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# The differentiation and transdifferentiation of epithelial cells in vitro – is it a new strategy in regenerative biomedicine?

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## Abstract

In modern medical research, stem cells are one of the main focuses, believed to be able to provide the solution to many currently unsolvable medical cases. However, their extraordinary potential for differentiation creates much obstacles in their potential application in clinical environment, without understanding the whole array of molecular mechanisms that drive the processes associated with their development and maturation. Because of that, there is a large need for studies that concern the most basic levels of those processes. Progenitor stem cells are a favorable target, as they are relatively lineage committed, making the amount of signaling required to reach the final form much lower. Their presence in the adult organism is also an advantage in their potential use, as they can be extracted without the need for storage from the moment of pre-natal development or birth. Epithelial tissues, because of their usual location or function, exhibit extraordinary level of plasticity and proliferative potential. That fact makes them one of the top candidates for use in applications such as tissue engineering, cell based therapies, regenerative and reconstructive medicine. The potential clinical application, however, need to be based on well developed methods, in order to provide an effective treatment without causing major side effects. To achieve that goal, a large amount of research, aiming to analyze the molecular basics of proliferation and differentiation of epithelial stem cells, and stem cells in general, needs to be conducted.

**Running title:** epithelial cells in vitro development

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

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## Introduction

The developed organ is a main source of progenitor stem cells characterized by pluri-, and/or totipotency, with an increased capability of differentiation from immature form into fully mature and specialized cells and tissues. The proper direction or choosing the way of differentiation is mostly determined by genetically programed internal features as well as the properties of external environment [1]. Recently, it was postulated that tissue separated as the source of cells, using primary cultivation model have stemness properties and specificity. The unique plasticity of cells in primary culture is recognized as the their ability to differentiate during long-term cultivation. It was well determined, on animal and human model, that ovarian granulosa cells (Gcs) cultured *in vitro*, for long-term display the capability for differentiation and transdifferentiation into several other cells types [2]. Kossowska-Tomarczuk show that human Gcs cultured for 30 days in primary culture can transdifferentiate into chondroblasts and osteoblasts [3]. Much experimental data also, mainly in rodent model, indicates the transdifferentiation potency of different cell types in primary model into adipocytes and neuroblasts. Recent article from Nature Methods by Vivien Marx identified possibilities of building of organoids from neuroblasts on a „single dish" [4]. These experiments open new gate in biomedicine in regard to building of artificial organs by using advanced tissue bioengineering. Additionally our recent studies on pig ovarian granulosa cells indicating the huge proliferative capacity of these cells in vitro, cultured short-, and long -term. Moreover, we showed that cumulus cells (CCs), tightly attached to oocyte, are characterized by increased proliferation potency in oocyte-enclosed and denuded in vitro model. Although increasing number of mentioned above data regarding Gcs and or Ccs primary culture on experimented on both animal and human model exists, our knowledge regarding epithelial cells or cells with epithelial origin differentiation/transdifferentiation capability is still not well discovered. Furthermore, the frame of advanced biomedicine based on tissue grafting and/or transplantation was, up to now, poorly explored. In this article, the current knowledge regarding new discoveries in cell/tissue engineering with using of epithelial cells as the experimental model, was presented. Moreover we discussed the current and further possibilities of application of advanced cellular bioengineering in reconstructive and regenerative medicine.

## Ways and directions of progenitor stem cells differentiation in vivo and in vitro

Stem cells are basic units of biological organization. Being responsible for development, growth, regeneration and maintenance of homeostasis of tissues and organ systems, they serve as essential elements in those processes through their specific abilities for proliferation and differentiation [5]. Stem cells are characterized by their clonogenicity, capability for self-renewal and multilineage differentiation [6]. Degree of their multipotency depends highly on the developmental stage in which they perform their functions, and divides stem cells for groups varying in the extent of their stemness. There are totipotent cells, present in early zygote which then differentiate into pluripotent cells of inner cell mass that give rise to all the groups of cells creating the complex patterns of adult organ systems. That process involves a large range of cellular signals, growth and transcription factors as a group of uniform cells needs to progress to a number of different collections of more specialized cells, performing their respective function in the adult organism [5]. These pools of cells, so called progenitor cells, occupy specific niches across the body, functioning as a vessel for constant proliferation and differentiation associated with specificity of certain organs or organ systems [7]. They are usually associated with areas that need constant cell replacement, because of their function or location. These adult stem cell lines become more specialized, losing the primary ability for pluripotency. Instead, *in* vivo, they are usually oligopotent or with single differentiative fate, but possessing the unique stem like proliferation and self-renewal abilities [5]. That allows them to function effectively without the need for the extraordinary amount of signaling needed to define a certain tissue from a pluripotent stem cell. There are multiple types of such cells, dependent on the niche in which they function, varying in the degree of their multipotency [7]. For example, unipotent myoblast satellite cells, function in repair and build-up of muscles [8], [9]. Unipotent adipoblast cells play a role in maintenance of the adipose tissue [10]. Bipotent chondrogenic-osteogenic stem cells of marrow function in repair and maintenance of the skeleton [11]. While hematopoietic stem cells of marrow are multipotent and essential for preservation of numbers and diversity of blood cell population [12]. The former stand as the best characterized progenitor cells, with widespread applications in clinical use.

In tissues that undergo radical cyclic changes, or are subject to constant damage/ shedding due to their location or function, progenitor cells are usually located in the layers of said tissues that remain relatively constant [13]–[15]. In these instances, progenitor stem cells usually perform no other function than that of proliferation and differentiation into the lineages they are committed to. Cells located in the basal layers of the epidermis are a good example of that model. Constant keratinization, together with continuous shedding of the stratum corneum requires the presence of keratinocyte stem cells, which serve no other function

than that required for maintenance of numbers of epidermal cells [16]. Alternatively, progenitor cells may perform other functions, retaining the ability to self-renew and differentiate into other types of cells. The example of that can be oviductal epithelial cells. There are two kinds of cells in the oviduct, performing their respective functions, mostly in order to maintain the transport and survival of gametes and/or fertilized zygote [17]. The proportion of those cells is constantly changing, depending on the stage of menstrual cycle. It has been proven, by both functional and genetic lineage analysis, that one of the types of those cells, secretory cells, are responsible not only for their secretory function but also function as progenitors for the other type of oviductal epithelial cells, the ciliary cells [14].

It has been a widespread assumption, that progenitor cells are a relatively lineage-committed group of stem cells, with no transdifferentiation occurring naturally. However there results from a range of studies suggests that some adult stem cells exhibit previously unexpected level of plasticity. Bone marrow cells provide various examples of such plasticity, also being one of the best analyzed types of adult stem cells. They have been reported to participate in angiogenesis [18], somatic muscle development [19], hepatic regeneration [20] and formation of cell types of central nervous system [21], which suggests that some types of adult stem cells can retain larger ability for differentiation than previously suspected. This fact has sparked research, that is aimed in determining if the developmental fate of progenitor cells can be influenced *in vitro*, in order to better understand the basics of various cancers, as carcinogenesis is often associated with areas of progenitor cell activity, while also testing the possibilities of different progenitor cells in tissue engineering. It has  There are proven examples that under the influence of cellular or environmental factors progenitor cells can differentiate into a range of cell types *in vitro*. Sapir *et al.*, for example, have successfully induced transdifferentiation of adult human liver cells to form fully functional β-cells of the pancreas, using the pancreatic and duodenal homeobox gene 1 (PDX-1) [22]. Mesenchymal stem cells, extracted from bone marrow of iliac crest, have also been induced to form a range of mesenchymal tissues, including bone, cartilage, fat, tendon, muscle and marrow stroma, retaining their multilineage potential in *in vitro* primary culture [23]. Hu *et al.* have successfully stimulated myoblasts to transdifferentiate into adipoblasts, by using adipogenic transcription factors [24]. In a similar way, Davis *et al.,* managed to convert fibroblasts to myoblasts, using specific cDNA [25]. These examples show, that while usually being committed to their respective lineages, progenitor cells can transdifferentiate, while being subjected to treatment by specific growth or transcription factors. That fact, apart from highlighting the prospects of *in vitro* engineered tissue use in advanced clinical applications, provides additional information about the possible origin of many types of cancer. It has been proven that carcinomas are especially prone to arise in areas with large developmental potential. This fact can be linked to progenitor cell presence in those regions [26]. That, together with the fact that some tumors exhibit characteristics of different tissues, even ones coming from distinct germ layers, can indicate that dedifferentiation or transdifferentiation of progenitor cells could be the basis of some forms of tumorigenesis. Cancers originating in the region of female reproductive tract are a good example of that occurrence [26]–[28].

## Differentiation and transdifferentiation of epithelial cells

Epithelia are a diverse group of tissues that, depending on their location, exhibit various properties and cell types. Performing multiple functions, from mechanical and chemical protection and transport regulation, through sensation and glandular secretion, to secretion of hormones, there is a large potential for differentiation required, not only between different epithelial types, but also inside most of them[13]. Because of the fact, that there is no direct vascularization of epithelial tissue, most of the communication occurs at the intercellular level. Nutrients and waste, as well as signaling and regulatory molecules, diffuse through the epithelia from the underlying connective tissue-the basement membrane. This structure is essential in development and functioning of epithelial tissue, providing highly specific information that regulate its phenotype in various locations[29]. This is well presented in studies by Streuli *et al.*, which use rat mammary gland to highlight the role of basement membrane in epithelial tissue differentiation and functioning. While multiple factors are highlighted as necessary for development of mammary gland cells, that are competent for lactation, removal of basement membrane causes lack, or minimal milk production despite being  provided other necessary signals [29], [30]. The process of differentiation itself, usually proceeds as a series of biochemical, metabolomic and morphological changes to primary stem cells, extent of which is dependent on the type of epithelial tissue concerned. In some cases, however epithelial tissue is uniform, consisting of one cell type only and do not undergo cyclical changes or shedding. In that situation, there is no need for continuous differentiation, as mitotic proliferation of already differentiated cell is sufficient to maintain the continuity of said epithelia. Endothelia are a good example of such tissue. Their precursors are present in the bone marrow, but endothelial cells generated *de novo* circulate the bloodstream. They are only used if the duplication of existing cells proves insufficient[31]. Some epithelial tissues, how-

ever, are located in areas that undergo constant, cyclical changes, including almost complete shedding of the epithelial layer. A good example of this kind of tissues are the epithelia of female reproductive tract. The menstrual cycle requires the endometrium (epithelial layer of the uterus) to withstand continuous damage, through the whole course of reproductive life of a mammalian female. The extent of changes that the endometrium undergoes is extreme, with major variations in the thickness of the epithelial layer[32]. During menstruation, the endometrium is shed almost completely. That prevents the possibility of that tissue to be regenerated by mitotic proliferation of already differentiated cells. Instead endometrial progenitor cells are located in its basal layer, that remains relatively unchanged through the menstrual cycle. The cells of the basal layer proliferate to maintain own population, differentiating when, after the menstruation, there is a need to regenerate the uterine epithelium [33], [34]. A similar situation occurs in the epithelial lining of the intestine. The intestinal villi are constantly exposed to the digestive enzymes and remains of stomach contents, hence need constant regeneration. Again, the progenitor cells are not located in the functional tissue, but in the crypts between the villi. They maintain their population, progressively differentiating across the surface of the villus, resulting in creation of number of cells types necessary for proper function of the intestine. This process is continuous, and results in the replacement of all the epithelial cells every 4-5 days[35]. In oviductal epithelium, the cyclical changes in its contents are not dictated by damage, but rather the different functional needs, dependent on the phase of reproductive cycle. Two types of cells are primarily present, ciliated cells that facilitate the flow of oviductal fluid to allow the progression of oocyte and/or fertilized zygote, and secretory cells, responsible for secretion of contents specific to said fluid [36]. The amount of ciliated cells varies highly, peaking just before and during ovulation and reaching levels close to zero during the luteal period [37]. The overall proportion of the two types of oviductal epithelial cells is regulated, by both proliferation and differentiation of secretory cells. This process is made possible by the fact, that secretory cells also serve as progenitors for ciliated cells. This information has been confirmed by both functional and genetic tracing analysis [14], [38]. In this case, it is possible for the stem cells to be located within the tissue that they support, as there is no significant risk of damage during normal functioning of said tissue.

Most of the differentiation processes, described above, can be potentially replicated *in vitro*. However, there is a number of limitations that need to be overcome in order to achieve *ex vivo* proliferation and differentiation of such tissues. Firstly, the material needs to be available and ready obtainable. Because of relatively small amount of non-invasive surgical procedures, that would provide researchers with source material without raising medical and ethical concerns, model animals are often used as a mean of research [13]. Every model, however possesses its own limitations. Lack of morphological similarities to human, different functioning of analyzed tissues, long gestation time, high maintenance costs and difficulties in material extraction are just examples [39]. Even if all of those obstacles are overcome, there are still matters of specific cell cultures that need to be resolved, before successful trials. Then, the right factors of differentiation need to be discovered, isolated and applied within the right time windows, to obtain the desired types of cells, which then need to be identified either based on their morphological distinctions or specific markers [7]. Despite that limitation, there is a large amount of successful examples of *in vitro* differentiation of epithelial cells [40]. There is a large potential in trans-differentiational ability of that cell type. Certain types of epithelia, while exposed to factors specific to other types, are able to drastically change their morphological, metabolomic and biochemical properties, morphing into different types of epithelial tissue, as well as reversing their state to a less lineage committed stage [3], [41], [42]. This fact opens gates to many different potential clinical approaches, that could lower and eliminate the risks, or side effects of various treatments associated with transplantology, reconstructive and regenerative medicine.

## Stem cell strategy of advanced 21st century medicine

Since the early days of stem cell discovery, the specific properties of this group of cells have sparked a big debate about their possible applications in the modern and future medicine. Their extraordinary plasticity, together with the ability to maintain a clonogenic population of steady size, for virtually unlimited amount of time, has suggested that therapies involving stem cells could be a potential cure for various, previously incurable diseases [6]. Pluripotent cells, could be potentially used to create almost any type of transplantable tissue, and in perspective organ without the possibility of rejection by host [43]. However, the source of cells for such therapy needed to be verified, before any potential clinical applications could be brought to life. That fact has highlighted the first major obstacles. There are no sources of truly pluripotent stem cells in the adult organism [5]. Because of that, an alternative way to obtain those cells would be needed. Extraction of pluripotent cells from the embryo, would be difficult, even when said embryo is created using *in vitro* fertilization. Then, there are several other obstacles, mostly associated with storage of such cells, with maintenance of their integrity, over the large periods of time before eventual application. There has been some research, that have managed to dedifferentiate lineage committed

cells to stages of greater plasticity, which in perspective could provide a solution to the aforementioned problems [16]. However, there is another complication, that advocates against the use of embryonic, or embryonic-like, stem cells. Extraordinary amount of signaling would be needed for pluripotent stem cells to achieve the final desired form. Even if, in the future, the exact developmental events underlying differentiation of embryonic stem cells through the various stage of lineage commitment were discovered, subjecting the previously extracted cells to these conditions in just the right amount, in the right time would be almost impossible [40]. Because of that facts, the adult stem cells receive much more focus as means of prospective stem cell based therapy. Progenitor cells are relatively lineage committed, which significantly decreases the amount of signals required for their differentiation to the required form. Additionally, lack of full pluripotency is advantageous, as there is a smaller chance of wrongful development into an undesired tissue [7]. Because of that, there is a lot of research that aims to analyze the exact molecular mechanisms of adult stem cells [44], [45]. This approach is a basis for various clinical applications. *In vitro* cell and tissue engineering is one of the leading fields of recent study. By analyzing the behavior of cell and tissue *in vitro* cultures, the researchers try to better understand the processes that accompany their proliferation and differentiation. This knowledge is then applied, to influence progenitor cells to form structures that are needed for purposes such as transplantation [13]. Additionally, the knowledge about the genetics underlying the normal functioning of certain tissues, obtained during *in vitro* study, can also, as a reference point for other researchers, be translated into *in vivo* applications. Understanding all the molecular basics of normal and malignant development of various types of tissue, could help designing new kinds of treatments for various diseases associated with lack, or overexpression of certain gene products that lead to diseased phenotypes [46].

There are several examples of stem cell associated therapies, that are already widely conducted. One of the most prominent examples, that has its place in the modern medicine since the late 20$^{th}$ century, is bone marrow transplant. Despite being performed from the 1960s, constant improvements, that aim to increase success rate, survivability and effective lifespan of the patients, are constantly in development. Because the transplant requires extraordinary measures both before and after the actual process, to minimize the damage done by the pre-transplant chemotherapy, as well as the following immunodeficiency, it is essential to minimalize the risks associated with rejection of the graft by host [47]. While, the current clinical techniques and growing databases, allow for identification of potential donors that closely match with host, the risk of graft rejection is minimal, but still present. Therefore, the concept of autologous transplant has been a major focus in the studies concerning the advancements in this field. There are many potential sources of host hematopoietic stem cells, the ones that rely on banked cells from umbilical cord blood, as well as various methods that aim to extract the desired progenitor cells from the circulating blood, using separation methods to eliminate the ones affected by the disease from the pool [48], [49]. By eliminating the risk of graft-versus-host disease, the survivability and prospective lifespan is greatly improved [47], [50]. This approach could potentially be applied to other tissues, especially epithelia, as it could take advantage of their extraordinary plasticity, in order to allow for minimizing the impact associated with extraction of the source tissue and provide a graft that most closely resembles the original [43]. Advancements in methods of cell culture, could also allow to create stable populations of epithelial cells coming from the host, that could be easily banked in order for potential use in tissue engineering for the purposes of transplantology, tissue reconstruction and regeneration. There are various other examples of stem-cell associated therapies, that could one day lead to treatment of many malignancies, that are currently incurable, or carry significant side effects associated with the treatment [22], [51], [52]. These are mostly diseases associated with defects of progenitor-cells themselves, or requiring the presence of stem-cells that do not normally occur in adult organism. However, even if the source of the cells is secured, there is still large amount of analysis needed in order to discover the exact molecular mechanisms driving the processes of stem-cell development, proliferation and differentiation, to refine the methods of the treatment to maximize the possibility of achieving the desired effects, without causing further damage [46]. This studies will be absolutely essential, to the progress of modern clinical stem-cell applications.

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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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