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FEMALE GENITAL TRACT INFECTIONS (J SOBEL, SECTION EDITOR)

Contribution of Epithelial Cells to Defense Mechanisms in the Human Vagina

Iara M. Linhares[1] · Giovanni Sisti[2] · Evelyn Minis[2] · Gabriela B. de Freitas[1] · Antonio F. Moron[3,4] · Steven S. Witkin[3,5]

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Abstract

Purpose of Review The vaginal milieu in women differs from that of other mammals, including non-human primates, in composition of secretions, the endogenous microbiota, and level of acidity. These changes apparently reflect evolutionary variations that maximized productive responses to a uniquely human vaginal environment. This review will highlight recent findings on properties of human vaginal epithelial cells that contribute to maintenance of a healthy vaginal environment.

Recent Findings Vaginal epithelial cells are responsive to the composition of the vaginal microbiome even in women who are in apparently good health and do not exhibit any adverse physical symptoms. This is especially important during pregnancy when immune defenses are modified and an effective epithelial cell-derived anti-microbial activity is essential to prevent the migration to the uterus of bacteria potentially harmful to pregnancy progression. When *Lactobacillus crispatus* numerically predominates in the vagina, epithelial cell activity is low. Conversely, predominance of *Lactobacillus iners*, *Gardnerella vaginalis*, or other non-*Lactobacilli* evokes production and release of a large variety of compounds to minimize the potentially negative consequences of an altered microbiome. The extent of autophagy in vaginal epithelial cells, a basic process that functions to maintain intracellular homeostasis and engulf microbial invaders, is also sensitive to the external microbial environment Vaginal epithelial cells bind and release norepinephrine and upregulate their anti-microbial activity in response to external stress.

Summary Vaginal epithelial cells in women are responsive to local conditions that are unique to humans and, thereby, contribute to maintenance of a healthy milieu.

Keywords Autophagy · Stress · Vaginal epithelial cells · Vaginal microbiome

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✉ Iara M. Linhares
iara.linhares@yahoo.com.br

Giovanni Sisti
gsisti83@gmail.com

Evelyn Minis
evelyn.minis@gmail.com

Gabriela B. de Freitas
gabi_boufelli@yahoo.com.br

Antonio F. Moron
antonio.moron@uol.com.br

Steven S. Witkin
switkin@med.cornell.edu

[1] Department of Gynecology and Obstetrics, University of Sao Paulo Medical School, Sao Paulo, Brazil

[2] Department of Obstetrics and Gynecology, Lincoln Medical and Mental Health Center, Bronx, NY, USA

[3] Institute of Tropical Medicine, University of Sao Paulo Medical School, Sao Paulo, Brazil

[4] Department of Obstetrics, Federal University of Sao Paulo, Sao Paulo, Brazil

[5] Department of Obstetrics and Gynecology, Weill Cornell Medicine, New York, NY, USA

Introduction

The vaginal microbiome in most reproductive age women is dominated by species of *Lactobacilli* and vaginal fluid is acidic due to production of lactic acid by these bacteria [1••]. This differs from what is present in all other mammals, including non-human primates, where *Lactobacilli* are scarce and vaginal pH approaches neutrality. These changes are likely a consequence of the unique behavioral, dietary, and environmental exposures of humans [2, 3]. Vaginal epithelial cells in women have had to adapt to these species differences to optimize a lower genital tract environment most compatible with health and reproductive efficacy. This communication will review properties of human vaginal epithelial cells that monitor and respond to external variations in the local environment.

Epithelial Cell Turnover and Survival in an Acidic Environment

Several layers of rapidly regenerating stratified squamous epithelial cells line the human vagina. The layer closest to the vaginal lumen exfoliates approximately every 4 h [4]. This serves a protective function as any potential microbial pathogen that have gained entry and adhered to the vaginal epithelium will be rapidly disengaged from the vagina and eliminated. In addition, the degradation of sloughed epithelial cells results in the release of glycogen into the vaginal lumen. The breakdown of glycogen by alpha amylase, an enzyme present in human vaginal secretions [5], results in production of small carbohydrates that are utilized by *Lactobacilli* to preferentially facilitate their proliferation in the vagina [6].

Resident *Lactobacilli* are the principal source of lactic acid, the major acid in the vagina [7, 8], responsible for maintaining an acidified vaginal lumen. The acidic pH lyses many non-endogenous bacterial species and prevents their maintenance at this site [9, 10]. To remain viable in this acidic environment, the vaginal epithelial cells must be able to regulate the influx and egress of hydrogen ions. This is accomplished by the activity of a protein, monocarboxylate transporter 1 (MCT-1), on the epithelial cell surface. MCT-1 activity requires the presence of an essential co-factor, extracellular matrix metalloproteinase inducer (EMMPRIN) [11]. EMMPRIN is also produced by vaginal epithelial cells and its concentration in vaginal fluid is directly proportional to the lactic acid level [8]. This suggests that the vaginal epithelial cells are sensitive to the level of acidity and respond by adjusting their production of EMMPRIN.

Epithelial Cell Recognition of Bacteria

The dominant *Lactobacilli* species in most reproductive age women are *Lactobacillus crispatus* and *L. iners*. The dominant non-*Lactobacillus* species is usually *Gardnerella vaginalis* [12]. Recent studies have demonstrated that the expression of genes in vaginal epithelial cells differs according to the dominant bacterium that is present. One mechanism regulating gene transcription is the epigenetic alteration of the acetylation state of histones that are associated with a particular gene. Acetylated histones do not bind as tightly to chromosomes as do histones whose acetyl groups have been removed. A specific enzyme, histone deacetylase (HDAC), removes acetyl groups from histones and, thereby, inhibits gene activation [13]. In a study of 150 pregnant women, the HDAC concentration in vaginal epithelial cells was lowest when *L. crispatus* was the dominant vaginal bacterium and significantly elevated when non-*Lactobacilli* dominated the microbiome [14]. The HDAC level was positively associated with the concentration of matrix metalloproteinase-8 (MMP-8) and the stress-inducible 70 kDa heat shock protein (hsp70) in vaginal secretions. Many studies have concluded that *L. crispatus* numerical dominance is associated with vaginal health and maintenance of conditions conducive to successful pregnancy progression and outcome [15, 16]. Thus, it appears that the differential regulation of HDAC production by vaginal epithelial cells in response to the bacterium that is dominant in the vagina influences the production and release of specific bioactive compounds from these cells. Extracellular hsp70 is a potent inducer of pro-inflammatory immunity [17], while MMP-8 releases hyaluronan from the extracellular matrix leading to activation of anti-microbial immunity [18]. A second study has provided additional evidence of epigenetic gene regulation in vaginal epithelial cells by *Lactobacilli*. Expression of the gene coding for human beta defensin-1, *DEFB1*, in an immortalized vaginal epithelial cells line was shown to vary between different strains of *Lactobacilli* through species-specific alterations in DNA methylation and histone modification [19].

Production of other compounds by vaginal epithelial cells has also been shown to be sensitive to the bacterial milieu. Neutrophil gelatinase-associated lipocalin (NGAL) production is induced in these cells when *Lactobacilli* predominate [20]. This protein inhibits bacterial uptake of iron and, therefore, inhibits proliferation of those microorganisms that require iron for growth [21]. *G. vaginalis* is an iron-dependent bacterium [22], while *Lactobacilli* can proliferate in the absence of this element [23]. Other iron-binding compounds released from vaginal epithelial cells include lactoferrin [24] and calprotectin [25]. Thus, the capability of vaginal epithelial cells to influence the vaginal level of iron, and possibly other elements, will impact the likelihood of specific bacterial dominance at this site. A direct comparison of levels of compounds in vaginal fluid from pregnant women when either *L. crispatus* or *L. iners* was numerically dominant revealed that levels of NGAL and calprotectin, as well as other compounds involved in antimicrobial defense—stress-induced hsp70, MMP-8, and

hyaluronan—were preferentially induced by *L. iners* [26]. This reinforces studies demonstrating that *L. iners* dominance in the vaginal microbiota is associated with induction of a stress response in the vaginal epithelium [27].

Other anti-microbial compounds differentially released by vaginal epithelial cells in response to the presence of specific microorganisms include secretory leukocyte protease inhibitor [28], mannose-binding lectin [29], beta defensins [30], and cathelicidins [31]. The surface of vagina epithelial cells contains a number of Toll-like receptors (TLR) that recognize invariant molecular patterns on microorganisms [32]. TLR-agonist binding results in the production of a large number of pro-inflammatory cytokines—interleukin (IL)-1, IL-6, IL-8, IL-12, and tumor necrosis factor-alpha [33, 34]. The release of these cytokines from in vitro-cultivated vaginal epithelial cells could not be demonstrated when either *L. crispatus* or *L. jensenii* was present. Furthermore, these two *Lactobacillus* strains inhibited epithelial cell cytokine expression when TLR agonists were added to the cultures [35]. This further highlights the sensitivity of vaginal epithelial cells to the local external environment and its influence on composition of the vaginal milieu.

Epithelial Cell Responses to Stress

Studies in a mouse model have demonstrated that maternal stress changes the composition of the vaginal microbiota, resulting in a decreased level of *Lactobacilli* [36]. Evidence for a possible involvement of vaginal epithelial cells in the stress-related alteration of vaginal microbial abundance comes from a recent study demonstrating that two human vaginal epithelial cell lines secreted both norepinephrine and dopamine. In addition, these cells recognized and bound exogenous norepinephrine [37]. Interestingly, norepinephrine by itself did not induce production of pro-inflammatory compounds from vaginal epithelial cells, but its presence resulted in a significant upregulation of the release of these mediators in the simultaneous presence of immune system activators. These observations led us to postulate a stress-vaginal dysbiosis relationship based on vaginal epithelial cell responses [1••]. Production of norepinephrine in woman experiencing prolonged stress results in its appearance in the vagina due to transduction from the circulation. Norepinephrine binding to vaginal epithelial cells coupled with its local production by these cells leads to the decrease or loss of *Lactobacilli* dominance in the vagina. The subsequent increased production of non-*Lactobacilli* and their induction of inflammation are enhanced by the presence of norepinephrine. Thus, disparities between individual women in the magnitude of their response to various stressors may determine their propensity to develop a symptomatic vaginal disorder. A strain of *Lactobacillus*, *L. salivarius*, has very recently been shown to possess receptors for the uptake of neuroactive biogenic amines [38••]. If *Lactobacilli* in the vagina possess a similar mechanism, still to be determined, then vaginal epithelial cell-*Lactobacilli* cross-communication may have even a more enhanced influence on the stress-associated vaginal environment.

The stress-induced reduction in the vaginal *Lactobacillus* level is also a consequence of the effect of cortisol on vaginal epithelial cells [39]. Elevations in cortisol as a result of prolonged stress inhibit glycogen deposition in the epithelial cells. This reduces the glycogen concentration in the vaginal lumen resulting in local conditions that are less than ideal for the preferential proliferation of *Lactobacilli*.

Vaginal Epithelial Cell Autophagy

Autophagy is a mechanism present in all multicellular organisms to maintain intracellular homeostasis [40]. Misfolded or

Table 1 Properties of vaginal epithelial cells responsive to the external milieu

Mechanism	Consequence
Sloughing from the vaginal wall	Removal of attached microorganisms
Accumulation of glycogen	Provides compounds favoring lactobacilli
Production of EMMPRIN	Survival in acidic vaginal environment
Regulation of HDAC production	Milieu-specific gene activation
Differential bacterial recognition	Selective destruction of microbial pathogens
Release of NGAL and other compounds	Prevents proliferation of iron-requiring bacteria
Induction of anti-microbial activity	Elimination of potential pathogens
Release of the 70 kDa heat shock protein	Stimulation of pro-inflammatory immunity
Regulation of autophagy	Engulfment of intracellular microorganisms
Responsive to systematic stress	Regulation of pro-inflammatory immunity

EMMPRIN, extracellular matrix metalloproteinase inducer; *HDAC*, histone deacetylase; *NGAL*, neutrophil gelatinase-associated lipocalin

aggregated proteins, aged mitochondria as well as fungi, bacteria and viruses that have entered the cytoplasm are engulfed in autophagosomes. The subsequent fusion with a lysosome results in degradation of the engulfed macromolecules or microorganisms by lysosomal enzymes and the resulting amino acids, nucleotides, carbohydrates, and lipids are returned to the cytoplasm for reutilization. The induction of a stress response results in upregulation of hsp70, an inhibitor of autophagy [41]. Unlike autophagy, which removes non-functional proteins, hsp70 binds to intracellular proteins to maintain their functional activity and prevent their misfolding [42]. This latter process appears to take precedence over autophagy under non-physiological conditions [43, 44]. A recent study evaluated the level of autophagy in vaginal epithelial cells from pregnant women in relation to bacterial dominance in the vaginal microbiome [45•]. It was determined that *L. crispatus* dominance was associated with the highest level of epithelial cell autophagy and the lowest intracellular hsp70 concentration. These levels were significantly different from what was observed when *L. iners* was dominant. The highest hsp70 level and lowest autophagy corresponded to *Streptococcus* and *Bifidobacterium* dominance. It thus appears that vaginal epithelial cells modulate their level of autophagy in response to the vaginal bacterial composition and the predominance of *L. crispatus* at this site results in the maintenance of an optimal intracellular environment. This may account, at least in part, for the association between *L. crispatus* vaginal dominance and normal pregnancy progression [15, 16]. A low level of autophagy has been associated with elevations in reactive oxygen species, possibly from defective or aged mitochondria, and induction of preterm birth [46]. In addition, vaginal epithelial cell homeostasis would maximize the ability of these cells to recognize and respond to potential pathogens by the induction of innate immunity [47].

Candida albicans that has penetrated into vaginal epithelial cells is sequestered into autophagosomes and destroyed by autophagy [48••]. Inhibition of autophagy in these cells permitted *C. albicans* to proliferate and kill the infected cell [49]. Conversely, the detection of *Streptococci* in vaginal secretions from pregnant women is followed by the inhibition of autophagy in vaginal epithelial cells and the upregulation of the autophagy inhibitor, hsp70 [45•, 50]. Thus, the differential capacity of microorganisms that are present in the vagina to either promote or inhibit autophagy modulates this antimicrobial defense mechanism in vaginal epithelial cells.

Conclusion

There is a symbiotic relationship between human vaginal epithelial cells and the resident vaginal microbiota in the exchange of macromolecules and creation of an environment that protects against the invasion and establishment of potential pathogens. Changes in the bacterial environment and the presence of factors that alter the vaginal microbiome induce differential gene activity and the upregulation by vaginal epithelial cells of compounds with anti-microbial and immune-inducing activity. Properties of vaginal epithelial cells that are responsive to variations in the local environment are summarized in Table 1. This adaptation to a milieu—namely vaginal acidity and *Lactobacilli* dominance—specific to humans maximizes conditions conducive to pregnancy progression.

Compliance with Ethical Standards

Conflict of Interest Iara M. Linhares, Giovanni Sisti, Evelyn Minis, Gabriela B. de Freitas, Antonio F. Moron, and Steven S. Witkin declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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