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RESEARCH ARTICLE

How many cell types form the epithelial lining of the human uterine tubes? Revision of the histological nomenclature of the human tubal epithelium

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ABSTRACT

Introduction: Many widely used international histological textbooks claim that the epithelium of the human uterine tube consists of two, three, and, eventually, four types of cells. Most discrepancies among these textbooks relate to debates regarding the presence or absence of basal cells, whether the peg/intercalary cells and secretory cells are the same or distinct cell populations, and if the epithelium contains a population of immunologically active cells (T- and B-lymphocytes, NK cells, macrophages and dendritic cells) or dispersed endocrine cells.
Methods: Uterine tubes were obtained from 22 women (average age: 46.73 y) undergoing gynecological surgery. The women were in fertile age, mostly in the middle of the menstrual cycle (ovulation phase). Tissue samples were processed for immunohistochemistry using primary antibodies against proliferation markers (Ki67 and PCNA), immune system cells (CD1a, CD3, CD4, CD8, CD20, CD45RO, CD56, CD68, granzyme B and S100) and disperse endocrine cells (chromogranin A and synaptophysin).
Results: Most of the mature tubal epithelial cells, ciliated cells, and secretory cells were mitotically active (PCNA+), a population of basal undifferentiated cells was not identified. The dividing cells had a narrow-shaped nucleus (Ki67 positive). These cells were morphologically identical to – by the terminology mentioned – intercalary cells, assuming they represented actually dividing cells *(epitheliocytus tubarius mitoticus)*. The tubal "basal cells" displayed small, hyperchromatic nuclei and very pale cytoplasm (clear cytoplasmic halo). They were located in the epithelium adjacent to the basement membrane, were non-mitotically active and their immunophenotype corresponded to intraepithelial regulatory T-lymphocytes (CD3+, CD8+, CD45RO+, CD4−, CD20−, CD56− and granzyme B−). Intraepithelial B-lymphocytes were only rarely identified. Intraepithelial NK cells, dendritic cells, macrophages and dispersed endocrine cells were not identified.
Conclusions: We recommend replacing the term "*epitheliocytus tubarius basalis*" in the *Terminologia Histologica* with the term "*lymphocytus T intraepithelialis tubarius*", which represents intraepithelial regulatory T-cells (CD8+, CD45RO+) of the uterine tube. Additionally, we propose that intercalary/peg cells are actively dividing cells, instead of effete or degenerating cells. Finally, the histological nomenclature should be corrected in a way that peg/intercalary cells are not considered synonymous terms for secretory cells.

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1. Introduction

Initial morphological description of the uterine tubes is derived from the work of the Italian anatomist Gabriele Falloppio in 1561. He named the "female semen-conveying duct" the *tuba uteri* because each tube resembled a musical instrument: the brazen trumpet named tuba. Fallopio also coined the term "Fallopian tubes" for these structures (van Gijn and Gijselhart, 2011; Macchi et al., 2014). The uterine tube *(salpinx*, oviduct) is a paired muscular tube. The abdominal ostium of the uterine tube opens into the peritoneal cavity near the ovary and the other end of the uterine ostium opens into the uterine cavity. The length is 10 cm on average (ranging from 7 to 14 cm) and the histological composition is ostensibly simple. The wall of the uterine tube consists of three layers called coats *(tunicae)*, which include the mucosa, the muscular layer, and the serosa. The mucosa of the uterine tube consists of simple columnar epithelial lining and connective tissue lamina propria with an abundance of blood vessels and wide lymphatic lacunae (Varga et al., 2018a). The interactions of sperm cells, ova, and/or the early embryos with the epithelial lining of the tubal mucosa play an important role in reproduction.

Similar to the ovary and uterus, the uterine tubes also undergo hormonally regulated cyclical changes. These changes predominantly affect the epithelial lining, resulting in changes in the epithelial cell height and the frequency of ciliary beating. For example, epithelial cells of the mucosa are shortest during the menstrual phase, and they subsequently increase in height during the proliferation phase, reaching their maximum height (up to 30 μm) during the ovulation period. During the period that follows ovulation (the secretory phase), secretory cells are the most active, displaying high levels of secretion and the greatest frequency of ciliary beating (Lyons et al., 2002, 2006). An ultrastructural study performed by Verhage et al. (1990) proved that estradiol induces hypertrophy, hyperplasia, ciliogenesis, and secretory activity of the tubal epithelium. In contrast, progesterone causes atrophy, deciliation, apoptosis, and the loss of secretory activity. Furthermore, the ultrastructure of the epithelial lining of the uterine tubes changes significantly not only during the menstrual cycle, but also during pregnancy (Smith and Copenhaver, 1944), puerperium (Cigánková et al., 1996), menopause (Correr et al., 2006), and even after surgical ligation of the uterine tubes (Li et al., 1996). In all of these cases, the loss of cilia and epithelial height reduction are observed. However, most of this research was performed using animal model systems, and significantly fewer scientific papers have studied the human tubal epithelium during these states.

The histological findings in normal uterine tubes have been described sporadically in the scientific literature. The major reason for the lack of investigation in this regard has been the success of *in vitro* fertilization techniques in which the uterine tubes are bypassed. This has decreased the medical community's interest in studying tubal morphology.

Within the lining of the uterine tube epithelium, we can morphologically and functionally distinguish different cell populations by the 12th week of gestation. These include three epithelial cell types that line the derivatives of the paramesonephric (Müllerian) ducts: basal cells, cells with microvilli, and ciliated cells. Even on the apical surface of cells with microvilli, a single cilium is often detected (Barberini et al., 2005). In general, there is no consensus among histologists regarding how many types of epithelial cells form the human uterine tube epithelium during a woman's reproductive life. According to the most well-known international histological textbooks, the tubal epithelium consists of two, three, and, eventually, four types of cells (Table 1). Most of the terminological discrepancies are associated with a debate over the presence or absence of "enigmatic" basal cells, and whether the peg/intercalary cells and secretory cells represent the same or different cell populations. These discrepancies are due to the fact that there is no specific marker (histochemical or immunohistochemical) that can reliably distinguish these cell types. According to the internationally accepted and still-valid nomenclature *Terminologia Histologica* (FICAT, 2008), four types of cells can be distinguished within the simple columnar epithelium of the uterine tube, including:

- *Epitheliocytus ciliatus* (ciliated epitheliocyte);
- *Exocrinocytus tubarius* (tubal secretory epitheliocyte);
- *Epitheliocytus tubarius angustus* (peg cell or intercalary cell); and
- *Epitheliocythus tubarius basalis* (basal epitheliocyte).

Currently, the *Terminologia Histologica* catalogs the terminology describing all tissues and organs at the cellular level visualized using light and electron microscopy (Allen, 2009). However, it should be noted that no updates have been made since 2008 - the year of the publication of the most recent edition of the *Terminologia Histologica*. Therefore, it contains dozens of inaccuracies and errors, which should be corrected in the future (Varga et al., 2018b).

Table 1
Types of epithelial cells lining the uterine tube according to various internationally accepted histological textbooks (in alphabetical order for the authors).

Author(s), Title, and Year	Number of Cell Types	Nomenclature used
Ash et al., The Big Picture: Histology. 2013.	2	Ciliated and secretory (peg) cells
Cui, Atlas of Histology. 2011.	2	Ciliated and peg (secretory) cells
Dudek, High-Yield Histopathology. 2011.	2	Secretory (nonciliated) and ciliated cells
Eroschenko, diFiore's Atlas of Histology. 2012.	2	Ciliated and nonciliated peg (secretory) cells
Gartner, Color Atlas and Text of Histology. 2018.	2	Ciliated columnar cells and peg cells
Kierszembaum and Tres, Histology and Cell Biology. 2016.	2	Ciliated and nonciliated secretory cells (called peg cells)
Leboffe, A Photographic Atlas of Histology. 2013.	2	Ciliated and secretory non-ciliated (peg) cells
Lowe and Anderson, Stevens and Lowe's Human Histology. 2015.	4 (?)	Ciliated cells, secretory cells, peg cells, and reserve basal cells (the authors also mentioned that peg cells are likely effete secretory cells and basal cells are intraepithelial cells of the lymphoid series)
Mescher, Junqueira's Basic Histology. 2016.	2	Ciliated and secretory peg cells
Mills, Histology for Pathologists. 2012.	4	Ciliated, secretory, intercalated (peg) cells, and endocrine cells. Intercalated cells may be effete secretory or reserve cells. Basal cells do not exist, and these cells are lymphocytes (as a part of mucosa associated lymphoid tissue)
Ovalle and Nahirney, Netter's Essential Histology. 2013.	2	Ciliated and nonciliated secretory cells named peg cells
Ross and Pawlina, Histology. A Text and Atlas with Correlated Cell and Molecular Biology. 2016.	2	Ciliated cells and nonciliated peg cells
Standring, Gray's Anatomy. 2016.	2 + 1	Ciliated and secretory (peg) cells + occasional intraepithelial lymphocytes
Treuting and Dintzis, Comparative Anatomy and Histology. 2012.	2	Ciliated and nonciliated peg cells
Young et al., Wheater's Functional Histology. 2014.	3	Ciliated, non-ciliated secretory cells, and intercalated cells (intercalated cells may be a morphological variant of secretory cells)

Table 2
Immunohistochemical description of cell types of the human tubal epithelium.

Marker	Detected cell type	Presence in human tubal epithelium
Ki67	Proliferation marker protein; marker of "*tubal basal epitheliocytes*"	Yes, nuclear positivity of narrow shaped nuclei, morphologically similar to peg/intercalary cells
PCNA	Proliferating cell nuclear antigen; "*tubal basal epitheliocytes*"	Yes, nuclear positivity of most of epithelial cells
CD1a	Membrane marker of dendritic cells; *tubal intraepithelial dendritic cells*	No, tubal epithelium is without dendritic cells
S100	One of the markers of dendritic cells; *tubal intraepithelial dendritic cells*	No, tubal epithelium is without dendritic cells
CD3	Differentiation marker for T-lymphocytes, expressed in all mature T-lymphocytes; *tubal intraepithelial T-lymphocytes*	Yes, spherical cells localized mostly near the basement membrane are tubal intraepithelial T-lymphocytes
CD4	Surface marker of helper T-lymphocytes; *tubal intraepithelial helper T-lymphocytes*	No, tubal intraepithelial T-lymphocytes are not helper T-lymphocytes
CD8	Surface marker of cytotoxic and regulatory T-lymphocytes; *tubal intraepithelial regulatory T-lymphocytes*	Yes, intraepithelial T- lymphocytes are probably regulatory T-lymphocytes
CD45RO	Marker of activated T-lymphocytes, most of regulatory and memory T-lymphocytes are positive; *tubal intraepithelial regulatory T-lymphocytes*	Yes, intraepithelial T- lymphocytes are probably regulatory or memory T-lymphocytes
CD20	A differentiation marker for B-lymphocytes; *tubal intraepithelial B-lymphocytes*	No, intraepithelial lymphocytes are not (or only rarely) B-lymphocytes
CD56	Prototypic marker of Natural Killer (NK) cells; *tubal intraepithelial NK cells*	No, tubal epithelium is without NK cells
Granzyme B	Serine protease in the granules of cytotoxic T-lymphocytes and NK cells; *tubal intraepithelial cytotoxic T- lymphocytes and NK cells*	No, tubal epithelium is without cytotoxic T-lymphocytes and NK cells
CD68	A glycoprotein highly expressed by macrophages*; tubal intraepithelial macrophages*	No, tubal epithelium is without intraepithelial macrophages
Chromogranin A	A member of neuroendocrine secretory proteins; *tubal dispersed endocrine cells*	No, tubal epithelium is without intraepithelial dispersed endocrine cells
Synaptophysin	A marker protein in neuroendocrine cells; *tubal dispersed endocrine cells*	No, tubal epithelium is without intraepithelial dispersed endocrine cells

The present article focuses on clarifying the nature of the basal cells and peg/intercalary cells within the human tubal epithelium as well as the occurrence of intraepithelial immunologically active cells and endocrine cells. This work is not only important for refining the histological nomenclature. It also has important clinical implications. Over the last few years, our understanding of the pathogenesis of ovarian serous tumors has shifted dramatically. High-grade ovarian tumors are now thought to likely originate from the epithelial cells of uterine tubes. Most notably, serous tubal intraepithelial carcinomas are thought to derive from cells within the fimbriated end of the uterine tube (Vang et al., 2013). This is another reason why research into the histology of epithelial cells within the uterine tube is essential. This study considered four following hypotheses:

1) In other organs, basal cells are responsible for tissue regeneration. Therefore, we hypothesized that the tubal basal cells have a similar function, providing a source for epithelial regeneration. We expected that basal cells would be mitotically active, and they would express proliferation markers.
2) If intercalated cells are effete/degenerating secretory cells, we hypothesized that they would not express cell proliferation markers.
3) The epithelium of the uterine tube was hypothesized to contain a population of immunologically active cells (namely, T- and B-lymphocytes, NK cells, macrophages and dendritic cells), which have not been listed in the *Terminologia Histologica.*
4) The *Terminologia Histologica* does not mention the presence of endocrine cells within the epithelium, although this cell population is present in other lining epithelia (digestive tube, or airways). We would like to confirm or deny this statement.

2. Materials and methods

2.1. Patients

Uterine tubes were obtained from 22 women (average age: 46.7 ± 4.2 years) in fertile age. The women were undergoing gynecological surgery (salpingectomy and/or hysterectomy) as a result of various medical indications, such as tumors of adnexa and uterine fibroids. Therefore, all performed surgeries were elective and planned during ovulation period (middle of menstrual cycle, less blood loss). This study was approved by the Ethical Committee of the General Hospital in Komárno, Slovakia where the tissue samples were obtained. Informed consent was obtained from all patients.

2.2. Histology and immunohistochemical staining

After surgical extraction, tissue samples from anatomically distinct regions of the uterine tubes (infundibulum with fimbriae, ampulla, and isthmus) were immediately fixed in 10% formalin for 24 h at room temperature and embedded in paraffin. Next, 5-μm thick sections were obtained for hematoxylin and eosin staining and immunohistochemistry. Samples were processed at the Institute of Histology and Embryology and Institute of Pathology, Faculty of Medicine, Comenius University in Bratislava, Slovakia.

For immunohistochemistry, slides were deparaffinized, rehydrated in phosphate buffered saline solution (10 mM, pH 7.2) and processed according to the staining procedure recommended by DAKO (Glostrup, Denmark). The tissue epitopes were demasked using the automated water bath heating process in DAKO PT Link using retrieval solution recommended for the appropriate antibody, at 98 °C for 20 min. The slides were subsequently incubated for 1 h at room temperature with the primary antibody against: prediluted FLEX Ready-to-Use antibodies: proliferation marker protein Ki67, proliferating cell nuclear antigen PCNA, CD1a, S100, CD3, CD4, CD8, CD20, CD45RO, CD56, CD68, chromogranin A, synaptophysin; granzyme B diluted 1:100 (Table 2). Immunoreaction was detected with anti-mouse/anti-rabbit immuno-peroxidase polymer (EnVision FLEX/HRP), during incubation for 30 min at room temperature, according to the manufacturer's instructions. For visualization, the slides were reacted with diaminobenzidine substrate-chromogen solution (DAB) for 5 min. Finally, the slides were counterstained with hematoxylin and mounted. Slides stained with the same procedure, but omitting the application of the primary antibody served as negative control.

Sections were visualized using NIKON Eclipse i80 microscope or LEICA DM 2500 light microscope, and images were captured using built-in digital camera.

3. Results

The proportions of the different types of epithelial cells vary in distinct anatomical regions of the uterine tube. Using the light

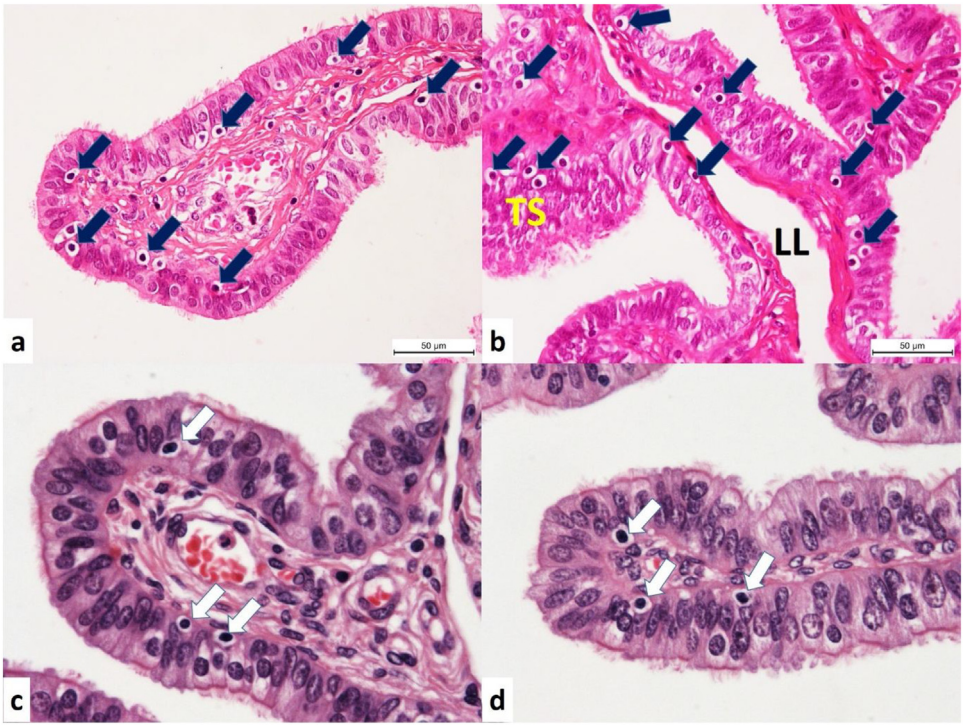

Fig. 1. The epithelial lining of the uterine tube stained with hematoxylin and eosin from 4 different individuals. Arrows indicate basal cells possessing small, hyperchromatic nuclei and very pale cytoplasm (clear cytoplasmic halo) located adjacent to the basement membrane. TS – Tangential section where the epithelium resembles the stratified type; LL – Wide lymphatic lacuna in the center of a mucosal fold. Orig. Magnification 200× (a + b) and 400× (c + d).

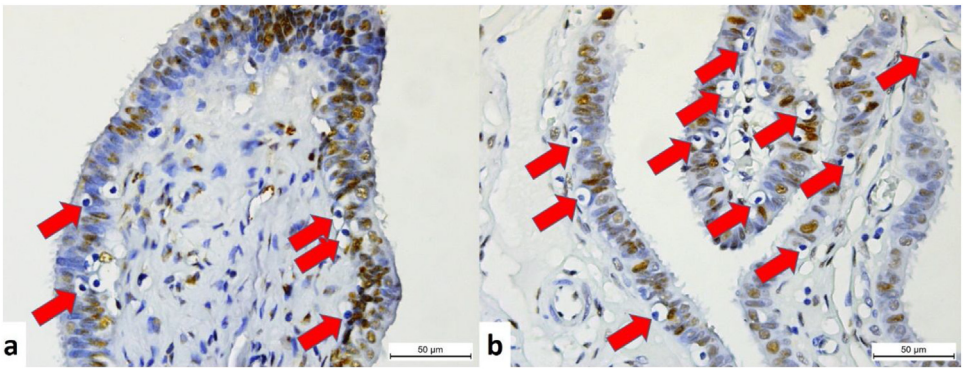

Fig. 2. Most of nuclei of the epithelial cells are positive for proliferating cell nuclear antigen (anti-PCNA immunostaining; brown color) with the exception of basal cells (arrows). Orig. Magnification 200×.

microscopy and hematoxylin and eosin staining, we morphologically distinguished within the simple columnar epithelium of the human uterine tubes (1) Cells with cilia, (2) Cells without cilia (secretory exocrine cells), (3) Cells with narrow nuclei that were perpendicularly oriented to the apical surface of the epithelium, and (4) Spherical cells with round nuclei with predominance of heterochromatin, and pale cytoplasm localized in the basal region of the epithelium (Fig. 1). Additionally, in tangential sections, the simple columnar epithelium appears pseudostratified or sometimes even stratified. Similar image is seen in abnormal hyperplastic changes. However, in our specimens, we did not notice a significant number of atypical nuclei.

We also assayed for the presence of "basal epithelial cells". We observed round cells with small, spherical, hyperchromatic nuclei and very pale cytoplasm (clear cytoplasmic halo), which were located in the epithelium adjacent to the basement membrane (Fig. 1). Generally, basal cells in other epithelia (*e.g.,* of gut or airways) are usually described as mitotically active cells capable of facilitating epithelial regeneration. As such, we next examined the nuclear expression of PCNA and Ki67 in these cells to determine if they were proliferating. Surprisingly, most of the nuclei of ciliated and secretory epithelial cells – but not those of the cells typically referred to as basal cells – were PCNA positive (Fig. 2). A similar result was obtained for the expression of Ki67. The nuclei of many columnar epithelial cells were Ki67+, but the nuclei of cells thought to be basal cells were all negative for Ki67 (Fig. 3). This supported our hypothesis that there are no basal epithelial stem cells within the tubal epithelium that facilitate regeneration (eventually, they are rare and/or quiescent, so it might be hard to catch a PCNA or Ki67+ cell at any given time point, especially in the absence of an injury). In support of this, many differentiated epithelial cells were found to have the potential for mitotic division or were mitotically active (Figs. 2 and 3). Therefore, according to our results, basal cells are not required for the renewal of the tubal epithelium.

Dividing cells positive for nuclear Ki67 had a predominantly narrow shape and were arranged perpendicular to the epithelial

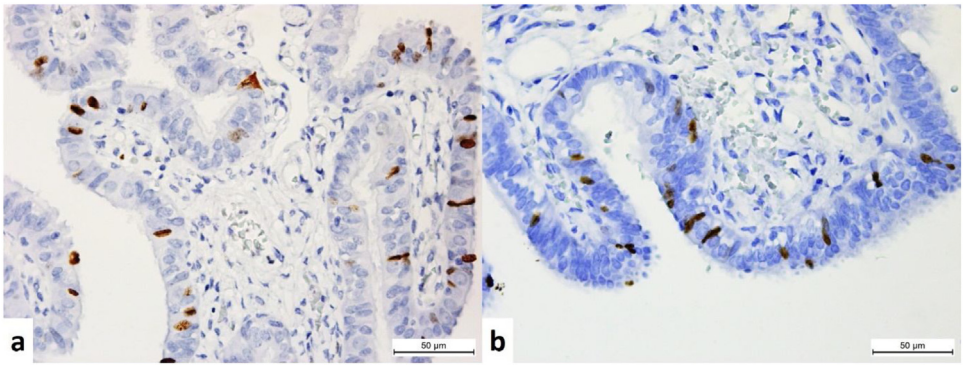

Fig. 3. The nuclei of some epithelial cells are positive for Ki-67 (anti-Ki-67 immunostaining; brown color), a marker of proliferating cells. These cells display narrow-shaped nuclei, and they morphologically resemble peg/intercalary cells. The nuclei of basal cells are Ki67 negative. Orig. Magnification 200×.

apical surface. These Ki67+ nuclei were morphologically similar to the nuclei of cells termed "peg/intercalary cells" in the *Terminologia Histologica*. We suspect that these cells with narrow shaped nuclei are not "effete or degenerating cells," as denoted in some textbooks, but are instead mitotically active.

Intraepithelial small spherical cells were CD3+, CD8+, CD45RO+, but were CD4 and granzyme B negative (membrane-localized markers of different subpopulations of T-lymphocytes). According to these findings, intraepithelial T-lymphocytes are mostly memory or eventually regulatory (suppressor) T-lymphocytes. We find only rarely CD20+ B-lymphocytes, and neither CD68+ macrophages nor CD56+ NK cells were observed within the epithelial layer of the uterine tube. We have not found any tubal intraepithelial dendritic cells (the epithelial lining was S100 and CD1a negative) or intraepithelial dispersed endocrine cells (the epithelial lining was chromogranin A and synaptophysin negative). The presence of the above mentioned cells were similar in all anatomical parts of the human uterine tube. The results are summarized in Table 2 and Fig. 4.

4. Discussion

Epithelial lining of the uterine tubes has been traditionally considered to be composed of simple columnar cells. Most of the mature tubal epithelial cells, ciliary cells, and secretory cells were mitotically active (PCNA+). The actually dividing cells had a narrow-shaped nucleus (Ki67 positive). The tubal "basal cells" located in the epithelium adjacent to the basement membrane, were non-mitotically active and their immunophenotype corresponded to intraepithelial memory T-lymphocytes (CD3+, CD8+, CD45RO+, CD4−, CD20−, CD56− and granzyme B−). From other immunologically active cells, intraepithelial B-lymphocytes were identified only rarely and no intraepithelial NK cells, dendritic cells, or macrophages were detected. Other result indicates the absence of dispersed endocrine cells inside the tubal epithelium (if there, they should have been synaptophysin and chromogranin A positive). Synaptophysin and chromogranin A are general markers of the endocrine cells (Rindi et al., 2004).

All histological textbooks indicate that two principal cell types form the epithelial lining: **ciliated cells and secretory cells**. The distribution of these cell types is not uniform along the length of the uterine tube, and progressively increasing numbers of ciliated cells are observed from the proximal end of the tube toward the distal end (Crow et al., 1994). Furthermore, the histological structures of the ciliated cells and secretory exocrine cells are not uniform. It seems that the population of secretory cells express heterogeneous ultrastructure [with respect to the number of putative secretory granules (Abe, 1996)]. There are clear morphological differences within the group of ciliated cells [some of them are pale or "light" (Suuroia et al., 2002)] as well. There is a theory, that at least these pale ciliated cells and non-ciliated secretory cells are functional stages of the same tubal epithelial cell (Suuroia et al., 2002). Evidence behind this is a discovery that ciliogenic cells in early stages of ciliogenesis contain secretory granules-like vesicles in the apical cytoplasm, which once again leads to the assumption that the ciliated cells are differentiated from secretory cells in the late secretory phase on demand (Hagiwara et al., 1992; Hagiwara, 1995). Thanks to the results of Jirsová and Vernerová (1990), there is one argument against the possibility that the secretory cells are some sort of precursor cells for the ciliated cells. During their studies of ciliogenesis in the rat epithelium of the uterine tube, they found out that it starts between the 8th and the 10th day after fertilization. A continuous kinociliary apparatus is formed on the basis of centriole replication. But the first secretory cells appear towards the end of the second week — therefore later than ciliated cell. This result still allows explanation, that the secretory and ciliated cells represent different states of the same cell type, while not saying which of these two cell types is "more differentiated". On the other hand, mainly in recent literature, ciliated and secretory cells are routinely regarded as two separated cell types (*e.g.* Lee et al., 2007 or Cochrane et al., 2017). Moreover, this tendency of clear differentiation between ciliated and secretory cell type (or even "cell lineages") seems to bring consistent data and outcomes for usage in clinical practice.

According to our results, in the epithelial lining of the human uterine tube, large number of immunologically active cells is present. In most of the cases, we have identified **regulatory T-lymphocytes** (CD3+, CD8+, CD45RO+, CD4− and granzyme B−). Similarly, presence of intraepithelial CD45RO+ and CD8+ T- lymphocytes located between intestinal epithelial cells were described in the human gut (Ebert, 1993). In our study, intraepithelial B-lymphocytes have been detected only rarely and we have identified neither intraepithelial NK cells, dendritic cells nor macrophages. Our results are in agreement with the observation of lymphocytes within the epithelium of bovine uterine tubes (Abughrien et al., 2000). In the past, Rasweiler (1972) postulated a theory regarding the origin of basal cells. He proposed that they arose primarily from connective tissue mast cells, which migrate into the epithelium and undergo degranulation. However, we do not agree with this theory. Mast cells are not CD3+, and in our preliminary studies (Urban et al., 2016; Varga et al., 2016), we did not find c-KIT -positive cells within the uterine tube epithelium (c-KIT expression is a marker for mast cells).

Intraepithelial T-lymphocytes can be involved in the process of immune tolerance, which could lead to the tolerance of non-self cells (sperm) and partially non-self cells (a developing embryo) without the activation of local immune responses. It is also likely that macrophages play a similarly important role in this regulation

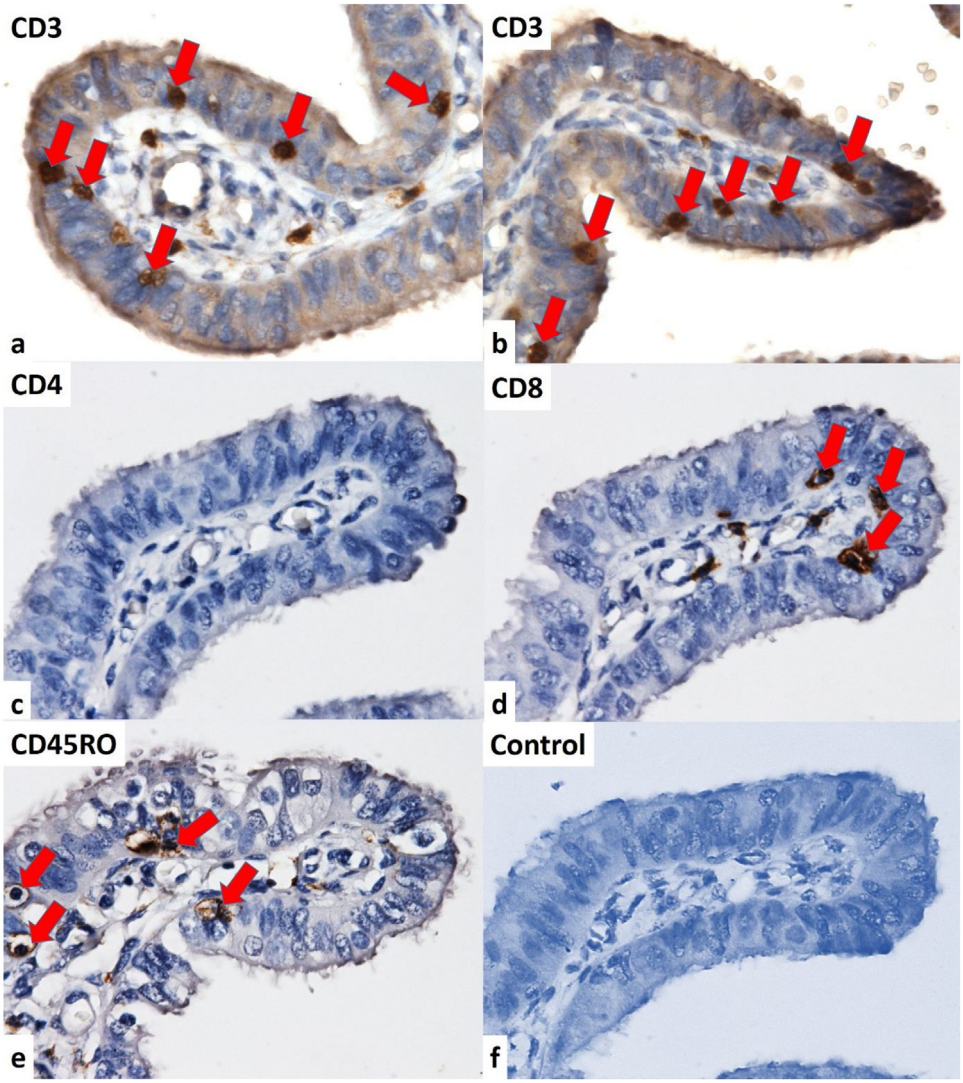

Fig. 4. The "basal cells" are CD3+, CD4-, CD8+ and CD45RO+. Based on antigenic characteristics, these cells represent intraepithelial T- lymphocytes, most probably regulatory T- lymphocytes. Fig. 4f represents negative control with omitting of the primary antibody. Orig. Magnification 400×.

of the immune response (Safwat et al., 2008), but we could not confirm the presence of macrophages intra-epithelially, only within the lamina propria. In other animal species (*e.g.*, in the bovine tubal epithelium), some basal-like cells are macrophages (Abughrien et al., 2000). Morris et al. (1986) proposed the existence of mucosa-associated lymphoid tissue (MALT) in the uterine tube and the predominance of cytotoxic and regulatory T-lymphocytes within the epithelium, in addition to other immunologically active cells within the connective tissue of the lamina propria. On the other hand, lymphoid nodules as a part of "typical" MALT are present only in approximately 2% of surgically removed uterine tubes (Hunt and Lynn, 2002). In the male epididymis, intraepithelial T-lymphocytes are termed halo cells. In young rats, halo cells consist of helper T-lymphocytes, cytotoxic T-lymphocytes, and monocytes, but not B-lymphocytes (Robaire and Hinton, 2015).

In our study we did not identify mitotically active **basal epitheliocytes** (they should have been positive for markers of proliferation). The presence of basal, undifferentiated cells in the tubal epithelium has long been a cytological enigma. The presence of undifferentiated basal cells within the human tubal epithelium was first described by Pauerstein and Woodruff (1967). These authors assumed that these cells represented reserve cells that give rise to the ciliated and secretory cells of the tubal epithelium because mitotic figures are rarely seen in the tubal epithelium. Their results were later confirmed by Bullón et al. (1980) in the uterine tube epithelium of rats. In this study, we clearly detected ciliated epithelial cells, secretory (exocrine) epithelial cells, and intraepithelial T-lymphocytes. Basal, undifferentiated cells were not identified in the uterine tubes. Instead, basal cells are actually intraepithelial memory T-lymphocytes. Based on these data, we propose that the cells termed "basal cells" in the internationally accepted *Terminologia Histologica* are actually intraepithelial T-lymphocytes instead (probably regulatory T-lymphocytes).

The histological textbooks use the terms "peg cells" and "intercalary cells" interchangeably. In Latin, this cell population is termed *epitheliocytus tubarius angustus*, or "narrow epitheliocyte." Based on our results, **intercalary/peg cells** do not form an independent cell population. They are actually dividing cells, which have a narrow-shaped Ki67 positive nucleus. Paik et al. (2012) isolated peg cells for the first time and demonstrated that they are the likely cellular source of regeneration for the uterine tube *in vitro* ("stem cells"). Furthermore, they found that these apparent stem cells are concentrated in the fimbriated end of the uterine tube, and they are expanded in tubal specimens from patients diagnosed with serous carcinomas. This finding is in contrast to the results of Bullón et al. (1980), who described peg/intercalary cells as necrobiotic cells. We

propose that the terminological discrepancies relating to this cell type should be corrected in histological textbooks. In fact, eleven internationally accepted textbooks (Table 1) currently use the term peg cells as the synonymous term for secretory nonciliated cells, which is clearly inaccurate. The exact morphological description of peg cells still needs further research. More ultrastructural data are necessary to elucidate if narrow-shaped peg cells represent a separate cell population, or they are in fact degenerating or dividing epithelial cells.

5. Conclusions

The *Terminologia Histologica* indicates that basal epitheliocytes are responsible for the regeneration of the uterine tube epithelium. In this study, we found that most of the "mature" tubal epithelial cells – ciliary cells as well as secretory cells – are mitotically active, and the tubal epithelium does not require a unique population of basal undifferentiated cells to facilitate regeneration. We showed that the round tubal basal cells with significantly pale cytoplasm are negative for markers of proliferation (such as Ki67 and PCNA), therefore not mitotically active. Instead, these cells likely represent a population of intraepithelial memory T-lymphocytes based on their expression of CD3, CD8, CD45RO, and negativity of CD4, CD20, CD56 and granzyme B. These putative intraepithelial lymphocytes probably play a role in regulating immune tolerance against non-self cells that the uterine tube becomes exposed to, such as sperm cells or an early-stage embryo. As such, we recommend removing the term "*epitheliocytus tubarius basalis*" from the *Terminologia Histologica* and replacing it with "*lymphocytus T intraepithelialis tubarius*." Additionally, we propose that intercalary/peg cells are actively dividing (due to their extremely narrow, Ki67+ nuclei), and not effete or degenerating cells. Furthermore, all histological textbooks in which the term "peg cell" is used interchangeably with "secretory cell" should be corrected, since we show that these cell types are distinct.

Ethical statement

I as a first and corresponding author of this article submitted to journal Annals of Anatomy certify that this study was approved by the Ethical Committee of the General Hospital in Komárno, Slovakia where the tissue samples were obtained. Informed consent was obtained from all patients.

Declaration of interest

The authors declare that they have no financial interests.

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