4) demonstrates an example of the visual effect of using this technology.

Conclusions

This article summarizes the importance of the exact morphology of human uterine/fallopian tube epithelium at the level of scanning electron microscopy for clinical outcomes. Visual referential micrographs reflect two options for imaging epithelial cell lining surfaces – a biopsy of natural tissue with epithelial cell surface with and without cilia and a monolayer cell culture surface. Cultures of human fallopian tube epithelial cells provide an opportunity to simulate the mechanisms of cancer development or may help to elucidate the genetic basis of several cancer diagnoses. Cell morphology evaluated by SEM seems to be useful. The detailed description of the ultrastructure in referential and pathological human uterine tube epithelium is undisputed regarding clinical outcomes in investigating high-grade carcinomas and possible prevention. The morphology of the epithelium by infectious pathogens is one of the diagnostic features and helps to understand the mechanisms of inflammatory processes leading to tubal infertility. Some animal models have not proved referential due to their different normal morphology compared to humans. Although older atlases do not reflect modern visual technologies, they contain accurate morphological descriptions of the phases of the menstrual cycle phase. Still, they may persist as an indicator for evaluating SEM images. New technical approaches in SEM provide higher resolution and detailed images. Very advanced cryopreserved tissue samples may serve for rapid evaluation under natural non-artificial conditions. The SEM modality is still one of the current options in diagnostics and may be helpful for the progress of human reproductive organ cancer research.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

This study was supported by grant from the Slovak Research and Development Agency APVV-18-0499.
This publication was also supported from the Operational Program Integrated Infrastructure for the project: Increasing the capacities and competences of the Comenius University in research, development, and innovation 313021BUZ3, co-financed from the resources of the European Regional Development Fund.

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