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Does migrative and proliferative capability of epithelial cells reflect cellular developmental competence?

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Abstract

Mammalian epithelial and epithelial-like cells are significantly involved in various processes associated with tissue development, differentiation and oncogenesis. Because of that, high number of research is focused on identifying cells that express stem-like or progenitor characteristics. Identifying such cells and recognizing their specific markers, would open new clinical opportunities in transplantology and oncology. There are several epithelia characterized by their ability to rapidly proliferate and/or differentiate. Due to their function or location they are subject to cyclic changes involving processes of apoptosis and regeneration. Literature presenting well-structured studies of these types of epithelia was analyzed in order to compare various results and establish if epithelial cells' migrative and proliferative ability indicates their stemness potential. Endometrial, ovarian, oviductal and oral mucosal epithelia were analyzed with most of the publications delivering relatively unified results. The ability to rapidly proliferate/ differentiate usually indicated the presence of some kind of stem/stem-like/progenitor cells. Most of the papers focused on pinpointing the exact location of these kind of cells, or analyzing specific markers that would be used for their future identification. There have also been substantial proportion of research that focused on discovering growth factors or intercellular signals that induced proliferation/differentiation in analyzed epithelia. Most of the research provided valuable insights into the modes of function and characteristics of the analyzed tissue, outlining the importance of such study for the possible clinical application of *in vitro* derived cell cultures.

Running title: Epithelial cells in vitro development

Keywords: pig, epithelial cells, *in vitro* growth and development

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Introduction

The mammalian somatic and germ cells are characterized by heritable status of cell survival and apoptosis. Additionally each cell type has genetically programmed ability to grow, and develop, leading to tissue formation and remodeling as well as proper orientation of organs. The cell survival or apoptosis is regulated by the ability to proliferate and differentiate, both of which significantly influence cellular physiology and morphology. The epithelial cells belong to one of the most common and important cell types involved in tissue modeling and organization of organs. The epithelial and/or epithelial-like cells are strongly associated with formation of connective tissue during physiological and pathophysiological processes that encompasses; angiogenesis, tissue morphological remodeling, and/or oncogenesis. The modifications of epithelial tissues are recognized as the most important processes of mammalian early morphogenesis and organogenesis. The processes of proliferation and migration of cells are significantly dependent on type of tissue and heritable physiological properties. Our recent results indicated that epithelial cells isolated from distinct tissue types have different proliferation and migration abilities in vitro during primary culture. Hence, we suggested that this may be an effect only proprietary to heritable physiological features of tissue, which significantly influenced on life/death balance of the cells. Additionally, epithelial cells collected from various organs reflect different metabolic and biochemical properties, which are modulated with the administration of hormones, signaling peptides and/or growth factors. On the other hand many types of epithelial cells collected from tissue organs have stem like specificity and plasticity. The stem like capability of epithelial cells bring new insight into the role of these cells in tissue morphogenesis during formation of other cell and/or tissue type. The potency of epithelial cells to differentiation in vitro opens a new window in possibilities of using in vitro generated tissues in advanced reconstructive and regenerative medicine. In this article, we are presenting the most recent findings related to epithelial cell proliferation and migration ability. Moreover, we concentrate on ovarian epithelial cells as the models used in osteogenic, chondrogenic and adipogenic lineage cell differentiation. The endometrial and buccal pouch epithelial cells differentiation capability is not yet well recognized. This review presents and discusses the possibility of application of epithelial based tissue constructs in regenerative medicine.

Ovarian epithelial cells

Epithelium is present in the ovary, in form of modified pelvic mesothelium, that covers the mammalian female gonads peritoneal aspect [1], also referred to as the ovarian surface epithelium (OSE) [2], ovarian mesothelium (OM) [1] or normal ovarian epithelium (NOE) [3]. It has been previously described as germinal epithelium, as it was believed to be the source of germ cells. However, current dogma concerning oocytes and primordial follicles states, that they all formed during the early development stage, and are not produced *de novo* in adult organism [4]. Despite several recent affords, with studies on human and mouse ovaries [5]–[7], there is no sufficient proof that OSE give rise to germ cells, [8]. It is also believed, that the cells of ovarian epithelium penetrate into the ovary and associate with oocytes forming granulosa cells becoming a part of the follicle [9]–[12]. However, recent publication from Hummitzch *et al.* describes bovine fetal research, with a solid proof that, in fact, granulosa cells do not arise from ovarian epithelium, but rather share a common precursor, so called Gonadal Ridge Epithelial Like cell (GREL) [13].

OSE is a single-layered, squamous-to-cuboidal epithelium, separated from ovarian stroma by a basal membrane and the tunica albuginea (dense, collagenous connective tissue layer) [8]. OSE has two major functions, transport of materials to and from the peritoneal cavity, and as a tool for the cyclical ovulatory ruptures repair [8]. These functions, especially the former one, are highly variable through the reproductive cycle, which suggests their dependence on sex hormones [1]. Ovarian epithelium exhibits large proliferative capacity, as it is needed to repair the post-ovulatory damage to the ovarian surface. This was proven by Osterholzer *et al.*, that there are differences between proliferation rates in rabbit OSE, observing the peaks in proliferative activity at, and immediately after the time of ovulation [14]. As the mechanism underlaying the process of follicular rupture during ovulation is still quite poorly understood, there have been some reports of possible role of OSE in that process [15], [16]. For example the controlled loss of the OSE due to apoptosis [17], near the time of ovulation, probably induced by prostaglandins [18], and mediated by Fas antigen [19]. It is possible, that the apoptosis occurs after the contact of the OSE with stroma of the ovary, following the alteration in structure of tunica albuginea near the time of ovulation. However, it cannot be ruled out that in this case, the signals from OSE are factors inducing the alteration of underlying connective tissue and stroma [8].

In nonovulating ovary, OSE is a stationary mesothelium (sharing both epithelial and mesenchymal characteristics. However, in contrast to the usual mesothelial properties, it can alter its state of differentiation. Apart from ectopic epithelium, OSE can modulate into fibroblast-like, stromal cells. This phenotype is achieved due to stimuli that initiate regeneration of the ovarian surface after ovulatory rupture [8]. The exact mechanisms of this process, are still yet to be defined. Ovarian epithelium shows large capacity to undergo epithelial to mesenchymal transition. That is a property that most probably exists in order to accommodate the need for

regular reparatory function. The capacity for EMT is functioning to increase motility and alter proliferative responses. It is also suggested that it may have a role in reintegrating the OSE cells trapped in the ovary at ovulation into the ovarian stroma. This could prevent cyst formation by preventing OSE aggregation within the stroma [8].

The ability of the ovarian epithelium to rapidly proliferate and migrate, together with the capacity to change their static epithelial fate and become stromal cells when that transformation is needed, give indication that they could possess stem-like abilities. Discovery of GREL cells, suggests that OSE is probably only a line of multipotent progenitor epithelial cells, as they quite certainly do not possess the previously attributed ability to differentiate into germ, or granulosa cells. However, the ovarian epithelium still remains largely unresearched. Lack of recognizable markers, that would directly indicate the presence of adult stem cells, is a barrier that needs to be overcome in order to even consider the possibility of application of ovarian epithelial cells in clinical environment.

Endometrial epithelial cells

The innermost, mucosal layer of the mammalian uterus, lining the walls of uterine cavity is referred to as the endometrium. It functions as the uterus lining, preventing adhesion between the walls of myometrium. However, its primary function is to provide the perfect environment for implantation of blastocyst into the uterine wall, and facilitate placental formation and future embryonic and fetal development [20]. Endometrium consists of a single layer columnar epithelium, resting on a layer of connective tissue that is referred to as the stroma [21]. There are two layers, that are distinguishable by their role in the uterus of women of reproductive age. The functional layer lays adjacent to the uterine cavity. This epithelial layer, contains tubular glands, held together by loosely by supportive stroma. The amount of cells present in the functional layer and their thickness, depends highly on the menstrual cycle. It is shed completely during menstruation and progressively rebuilt during the follicular and luteal phase [22]. The second basal layer, lies adjacent to the myometrium, below the functional layer. It contains branching glands, extending towards endometrial-myometrial interface, and is bound by stroma of higher density [23]. Contrary to the functional part of the endometrium, this layer doesn't undergo major changes during the menstrual cycle [24].

Endometrium, because of its dependency on the menstrual cycle, displays remarkable regenerative capacity. In relatively short time, it is able to grow from 0.5-1mm present initially after menstruation, to 5-7mm in final thickness [24]. That fact indicates that cyclical processes of proliferation, differentiation and breakdown need to occur as long as the menstrual cycle is present during years of reproductive ability. I has been long proven that endometrium responds mostly to the varying levels of sex hormones, especially estrogen and progesterone. The rising levels of estrogen, proprietary to the late follicular and ovulatory phase, have been proven to promote proliferation [20]. Progesterone on the other hand, with its levels peaking during early luteal phase, acts to promote differentiation, and inhibit mitotic proliferation of epithelia [24]. In the same time, stromal proliferation reduces [20] and the process of preparation for decidualization of endometrium begins around blood vessels and extend to the rest of the stroma. In case of fertilization, decidualization process ends, and cells of functional endometrium undergo differentiation [25]. In case of lack of fertilization, the functional epithelium regresses and is shed in the menstruation process, commencing the new menstrual cycle [24].

The need for regular, large scale proliferation and differentiation in the endometrium, and the ability to regenerate to the form allowing proper blastocyst implantation and pregnancy after almost complete resection [26] has long indicated the necessity for progenitors or adult stem cells among the endometrial cell population. Publications that suggested the presence of stem cells in the uterus are present, since the early 1990s, but lacked enough evidence to support their claims, and were more based on functional divagations similar to those described above [22]. Chan *et al.* used functional approach in their 2004 study, due to lack of properly characterized markers that would indicate the presence of adult stem cell/epithelial progenitor and their usually small populations [21]. They have hypothesized that the cells that they were aiming to identify, are probably present in the basal layer of endometrium, as its content is constant compared to the functional layer and does not undergo drastic changes through the menstrual cycle [24]. They related to previous research, describing clonogenicity as a typical stem cell property [27], to prove the existence and identify stem cell population in various tissues [28]–[30]. Growth factors, that are synthesized and secreted by endometrial epithelium have also been previously identified [31], and proven to be in constant interaction with sex hormones directly affecting the different stages of endometrial growth, co-acting through activation/repression of certain associated processes or modulating the effects of estrogen of progesterone by altering receptor expression [31], [32]. Endometrial tissues, collected from live patients that have not undergone exogenous hormonal treatment previous to extraction, were used as a source of endometrial epithelial and stromal cells. Then the clonal cultures were established, supplemented by known growth factors, fixed and analyzed. The study has proven the clonal identity of small groups of epithelial and stromal cells, additionally proving their multilineage

differentiation potentials, providing solid evidence for the possible adult stem cell presence among the populations of epithelial and stromal stem cells of the endometrium [21]. Wolff *et al.* have further proven the multipotency of endometrial stromal cells [33]. Culturing those cells in defined chondrogenic media, gave successful results in differentiating into heterologous chondrocytes. This ability was unique, compared to the other samples taken as control, and delivered further evidence for endometrium being a source of multipotent stem cells [33]. This approach was taken forward by Gargett *et al.* who used similar samples of endometrial tissue, subjecting them to treatment with multiple types of differentiation media [34]. The study resulted in the epithelial cells differentiating into their usually exhibited gland-like structures, while some stromal cells exhibited multipotency, by differentiating into smooth muscle cells, adipocytes, chondrocytes and osteoblasts. Clones of those stromal cells expressed multiple markers of mesenchymal stem cells, while not scoring positive results for endothelial or hematopoietic markers. The publication confirmed the presence of epithelial progenitors and mesenchymal stem cells within the endometrium. The MSCs were suggested to be involved in the large endometrial regenerative capacity, with their possible role in development of endometriosis and endometrial cancer. The study also suggests human endometrium as a source of mesenchymal stem cells for cell-based therapies [34]. Gargett and Masuda summarized most of the evidence concerning presence of adult stem cells within the human endometrium in their 2010 review [35]. They have underlined strong proofs for the presence of endometrial mesenchymal stem-like cells, analyzed the possible clinical application of the finding in cell-based therapies and better understanding of endometrial cancer, while also underlining the lack of current knowledge concerning their origin and the large amount of questions concerning such highly specific and complicated structure as endometrium that need to be answered before any of the potential clinical application could be introduced [35].

Oviductal epithelial cells

The mammalian oviduct, consisting of uterine and fallopian tube, is a highly specific structure assuming a fundamental role in the processes associated with reproduction. Apart from functioning as a transport canal for ovulated oocytes, spermatozoa and developing embryos between ovary and uterus, it is an organ designed to facilitate fertilization and early embryonic development[36]. Because of that, oviduct functions actively to maintain the perfect conditions for all of the above processes, mostly by modulating the production of the tubal (oviductal) fluid to optimal levels, as its desired amount is an important factor in sustaining many crucial developmental and reproductive events, as well as transportation of gametes and fertilized embryos to facilitate fertilization and implantation [37].

Oviductal epithelium consists of single layer of columnar cells, located within the oviductal mucosa [37]. There are two main types of epithelial cells present, performing their distinctive functions in order to maintain perfect conditions for reproductive and developmental processes occurring within the oviduct [37]. Ciliary cells, abundant along the oviductal luminal surface, function as facilitators of oocyte and early embryonic movement towards uterus, transporting the female gamete, or zygote (if fertilization occurs) along the oviduct by ciliary beating[38]. The suggested mode of such action includes interactions between epithelial cilia and sperm flagella, that capacitates sperm cells' fertilization ability [39], [40]. Secretory cells function in order to produce and release specific secretory materials. These secretions become one of the ingredients of oviductal fluid, the other being selective transudate of serum[38]. There are multiple functions attributed to the products of secretory cells. Some of them have been found to be associated with gametes/early embryo, with several possible effects on early embryonic development/gamete function [41]–[43]. There are reported examples, where *in vitro* development of mammalian embryos was improved, while they were co-cultured with cells of oviduct, or their medium [44].

Proportion of ciliated to secretory epithelial cells in the oviduct, especially in its ampulla, is not constant, and highly dependent on the menstrual cycle. Ciliated cells are found to be abundant during the follicular phase, with their proportion dropping drastically during luteal phase [45]. This is explainable, as the ciliated cells, have been proven to be necessary in proper transport of the cumulus-oocyte complex to the ampulla during ovulation, to make the fertilization possible [46]. It has been proven, that decrease or lack of cilia activity reduces fertility in women [47]. Again, the ability of oviductal epithelium to change its composition through the estrous cycle has sparked a search for cells with certain degree of stemness, allowing them to not only proliferate, but also differentiate. Ito *et al.* in their 2016 study, suggest that remodeling of oviductal epithelial structure is conducted through selective mitosis and differentiation of epithelial cells [48]. Studying bovine oviducts, with the stage of menstrual cycle estimated by macroscopic analysis of their respective uterus and ovaries, they used immunochemical analysis to look for markers of mitosis and differentiation into ciliated cells in oviducts of different menstrual stages. They have identified secretive cells as the primary type of epithelium, outlining the mode in which the cells are marked for either proliferation, or differentiation into ciliary cells [48]. This study proves, to an extent, the developmental potential of secretive ciliary cells, however it bases the assessment of their

developmental potential solely on functional analysis. Ghosh *et al.* provided further proof, supporting the ability of secretory cells to self-renew and differentiate, in their 2017 study [49]. Using *in vivo* genetic lineage tracing of mice derived oviductal epithelium, they have proven that secretory cells indeed have the stem-like abilities and are progenitors for ciliated cells.

Oral mucosal epithelial cells

Oral mucosa consists of two distinct layers, epithelium and lamina propria. It has received much attention from the scientific community, as it presents impressive regenerative ability, compared to other epithelial tissues [50]. The epithelium of oral mucosa is built of stratified, squamous cells with a basal layer containing three types of proliferating cells. Epithelial stem cells, transit-amplifying cells that are migratory and express limited proliferative capacity, and post mitotic differentiating cells [51]. The cells used in clinical trials involving cells cultures are usually buccal oral mucosa cells of porcine origin, as they express relative physiological and anatomical similarity when it comes to structure, level of keratinization and thickness of the human buccal oral mucosa [52]. However, number of different animal models are used, depending on the aim of research and the exact region of the oral cavity analyzed as similarity to human tissue and ability of colony formation and proliferation in vitro varies between species [53]. The *in vitro* cultures of buccal mucosa, can provide insight into several issues. Studies concerning membrane permeability, aim to determine the extent to which the mucous membrane can be used in drug delivery [54], [55]. Studies of cell engineering, circle around possible applications in transplantology [56], [57]. Finally, studies of oral cancer cell cultures provide valuable insight into cell cycle regulation and identification of adult stem/progenitor cell population [58]. As wound healing process in the oral cavity is characterized by early occurring, dynamic proliferation and migration, there is a strong indication for adult stem cell population presence within the oral epithelium [53]. However, there are other challenges, including problems with identification of the exact cells that exhibit stemness and their separation from the rest of the cultured cells. The general belief is that a characteristic indicative to stem or progenitor cells, is high nuclear to nuclear cytoplasm ratio[59], which can be used to identify the cellular candidates in cultures. Igarashi *et al.* have successfully separated these cells from the general population *in vitro* using their specific adhesiveness to collagen IV [60], which proves that discovery of specific stem cell markers and properties is a key to expand their potential for clinical use.

There have been two models proposed for epithelia differentiation . One, assuming that the differentiation fate is intrinsically determined, depends on the location of the epithelium. That way, if transplanted, epithelial cells would still develop into their respective tissues [61], [62]. The other theory, involves connective tissues underlying epithelia. This hypothesis states that signals from those tissues induce developmental fate of the epithelial cells. Chung *et al.* have delivered solid proof to support this theory .He used foreskin graft epithelia in co culture *in vitro* with buccal connective tissue, and directed it to develop into structures resembling oral mucosal epithelium [63]. There is also research proving, that grafts engineered with the use of cells extracted from oral mucosa can function in reconstruction of other epithelial tissues *in vivo* [64], [65]. However, this method is not ideal due to the limited source material, different patterns of regional epithelial keratinization and surgical procedures involved in its extraction. We are still looking for the right model for culturing oral mucosal tissue and assays for assessing the right proportion of epithelial cells in culture [50]. Improving methods of cell culture maintenance and validation, would open new ways in which oral mucosal cells could be implemented in advanced tissue engineering.

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Conflicts of Interest

The authors declare they have no conflict of interest

This paper does not contain any studies with human participants or animals performed by any of the authors

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