Crha et al.
Medical Journal of Cell Biology 2019
DOI: 10.2478/acb-2019-0020
Received: 1.10.2019
Accepted: 23.10.2019

The role of uterine microbiome and epithelial-mesenchymal transition in endometrial function

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Abstract

Reproductive period in woman is characterized by cyclic changes of endometrium and its regeneration. The factors important for proper function of the endometrium are anatomical structure, hormonal control and signalling pathways on molecular-genetic level. New knowledge on uterine microbiome, mutual epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET) of endometrial cells refine our conception of changes on cellular level, endometrial receptivity and possible causes of endometrial dysfunction. Substantial information on bacterial colonisation of endometrium were discovered by new diagnostic methods using analysis of ribosomal RNA in 16S subunit which are able to detect and exactly identify bacteria that are not detectable by classic cultivation methods. Endometrial microbiome prevents development of pathogenous microorganisms and modulates function of endometrial cells. It has been proven that stromal cells contribute to regeneration of not only the endometrial stroma, but also of the epithelium. Activity of ovarian steroids and other factors leads to EMT/MET, which ensures different functions of endometrium throughout the menstrual cycle and pregnancy. The endometrial microbiome and mutual transition of stromal and epithelial endometrial cells are necessary for physiological functions of uterine mucosa including implantation and development of an embryo.

Running title: Microbiome and cells transition in endometrial function

Keywords: endometrium, uterine microbiome, epithelial-mesenchymal transition, endometrial regeneration, endometrial receptivity, embryo implantation

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Introduction

Microbial colonization significantly contributes to physiological function of many organs and its alterations can be accompanied with many serious pathological conditions. At present, there is a lot of knowledge and evidence which changes the long-term concept on sterile environment in uterine cavity.

Microbial colonization of endometrium was proved as well as its metabolic activity that contributes to production of substances important for pregnancy development and detoxification of xenobiotics [1,2]. Recent studies have analysed relation between presence of bacteria in uterus and reproductive disorders and complications in pregnancy [3,4]. Presence of bacteria modulates the immune system in endometrium, which is an important factor for proper function of uterine mucosa [5,6]. Bacteria can also influence morphology of endometrial cells and prevent penetration and propagation of pathogenic species. Therefore, the endometrial microbiome contributes significantly to endometrial receptivity prior to embryo implantation, decidualization and proper development of placenta [7,8].

Reproductive period in woman is characterized by repetitive frequent structural and functional changes of endometrium – during menstrual cycle, in pregnancy or after intrauterine surgeries. The capacity of regeneration, remodeling and differentiation is a basic prerequisite of endometrial receptivity, embryo implantation and development [9]. An important factor of these processes is the mutual transition between mesenchymal and epithelial phenotype of endometrial cells – the epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET) [10]. These transitions have been studied mainly in relation to malignant endometrial tumours, however, new knowledge shows that they are necessary for physiological implantation and proper development of an embryo.

The aim of this paper is to present current knowledge on endometrial microbiome, EMT/MET and their potential role in reproductive disorders.

Endometrial microbiome

In general, microorganisms and human live in symbiosis. Microorganisms need constant supply of nutrients, the host utilizes benefits of the microbes for many physiological processes – homeostasis of epithelial cells, mucosal functions and physiological barrier against colonization by pathogenic bacteria. Bacterial colonization also significantly contributes to modulation of the host's immunity. Metagenomic analyses have opened an extensive research of physiological colonization of human organism and demonstrated presence of microbes in areas that were originally considered to be absolutely sterile. The original dogma of the "sterile uterus" was overcome with the new knowledge. Significant limits of the research in this field were sample collection and technologies for detection and identification of all microbial species present (**tab. 1**). In recent time, a growing number of studies have provided important information on endometrial microbiome [3,4,11] and commensal colonization of placenta [12].

Endometrium as a microbiome niche

A precondition of safe symbiosis between a host and bacteria is definition of an area for their propagation – a niche – and compliance with the defined boundaries. Invasion to host tissues must be limited in order to prevent an inflammatory reaction [2]. Three types of immunological barrier necessary for this homeostasis have been described – the anatomic layer preventing penetration of bacteria to immune system, protective mediators limiting direct contact between bacteria and epithelial cells and rapid elimination of bacteria that penetrated the barrier. The endometrium meets all these requirements [13]. The cells of single-layer cylindrical epithelium are tightly connected in an anatomical barrier. The uterine mucosa and endometrial fluid (EF) contain molecules of antimicrobial peptides (AMP). Their concentrations fluctuate during the menstrual cycle. One AMP is the leukocyte secretory protease inhibitor with bactericidal effect on Gram-negative bacteria (e.g. *Escherichia coli*) and

TABLE 1 Overview of bacteria in the endometrial microbiome most often detected by sequencing of the characteristic hypervariable regions V1-V9 of the rRNA 16S ribosomal subunit

Acinetobacter	Flavobacterium	Pseudomonas
Atopodium	Gardnerella	Shigella
Barnesiella	Lactobacillus	Sneathia
Bifidobacterium	Megasphaera	Sphingobium
Blautia	Moraxella	Sphingomonasor
Clostridium	Parabacteroides	Staphylococcus
Corynebacterium	Parvimonas	Streptococcus
Enterobacter	Prevotella	Vagococcus

Gram-positive bacteria (e.g. *Staphylococcus aureus*). In all phases of menstrual cycle, the endometrium is characterized by the presence of lymphocytes which are able to quickly respond to microbial invasion. The endometrium thus provides a space for safe niche of symbiotic bacteria, similarly to the intestinal mucosa.

Detection of commensal endometrial bacteria

A historical standard for detection of bacteria are cultivation methods used mainly for diagnostics of inflammation of the inner genitals. Studies on cultivation of bacteria from transfer sets in relation to pregnancy achievement and childbirth have been presented; nevertheless they have brought conflicting results [14,15]. However, the cultivation methods are not sufficient for exact qualitative and quantitative characterization of all bacterial species in microbiome. Fast-growing aerobic bacteria species dominate, slowly growing bacteria that require specific conditions are not detected. New knowledge came with molecular genetic methods for detection of various bacterial species [16] used quantitative PCR for detection of 12 bacterial species in samples of endometrial fluid and proved differences in their representation in the vagina and on the endometrium. Presence of bacteria was detected in 95 % of the analysed samples. In the vagina, more frequently detected species was *Atopobium vaginae,* in the endometrial fluid it was *Lactobacillus iners*. Other studies used the FISH (fluorescent in-situ hybridization) method or sequencing of the hypervariable 16S region of ribosomal RNA that is specific for individual bacterial species [17].

The endometrium – elementary factor of decidualization, implantation and placentation

Decidualization and transformation of the endometrium to receptive state – window of implantation – is enabled not only by cyclic changes of ovarian steroids, but also by cells and mediators of the immune system. Changes of adhesion molecules – integrins and L-selectin ligands (L-selectin ligands are present on the endometrial epithelium, L-selectin receptors are on the blastocyst trophoblast) were documented. Important information has been brought by proteomic analysis of the intrauterine fluid [7]. The endometrium plays a key role in physiological placentation and physiological course of pregnancy. The microbiome and its products can contribute to implantation and placentation of an embryo [18].

Effect of the microbiome on the immune system of endometrium

The immune system of endometrium is involved in endometrial changes necessary for its physiological function in reproductive process [6]. Cells of the immune system are a proven factor of trophoblast migration and proper remodeling of spiral arteries. The cells in focus are the natural killer (NK) cells, T-lymphocytes and antigen presenting cells (APC). Crucial interactions between the intestinal microbiome and the immune system of intestinal mucosa have been reliably proven [19] and possible analogical relation between the endometrium and its microbiome can be deduced.

Cell immunity

The NK cells represent a majority of the immune system cells present in the endometrium – approximately 70 %. There are phenotypical and functional differences among the endometrial eNK cells before decidualization, the dNK cells of the decidually transformed endometrium, the pNK cells of the placenta and the pbNK cells of the peripheral blood [6]. Predominant population in the endometrium are the eNK cells that do not produce cytolytic cytokines, only a small fraction is represented by the NK cells destroying infected cells. The dNK cells produce high amount of cytokines such as interleukin 10 (IL10) or tumour necrosis factor alpha (TNF-α) which can contribute to initial implantation and formation of the placenta.

The antigen-presenting cells (APC), mainly macrophages and dendritic cells (DC) represent approximately 10 – 20 % of the endometrial leukocytes. The APCs integrate individual stimuli including the microbial ones and they are essential for initiation of an adequate immune response. The T cells are another important fraction of the immune system cells present on the endometrium. Except pregnancy, they are stored in deeper layers of the endometrium, probably they contribute to formation of the placenta shortly after implantation. There is a growing evidence of the microbiome effect on ”tuning“ of individual T-cell groups. An acknowledged vector between the microbiome and host T-lymphocytes is polysaccharide A (PSA) originating in the capsule of *Bacteroides fragilis* [20]. Also the T regulatory cells of the mucosa play an important role, they take part in maintaining homeostasis of the microbiome and increase of the local immune system tolerance [21].

Cytokines and chemokines

Important factors for physiology of reproduction are cytokines and chemokines produced by the immune system and cells of the endometrium. During the implantation period, amounts of anti-inflammatory Th1 cytokines IL-6, IL-8 and TNF-α increase, which leads to activation of the immune system cells and activation of the endometrium. Also the CCL2 referred to as ”monocyte chemoattractant protein“ is significantly involved. This chemokine is produced by stromal endometrial cells and it attracts monocytes, T cells and dendritic cells to the uterine mucosa. The microbiome is a proven important factor for establishing physiological production of CCL2 and inducing homeostasis of plasmocytoid dendritic cells [22].

The microbiome and endometrium interaction mechanisms

Physiological homeostasis between presence of the microbiome and the immune system activity is ensured by mechanisms of the innate and adaptive immunity. Boundaries of the physiological microbiome must be maintained and the pathogens must be efficiently eliminated [13]. A part of the innate immune system are the pattern recognition receptors (PRR) that are able to recognize characteristic features of microbial pathogens – the pathogen-associated molecular patterns (PAMPs). The PAMPs are mostly cell wall molecules – lipopeptides, proteoglycans, lipopolysaccharides or mannans. The best known PRR include toll-like receptors (TLR), NOD-like receptors (NLR) and C-type lectin receptors [21]. The NLR and TLR were proven to participate in regulation of the microbiome and the endometrium in periconception period. New knowledge in this area can contribute to improvement of fertility disorders treatment by assisted reproduction methods [23,24].

Defence against pathogens

Stable colonization with commensal bacteria protects host from pathogens, the physiological microbiome is better adapted to its environment than the invasive pathogens. In their niche, the commensal bacteria competitively decrease amount of nutrients for pathogens, their mutual symbiosis prevents pathogens from entering their niche. The commensal bacteria also stimulate TLR and support their ability to respond to PAMPs of possible pathogens [21]. By similar mechanisms, the endometrium can be protected by its microbiome.

Another very important protective factor is the layer of epithelial cells and its solidity. An intact epithelium prevents bacteria from entering mucosal stroma and their contact with the immune system. Its structure and differentiation is significantly influenced by the microbiome. In the uterus, the commensal bacteria can participate in remodeling of the endometrium necessary for implantation. It has been documented that during implantation windows, in association with EMT/MET, strength of the junctions and number of desmosomes among the epithelial cells decrease, which facilitates invasion of trophoblast but at the same time also of bacteria that increase production of anti-inflammatory cytokines participating in implantation and placentation [7].

Mutual transition between mesenchymal and epithelial endometrial cells – EMT/MET

At the end of the 20th century, a series of studies brought evidence on the mutual transition between the mesenchymal and epithelial cells in embryos. Subsequently, this process was proven also in fully differentiated tissues in association with wound healing and development of malignant tumours [25,26]. The epithelial and mesenchymal cells have their own typical features. The epithelial cells are characterised by expression of cytokeratin, attachment to the basement membrane of the extracellular matrix (ECM) and formation of intercellular junctions. The mesenchymal cells have typical elongated spindle shape, vimentin expression and ability to move in the ECM using pseudopodia of the plasma membrane. The specific cellular markers are presented in an overview in **table 2**. The process of EMT and MET is defined as ability of cells to change the characteristic features of one cellular type to the other type. It is important to realize that this process is gradual in a certain period of time. During EMT/MET, cells of a "hybrid phenotype" expressing features typical for both the epithelial and mesenchymal cells can be detected. Such cells can contribute to formation and development of malignant epithelial tumours [27].

TABLE 2 Characteristic features and cellular markers of the epithelial and mesenchymal cells

CHARACTERISTIC FEATURES OF MESENCHYMAL CELLS	CHARAKTERISTIC M ARKERS OF MESENCHYMAL CELLS	CHARAKERISTIC FEATURES OF EPITHELIAL CELLS	CHARAKERISTIC MARKERS OF EPITHELIAL CELLS
irregular elongated shape	N-cadherin	cylindric, kubic or squamous shape	E-cadherin
absence of junctions	vimentin	strong intercellular adhesions	cytokeratin 8,9
multipolarity	fibronectin	fixation to basal membrane	B-catenin
ability to move	snail 1,2	apico-basal polarity	claudins
invasivity	colagens		laminin
	smooth muscle actin		desmoplakin

EMT/MET in development of female reproductive system

Transition of the mesenchymal and epithelial cells starts during embryonic development of the uterus and vagina from the Müllerian ducts. Mesenchymal cells of the mesoderm differentiate into epithelial cells of the nephric duct. Junction of caudal parts of the Müllerian ducts, which forms the uterus and the proximal part of vagina, is a result of destruction and resorption of the central septum. In these processes, the EMT/MET is applied [28].

EMT/MET in regeneration of the endometrium

During the reproductive period of woman, the endometrium has absolutely exceptional ability of repetitive regeneration and differentiation that occurs during the menstrual cycle, pregnancy, childbirth or after traumatization by surgeries. It has been documented, that renewal of the uterine mucosa and its structure is ensured by the stem cells. The endometrial mesenchymal stem cells (eMSCs) are found in the endometrial basal lamina near the borderline with the myometrium, another population of multipotent eMSCs is located perivascularly in both the functional and the basal zone of endometrium. They were also detected in the postmenopausal endometrium, where they maintained their activity [9]. The eMSCs stem cells differentiate into stromal fibroblasts, differentiation into epithelial cells has not been proven. Another line of progenitor cells with N-cadherin that differentiate into epithelial cells was found in the endometrial basal zone [29].

EMT/MET in decidualization of the endometrium

The most remarkable morphological changes within decidualization of the endometrium occur in the stromal fibroblasts – the characteristic elongated spindle shape changes into the typical shape of the epitheloid cells, the cytoplasm increases, shape of the nucleus rounds. Intracellular contents of glycogen and lipids increase, the rough endoplasmic reticulum expands, the actin microfilaments of the cytoskelet change, the number of phagosomes and lysosomes grows. The first changes occur in the area of terminal spiral arteries and gradually spread into the entire stroma [30]. A characteristic feature of decidualized endometrial cells is ability of a specific secretion. The main markers are prolactin and insulin-like growth factor binding protein (IGFBP-1). A series of studies have documented correlation between morphological changes of MET and increased levels of IGFBP-1 [30].

Molecular genetic aspects of decidualization

Molecular genetic analyses have proven changes of gene expression in relation to the MET and EMT. Whole-genome analyses have found increased or decreased expression of more than 3000 genes during decidualization. Mainly the Wnt and Snail signaling pathways have an important role [31]. During the EMT, they decrease production of E-cadherin and enhance cell migration. The Snail1 protein is coded by the gene of the same name, it belongs to the group of transcription factors that regulate production of adhesion molecules E-cadherin and play a role in the EMT. The Snail1 is a marker of mesenchymal cells. During epithelisation of the endometrial stromal cells, the Snail1 gene is downregulated and production of E-cadherin is increased [32].

EMT/MET in embryo implantation

At the time of embryo implantation, another transition of epithelial and stromal cells with changes in the extracellular matrix occurs in the decidualized endometrium. A key role is played by the mutual signalization between embryonal and maternal compartment. Changes in the markers of receptivity – the integrins have already been proven. Their expression in the endometrial cells could be induced only by growing embryos [33]. Newer studies have observed also the effect of miRNA on the EMT/MET at the site. It has been documented that decrease or increase of miRNA-429 expression regulates genes for cadherin - an important molecule of the intracellular bonds and morphology [34]. Various miRNA can thus efficiently control the EMT/MET by gene regulation at the site of implantation.

Endometrial EMT/MET in context of further research and clinical practice

The described knowledge on the EMT/MET of trophoblast and endometrial cells clearly shows that failure of implantation can be caused by abnormalities in signaling pathways that control these transitions [35]. Besides the effect of hormones [24,23], the immune system, the endometrial microbiome [36] or the endocrine disruptors [37,38,39] this is another area where more exact information is needed. New knowledge in this field could bring possibilities of their modulation or choice of treatment.

Conclusions

The endometrial microbiome together with the neurohumoral and immune system can be an important part of physiological adaptation necessary for a successful development of pregnancy. The historical opinion of sterile endometrium is no more valid. The mutual transition of stromal and epithelial endometrial cells is necessary for physiological function of the uterine mucosa including embryo implantation and its development. Current knowledge opens more space and justifies further research.

Ethical approval

The conducted research is not related to either human or animal use.

Acknowledgements

The work was supported by the Ministry of Health, Czech Republic – RVO (FNBr, 65269705) and the projects of the Ministry of Health, Czech Republic No. NV18-08-00291, NV-18-01-00544 and NV-18-08-00412.

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Conflict of interest statement

The authors declare they have no conflict of interest.

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