Lactic acid alleviates stress: good for female genital tract homeostasis, bad for protection against malignancy

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Abstract Women are unique from all other mammals in that lactic acid is present at high levels in the vagina during their reproductive years. This dominance may have evolved in response to the unique human lifestyle and a need to optimally protect pregnant women and their fetuses from endogenous and exogenous insults. Lactic acid in the female genital tract inactivates potentially pathogenic bacteria and viruses, maximizes survival of vaginal epithelial cells, and inhibits inflammation that may be damaging to the developing fetus and maintenance of the pregnancy. In an analogous manner, lactic acid production facilitates survival of malignantly transformed cells, inhibits activation of immune cells, and prevents the release of pro-inflammatory mediators in response to tumor-specific antigens. Thus, the same stress-reducing properties of lactic acid that promote lower genital tract health facilitate malignant transformation and progression.

Keywords Autophagy · Immune regulation · Histone deacetylase · Lactic acid · Malignancy · Pregnancy

Aerobic and anaerobic glycolysis is a prominent feature of malignantly transformed cells of both human and non-human origin. The end product of this pathway, lactic acid, is utilized to enhance tumor cell survival, dampen antitumor immunity, and increase metastatic potential. Lactic acid also accumulates in the vaginal lumen, but only in healthy reproductive age women and not in other mammals.

Vaginal lactic acid promotes antimicrobial and immune modulatory activities at this site and optimizes epithelial cell functions. These properties enhance the ability to successfully confront the onslaught of microbial and environmental agents to which the vagina is exposed to daily, maximize fertility potential, and, during pregnancy, facilitate prolongation of gestation until term. In this communication, the stress-reducing properties of lactic acid that promote malignancy and reproductive health are compared and possible explanations for the emergence of lactic acid dominance in the human vagina are presented.

Lactic acid production

A common feature of malignantly transformed cells is the production of high levels of lactic acid, even under aerobic conditions (the Warburg effect) (Warburg 1956; Hsu and Sabatini 2008). There is an upregulation of lactic dehydrogenase A (LDHA) in tumor cells. The resulting lactic acid is released from the cells and decreases the pH of the extracellular milieu to aid in immune system evasion and tumor progression (Brand et al. 2016). Inhibition of LDHA has been shown to diminish tumor cell functions (Fantin et al. 2006). Lactic acid is also the primary acid present in the vaginal lumen of reproductive age women and the principal determinant of the acidic vaginal pH (Huggins and Preti 1976). Vaginal lactic acid originates from two sources: resident bacteria and vaginal epithelial cells, with bacteria providing ≥ 85% (Boskey et al. 2001). Lactobacilli species, primarily *L. crispatus*, *L. iners*, *L. gasseri*, and *L. jensenii*, are the principal bacterial sources of lactic acid production in the vagina. When lactobacilli are absent but vaginal pH remains within a similar acidic range, other lactic acid-producing bacteria, such as *Atopobium*, *Megasphaera*, and *Leptotrichia*, may be

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present (Zhou et al. 2004). Vaginal epithelial cells are rich in glycogen. Its release into the vaginal lumen and its metabolism by host α -amylase provide the ideal substrate for lactobacilli-mediated production of lactic acid (Spear et al. 2014; Nasioudis et al. 2015).

Lactic acid is also the major by-product of glycogen metabolism by epithelial cells in the anaerobic environment of the vaginal mucosa. The vaginal mucosa undergoes recurring cycles of proliferation, maturation, and desquamation with a turnover time of approximately 96 h. Energy for this process is provided by metabolism of glycogen. The glycogen is metabolized first to pyruvic acid and then to lactic acid, which diffuses out of the cells and accumulates in the vaginal lumen (Gross 1961). Glycogen metabolism is maximal in the intermediate vaginal epithelial cell layer, and that is the location of the highest level of glycogen synthetase. Epithelial cell glycogen metabolism at this site is estrogen dependent (Ayre 1951; Bo 1970), and vaginal lactic acid concentrations are greatest during the period from 48 h prior to the luteinizing hormone surge until 24 h afterward (Preti and Huggins 1975). Lactobacilli in the vagina, with the exception of *L. iners*, produce both the D- and L- chiral isomers of lactic acid, while vaginal epithelial cells produce only the L-lactic acid isomer (Witkin et al. 2013).

Thus, acidification of the extracellular environment by lactic acid is a feature shared by developing tumors and the human vagina. A difference that should be noted is that while the pH in the region surrounding a tumor may decrease to 6.0–6.5 (Webb et al. 2011), the vaginal pH is typically ≤ 4.5 (Linhares et al. 2011).

Phylogeny of lactic acid production

While tumors from many different species synthesize and release lactic acid, the presence of lactic acid as the dominant organic acid in the vagina and the resulting acidic pH only occurs in women. The vaginal pH of the animals most frequently used in laboratory research—mice, rats, rabbits—is about 7 (Linhares et al. 2011). Even non-human primates have an elevated vaginal pH and a greatly reduced level or absence of lactic acid and lactobacilli (Witkin and Ledger 2012; Stumpf et al. 2013; Yildirim et al. 2014; Witkin and Linhares 2017). Possible explanations for the uniqueness of lactic acid dominance in reproductive age women as opposed to other mammals have been proposed (Stumpf et al. 2013; Witkin and Linhares 2017). Most non-human primates as well as other mammals have shorter estrogen cycles than do women, and so, estrogen-induced production of glycogen is reduced. Additionally, unlike most other mammals, humans engage in sexual intercourse throughout the menstrual cycle and even during pregnancy, and so, exposure to microorganisms in semen or

contamination from microbes present in the rectum or on the penis is enhanced. Another difference that elevates susceptibility to infection is the increased length of gestation in women in comparison to other mammals coupled with a decreased size of the uterine cervix in relation to the infant's head circumference. Increased promiscuity of human males compared to other mammals may also contribute to a larger diversity of microorganisms in the human male genital tract and a concurrent need for a more effective antimicrobial defense mechanism in human females. Lastly, the increased frequency of sexual intercourse in humans strongly suggests that women are exposed to spermatozoa more frequently than are non-human females. Spermatozoa are viewed as foreign by the female immune system, and development of antisperm antibodies is an established cause of infertility (Clark 2009). The vast majority of sexually active women do not have a detectable immune response to spermatozoa, suggesting the presence of a vaginal environment that favors induction of immune tolerance. Development of antisperm immunity as well as pregnancy failure after in vitro fertilization has been linked to the absence of vaginal lactobacilli (Eckert et al. 2003).

Lactic acid and immunity

The production and release of lactic acid into the tumor microenvironment aids malignant cell survival by several mechanisms. Reducing the pH in the region adjacent to the tumor hampers antitumor immune responses; the activity of cytotoxic T lymphocytes is decreased; secretion of pro-inflammatory mediators is blocked, and dendritic cell maturation is inhibited (Lardner 2001; Choi et al. 2013). Expression of the transcription factor, nuclear factor of activated T cells (NFAT), is inhibited by intracellular lactic acid accumulation resulting in a marked decrease in expression of the gene coding for interferon- γ . The consequent failure to activate T lymphocytes as well as natural killer cells results in a markedly diminished capacity for tumor immune surveillance (Brand et al. 2016). Exogenous lactic acid further interferes with T cell metabolism by inhibiting the release of lactate anions from T cells, thereby altering intracellular pH (Fischer et al. 2007). The preferential uptake by tumor cells of glucose for lactic acid production also results in a decreased availability of this essential nutrient for T cells and an inhibition of immune function (Chang et al. 2015). Macrophage activities are similarly impaired in the presence of lactic acid (Colegio 2015; Dietl et al. 2010; Colegio et al. 2014). Lactic acid promotes the polarization of tumor-associated macrophages to the immunosuppressive M2 phenotype. In addition, lactic acid-induced expression of arginase 1 by tumor-associated macrophages has been shown to facilitate tumor growth, possibly by

enhancing the synthesis of polyamines (Colegio et al. 2014). The mechanism appears to involve the induction of hypoxia-inducible factor 1 α (HIF-1 α) by lactic acid (Colegio et al. 2014). In the female genital tract, HIF-1 α participates in the onset and progression of cervical cancer (Cheng et al. 2013). Lactic acid has been shown to also stimulate the release of interleukin (IL)-17A from monocytes/macrophages in the setting of malignancy. The resulting selective enhancement of the Th17 subclass of CD4⁺ T lymphocytes and release of IL-23 inhibits CD8⁺ T cell toxicity and migration and enhances tumor cell development (Shime et al. 2008; Yabu et al. 2011; Haas et al. 2015). Lactic acid also aids in tumor metastasis by inducing the synthesis of hyaluronan by tumor cells to degrade the extracellular matrix (Stern et al. 2002).

The concentration and persistence of lactobacilli in the vagina, and thus, the level of lactic acid, increases when a woman becomes pregnant (Romero et al. 2014), undoubtedly due to increased estrogen production and possibly also related to changes in the composition of vaginal secretions. This change would further magnify the capacity of vaginal epithelial cells to participate in immune defense at this site. We have postulated that it would be advantageous in pregnancy to have a mechanism to eradicate potentially pathogenic microorganisms without inducing a level of inflammation that may interfere with progression of the pregnancy (Witkin and Linhares 2017). Lactic acid seems to fulfill this need. Studies have demonstrated that concentrations of lactic acid that are present in the vagina induce the release of anti-inflammatory mediators from cervico-vaginal epithelial cells (Hearps et al. 2017) while concomitantly inactivating human immunodeficiency virus (Aldunate et al. 2013), herpes simplex virus (Conti et al. 2009), *Chlamydia trachomatis* (Gong et al. 2014), *Neisseria gonorrhoeae* (Graver and Wade 2011), and a multitude of bacteria that are associated with bacterial vaginosis (Alakomi et al. 2000; O'Hanlon et al. 2011). In addition, lactic acid has been shown to downregulate the release of pro-inflammatory cytokines from epithelial cells even though microbial products are bound to their Toll-like receptors (Hearps et al. 2017; Aldunate et al. 2015). Lactic acid-induced stimulation of IL-17A production in the female genital tract would further dampen Th1-mediated pro-inflammatory immunity while maintaining local immune defense against vaginal pathogens (Witkin et al. 2011; Masson et al. 2015). Positive effects of HIF-1 α induction by lactic acid in the female genital tract include its role in the prevention of urinary tract infections (Lin et al. 2015) and promotion of neutrophil antimicrobial activity (McInturff et al. 2012). The induction of hyaluronan by lactic acid would facilitate degradation of exfoliated vaginal epithelial cells and release elevated levels of glycogen for utilization by lactobacilli, resulting in the enhancement and prolongation of lactic acid production. A lactobacilli-dominant vaginal microbiota in pregnant women has been

shown to protect against damage to the cervical barrier, inhibit bacterial passage to the uterus and amniotic cavity, and prevent preterm parturition (Witkin 2015).

Histone deacetylase activity

The ability of transcription factors to bind to the promoter region of specific genes and initiate active transcription depends, in part, on the acetylation status of histones that are associated with those genes. Acetylated histones do not bind tightly to chromatin and, thereby, permit transcription factors greater access to the DNA. Conversely, when histone acetylation is poor, the chromatin is compacted and gene access is restricted (Kelly and Cowley 2013). Histone deacetylase (HDAC) is a family of enzymes that regulate gene transcription as well as the ability of DNA repair enzymes to access damaged regions of chromosomes by removing acetyl groups from histones H3 and H4 (Kelly and Cowley 2013; Ma and Schultz 2008; Bhaskara 2015). In many human tumors, the pattern of histone acetylation is markedly different from that seen in the analogous normal tissue (Montezuma et al. 2015). It has been suggested that HDAC may promote the development of cervical carcinoma by selectively inhibiting transcription of tumor suppressor genes (Feng et al. 2013). Lactic acid inhibits HDAC (Latham et al. 2012). By increasing the efficacy of DNA repair and altering gene transcription, increased histone acetylation may promote malignant transformation and enhance tumor cell survival in response to anticancer radiation and chemotherapy (Latham et al. 2012; Wagner et al. 2015).

HDAC levels in vaginal epithelial cells are significantly reduced when lactobacilli are the predominant members of the vaginal microbiota as compared to when other bacteria are dominant (Nasioudis et al. unpublished). Thus, elevated concentrations of vaginal lactic acid would increase the capacity for initiation of gene transcription and the repair of damaged regions of the DNA in these cells. Since the lower female genital tract is in contact with the external environment and potentially pathogenic microorganisms as well as with toxic chemicals on a daily basis, an enhanced capability for gene transcription and DNA repair will facilitate epithelial cell participation in maintaining vaginal health.

Autophagy

Lactic acid induces autophagy (Xu et al. 2016; Ghadimi et al. 2010). This intracellular process, highly conserved throughout evolution, maintains cell homeostasis by the removal from the cytoplasm of degraded or aggregated proteins, dysfunctional mitochondria, and bacteria and viruses that have entered the cell (Wang and Klionsky 2003). Depending on the specific

Table 1 Lactic acid-induced consequences for vaginal epithelial cells (VECs) and malignantly transformed cells (MTCs)

Activity	VEC	MTC
Immunity	<ol style="list-style-type: none"> 1. Releases anti-inflammatory mediators from epithelial cells 2. Inactivates bacterial and viral pathogens 3. Induces Th17⁺ T cells and IL-17A production 4. Induces HIF-1α to prevent urinary tract infections and promote neutrophil antimicrobial activity 5. Induces hyaluronan to provide glycogen for growth of lactobacilli 	<ol style="list-style-type: none"> 1. Decreases cytotoxic T cell activity 2. Inhibits release of pro-inflammatory mediators 3. Inhibits dendritic cell maturation 4. Blocks interferon-γ gene transcription and T lymphocyte and natural killer cell activity 5. Inhibits T cell metabolism 6. Promotes polarization of macrophages to M2 phenotype 7. Induces HIF-1α to enhance tumor growth
Inhibition of histone deacetylase	<ol style="list-style-type: none"> 1. Increases ability of vaginal epithelial cells to survive by repairing damaged DNA and facilitating gene transcription 	<ol style="list-style-type: none"> 1. Increases ability of MTC to survive by repairing DNA damage and inducing selective gene transcription
Induction of autophagy	<ol style="list-style-type: none"> 1. Promotes optimal functioning by removal of toxic compounds and intracellular microorganisms 	<ol style="list-style-type: none"> 1. Facilitates survival in response to altered metabolism, radiation, and chemotherapeutic agents

malignancy and the stage in tumorigenesis, autophagy induction may either promote or suppress malignant progression (Orfanelli et al. 2014). In the early stages of many malignancies, the inhibition of autophagy allows the persistence of intracellular components that elevate levels of oxidative stress, induce DNA damage, and promote oncogenic transformation. Conversely, at later stages, induction of autophagy facilitates tumor cell survival in response to altered metabolism and the introduction of chemotherapeutic agents. Autophagy downregulation appears to contribute to the development of cervical squamous epithelial cancer, while its upregulation may facilitate endometrial cancer progression. Both the upregulation and downregulation of autophagy have been associated with ovarian cancer (Orfanelli et al. 2014). The involved mechanism of lactic acid regulation of autophagy during tumorigenesis involves the inhibition of cyclic adenosine monophosphate formation and the triggering of the mitogen-activated protein kinase (MAPK) pathway by lactic acid. This results in the induction of autophagy in malignantly transformed cells (Xu et al. 2016).

We have measured autophagy in vaginal epithelial cells and observed that the highest levels occur when *L. crispatus*, a potent lactic acid producer (Witkin et al. 2013), is the dominant bacterium in the vaginal microbiota (Leizer et al. 2017). Similar to the influence of lactic acid on inhibition of HDAC, the induction of autophagy in vaginal epithelial cells by lactic acid would expedite removal of potentially toxic agents as well as microorganisms and, thereby, assure optimal functioning of this component of the local innate immune system. A failure to induce adequate levels of autophagy during pregnancy has been associated with high levels of reactive oxygen species and the triggering of preterm birth (Ramos and Witkin 2016).

Conclusions

The consequences of lactic acid exposure for vaginal epithelial cells and malignantly transformed cells are summarized in Table 1. The utilization of cancer cell-produced lactic acid as a mechanism to stimulate oncogenesis occurs throughout the animal kingdom. However, as has been noted previously (McInturff et al. 2012), the majority of tumors arise after the time for reproductive potential has passed and, therefore, the effect of lactic acid on oncogenesis most likely did not influence species evolution. It was proposed that a primary function of host lactic acid production under physiological conditions is to resolve inflammation and downregulate excessive adaptive immune responses (Bronte 2014). In an analogous manner, lactic acid that is produced by bacteria in the intestines regulates the intensity of local inflammation in many mammalian species (Jang et al. 2013; Lynch and Pedersen 2016). However, the contribution of lactic acid to the maintenance of vaginal well-being is specific to humans. The adaptation of a lactic acid-based mechanism for the promotion of reproductive health and its persistence over generations is thus a relatively recent occurrence that likely arose as an effective response to the unique physiology, behaviors, and environment of the human species.

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