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Vaginal Microbiota and its Oncological Risk

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Abstract

***Background:** Microbes inhabit all the sites of the human body and play an important role in health; The normal vaginal microbiota is composed mainly of Lactobacillus, and these have a role in the carcinogenesis of cervical cancer (both protective and harmful), for the acquisition or persistence of infection by human papillomavirus and subsequent development of cervical precursors and cancer cervical; women with HPV infection have greater microbial diversity and a lower proportion of Lactobacillus spp; the use of next-generation sequencing techniques; has identified 5 bacterial groups associated with the severity of the cervical precursor lesions and their modulation towards a stable dominant microenvironment of Lactobacillus ssp., promotes the purification of HPV.*

***Conclusion:** The relationship between HPV infection, cervical precursor lesions and vaginal microbiota play a role in the tumor microenvironment; influencing the immune response, susceptibility to infection and development of cervical cancer; together with the other risk factors in the host. Women with vaginal microbiota Vaginal Microbiota of high diversity and cervical pathology should have greater vigilance and / or treatment.*

Keywords: *Bacterial vaginosis, HPV, HIV, lactobacillus, probiotics, cervical intraepithelial neoplasia, cervical cancer, lactic acid, hormonal contraception, carcinogenesis, community-state types (CSTs), high-grade squamous intraepithelial lesion.*

Background

Microorganisms inhabit all the sites of the human body and play an important role in health [1-2]. The vaginal microbiota of healthy women consists of a variety of anaerobic and aerobic microorganisms in equilibrium (or eubiosis) where lactobacilli are predominant, when this balance (or dysbiosis) is lost other microorganisms grow affecting the defense mechanisms (or pathogenesis), which depends on different factors (hormonal, douching, sexual practices, bacterial interactions, host defenses, etc.), promoting inflammatory disorders, loss of barrier function, diseases and even cancer [1-4]. Lactobacilli produce antimicrobial compounds (hydrogen peroxide, lactic acid, bacteriocin-like substances) that have the ability to adhere and compete for adhesion sites in the vagina with other pathogens, to maintain the homeostasis of vaginal microbiota in the host; the prolonged time of dysbiosis and other risk factors [4]; They are associated with several types of cancer mainly in the mucous membranes of the tissues where the bacteria inhabit [4]. Persistent infection with high-grade human papillomavirus (HPV), mainly (HPV-16/18) are cause necessary for the development of cervical cancer [3,4]; in addition, other factors in the local microenvironment, which alter the microbiota vaginal with elevation of pH [5-9].

Lactobacilli prevent genitourinary infections by maintaining a vaginal pH between 3.8 to 4.5, by the production of lactic acid, secretion of antimicrobial compounds and elimination of microorganisms. The composition of MV in women of reproductive age is dominated by lactobacilli, the four predominant species (Lactobacillus crispatus, Lactobacillus gasseri, Lactobacillus iners, Lactobacillus jensenii), associated with vaginal health, [1,2] in some women, the MV lacks high proportion of lactobacilli and is dominated by a diverse mix of anaerobic and microaerophilic bacteria (Gardnerella, Atopobium, Prevotella, Sneathia) associated with bacterial vaginosis[1,2], which is

characterized by a loss or decrease of Lactobacillus, high pH and infiltration of immune cells, anaerobic bacteria growth and complications and obstetric and gynecological infections with higher risk and predisposition to HPV infection, mainly when infection with the human immunodeficiency virus (HIV) coexists; producing changes in the composition of the vaginal microbiota [3.10-12].

Infection with HPV and Vaginal Microbiote

HPV infection is common in sexually active women; the majority is transitory; However, other associated factors play important roles in susceptibility, such as local immunity, hormonal and genetic levels. The vaginal microbiota plays a protective role in the health of women, the immune response serves as an indicator of vaginal health [3,4]; abnormal vaginal microbiota, as in bacterial vaginosis, is associated with increased health risk in the genital tract with spontaneous or recurrent miscarriage, preterm birth, and sexually transmitted infections (STIs), including HIV and HPV; Healthy vaginal microbiota contribute to health in women [3]. The Lactobacilli, are commensals of the vagina that protect from pathogens and infections, through the production of specific metabolites such as bacteriocins that eliminate related bacterial species, with adhesion to the mucosa, biofilm formation, and biosurfactants, which prevent their binding to the epithelium [1-5]. Next generation sequencing (NGS) facilitates the characterization of healthy vaginal microbiota, in 5 main types of group phases or community-state types (CSTs); CST I, II, III and V are dominated by Lactobacillus crispatus, L. gasseri, L. iners and L. jensenii respectively, while CST IV has a characteristically low number of Lactobacillus spp., and a greater diversity of anaerobic bacteria [1-4]. The vaginal microbiota is dynamic and hormonally influenced with a propensity to become less stable during menstruation and vice versa more stable and less diverse during normal pregnancy [6]. The stability and composition of the vaginal microbiota play an important role in determining the response Innate host immune and susceptibility to infection. Bacterial Vaginosis, (CST IV) is a disorder characterized by a greater diversity of species, with high prevalence, 12 to 50%, in women of reproductive age characterized by depletion of Lactobacillus spp., Anaerobic overgrowth and pH High vaginal discharge associated with increased susceptibility to ascending vaginal infection through sensitization and alteration of the host's innate immune system. The Vaginal Microbiota is influenced by estrogen levels, which also control the thickness of the vaginal epithelial tissue [3,6]. The vaginal microbiota of the predominantly columnar epithelium as in the immature cervix differs from the squamous and the vaginal microbiota of these immature epithelia contribute to vulnerability to HPV infections. One of the mechanisms associated with the clearance or persistence of HPV infection is Bacterial Vaginosis, which is associated with late HPV clearance and cervical intraepithelial neoplasia (CIN), suggesting that Lactobacillus Vaginal Microbiota depletion plays a role [3,6,10]. In sexually active women it was found that the depletion of Lactobacillus spp., Atopobium spp. (CST IV) is associated with the slowest regression of HPV, while a microbiota dominated by Lactobacillus gasseri (CST II) is associated with the fastest regression rates for HPV [3-5,10,11]. Lactobacillus spp., Confer resistance to HPV infection as well as protect against the colonization of pathogens. The E5 protein of HPV-16 is susceptible to a low pH [3.4]. Vaginal Microbiota with positive HPV is more diverse than in negative HPV [3,6,10,11]

Adhesion to the epithelial cells is crucial in the colonization, the invasion allows the bacteria to evade the immune surveillance of the host and to spread to deeper tissues, provoking pro-inflammatory responses that promote bacterial adhesion, to lodge in epithelial cells. HPV infection alters mucosal metabolism and host immunity, causing changes in the structure of the vaginal microbiota [1-4,10,11].

Carcinogenesis

There are more than 200 HPV genotypes; mainly HPV-16 and 18 that cause 70% CaCu; HPV infection is eliminated by more than 90% within 6-18 months [3,10], and only persistently in 10% of infected women. The factors responsible for persistence, which promote the initiation of carcinogenesis, are unknown; Risk factors such as immunodeficiency, age, smoking, oral contraceptives and Chlamydia trachomatis infection, which also negatively influence the vaginal microbiota, promote HPV carcinogenesis [12,13]; Vaginal health is associated with low microbial diversity with a prevalence of lactobacilli [14,15], preventing the proliferation of exogenous pathogens [16,17]. Abnormal vaginal microbiota with decreased Lactobacillus and increased microbial diversity facilitates the persistence of HPV infection and cancer development; 7.4% of women, of the CST IV subgroup, associated with bacterial vaginosis, together with the genus Atopobium spp (CST IV-VB) and sialidase of G. vaginalis are risk

factors or microbial markers for the persistence of HPV. The changes in the vaginal microbiota influence in 15 to 20% in the development of carcinogenesis without distinguishing if they are causes or effects of the cancer, by diverse mechanisms, like inflammation, inmodulation, damage to the DNA and production of metabolites in the tumor suppression; Drug manipulation as adjuvants of the vaginal microbiota improves the response to oncological management [9,18].

The risk in life to acquire any HPV infection probably exceeds 5% by 80%. HPV genotypes associated with alpha species predominate in the anogenital area, but beta and gamma types of HPV are also detected. Because the lifetime risk of developing cervical cancer is less than 0.6%, cervical cancer is considered a rare complication of a common infection and should be considered HPV as a commensal organism that plays a protective role against HPV [2.5,7]. The time from infection to the development of cervical cancer is 15 years; although there may be a rapid progression in rare cases [2,5].

Not all lactobacilli are necessarily stable or healthy. L. iners is present in all women including those with dysbiosis, while Lactobacillus crispatus is observed mainly in healthy women, the predominance of L. iners predicted the development of bacterial vaginosis, in comparison, to the predominance of L. crispatus that is protective against the development of bacterial vaginosis [2,5,11]. Most women have a relatively stable vaginal microbiota; in those with vaginal microbiota of greater diversity greater instability is observed [19,20]. Cervical carcinogenesis usually has a long precancerous phase and it is to be determined, what factors determine that the infection persists, progresses or, on the contrary, returns spontaneously [2,3,8,12].

In general, HPV is a non-lymphatic infection and the inflammatory response is less than other infections, such as C. trachomatis. The initial immune response to acute HPV infections is mediated by the local innate immune system, involving mechanisms such as activation of toll-like receptors and natural killer cells (NK) [2,5]. Persistent HPV infections are cleared by the adaptive immune response, which depends on the antigen-presenting cells. It is thought that HPV-16 decreases the innate and adaptive immune response; but, local microbial communities also play roles in the regulation of the immune response. The final pathways to cancer result in interference with telomerase activity and viral integration of the HPV E6 and E7 oncoproteins, controlling carcinogenic events (proliferation, senescence and apoptosis). Vaginal microbiota also manipulates these oncoproteins of HPV-ar, by HPV-induced dysbiosis involved in the natural history of the disease [5,11,16-19], chronic exposure to inflammation is toxic to cells resulting in DNA damage and carcinogenic changes [20-25]

The communities of vaginal bacteria in healthy women are usually populated by Lactobacillus spp., Which ensures a low pH, which provides the first line of defense against pathogens [5,14,19,20]. Vacterial Baginosis-CST IV is a disorder characterized by a greater diversity of species, with a prevalence of 12 to 50%, which has implications for public health [19,20]. The intestine is a reservoir for many vaginal microbiota species (healthy or pathogenic), the vagina is protected from the colonization of most intestinal and rectal species that is predictive of the development of vaginosis bacterial in women [19,20]; epithelial thinning in postmenopausal women is responsible for the change in MV distribution that improves with menopausal hormone therapy [7,14]. Evaluation of the vaginal flora with the degree of disease (normal, LSIL, HSIL and Cervical Cancer [19-25] L. crispatus can have a beneficial effect on the HPV burden both in HIV-infected women and in women not infected with HIV (independent of pH) [12].

The highest rates of CST IV (with depletion and high diversity of Lactobacillus)) were associated with increased severity in women with LSIL, HSIL and cervical cancer, compared with normal women [3]. The presence of high diversity with Lactobacillus depletion in the MV it is related to CaCu instead of the presence of the HPV genotype itself [3,9,10] and the difference in the composition of the MV is related to an increase in the severity of the precursor lesions [3].

Discussion

The vaginal vaginal microbiota has an important role in the health of the reproductive tract of women; HPV infection is common, rarely recurrent, and occasionally precancerous lesions develop. The greater diversity of vaginal microbiotico, combined with reduction of Lactobacillus spp., Is related to the acquisition and persistence of HPV infection, and the development of precancerous cervical lesions and cervical cancer [3,9,10,18]. Cervical cancer is common in women from emerging countries and the second most frequent tumor worldwide [17,19,20], cervical cancer generally progresses through a series of premalignant lesions [15], where the normal cervical epithelial cell needs

around 10-20 years to its malignant transformation and few women who develop CIN evolve to cervical cancer. HPV is the main known risk factor for cervical cancer despite its high prevalence of HPV infection, the incidence and evolution rates of untreated precancerous lesions are low [13.9,10,18], 90% HPV-induced infections and lesions are transient or disappear spontaneously, [3,10] other host and environmental factors are involved during the carcinogenesis process [21-25]; as the relationship of vaginal microbiota that plays a role in host susceptibility to persistent HPV infection and the subsequent development of precursor lesions and cervical cancer [3,9,10,18], healthy vaginal microbiota is dominated by Lactobacilli that has an immune system local modulates the inflammatory response [25,26] and controls cell proliferation/apoptosis [27-29]. The protective substances produced by Lactobacilli play an essential role in the balance of vaginal microbiote eubiosis with inhibition of the colonization of other pathogens [1,2,30] to achieve general health in women.

The importance of chronic inflammation in the development of precancerous lesions and vaginal infections are considered a risk factor for CIN [1,2,31,32]. Due to the antitumor effect of probiotics and normal maintenance of MV, due to its inhibitory effects on the excessive growth of pathogens in relation to vaginal infections and CIN [28]. Women with dominant vaginal microbiota CST IV or inert L. are those where injuries persist or progress to cancer; but, it is only an association; They are not the cause. The presence of abnormal MV without Lactobacillus spp. Makes some women susceptible to persistent HPV and the development of CIN and CaCu. Women with BV have higher rates of STIs, including HPV [28-31]. HPV infection has an impact on host immune defenses and mucosal metabolism with adverse effects on vaginal microbiota. The infection of the basal membrane of mucosal surfaces by HPV initiates a cascade of mechanisms mediated by inflammation, immune activation of the mucosa with proinflammatory cytokines, interferons, activation of macrophages and NK cells, and integration into viral DNA. All These inflammatory processes and changes of the mucosal immune environment have an impact on vginal microbiota [8,15]; This similar increase in diversity and with low lactobacilli is associated with the acquisition or seroconversion of HIV, mainly in the HPV infection that produces changes in vaginal microbiota [14,28 - 31].

It is possible that certain species participate more in the initiation and progression of the disease than others [81,2,30-35]. Metagenomics is a new and interesting field to identify strains or bacterial genes associated with cervical pathogenesis [1,2,30], it is possible to develop rapid tests, microchip for identify patients at higher risk for close monitoring or treatment, the use of probiotics reduce the recurrence of vaginosis bacterial and [120], elimination of HPV with the anticipation of cerivcal cancer, will be a great advance in the field of gynecological oncology. Currently, there is a lack of treatment for HPV infection and precursor lesions, the standard reference is surgical, but, it is associated with perinatal morbidity and mortality [1,2,28-35].

Conclusions

There is a relationship between the host and vaginal microbiota, which plays a role in susceptibility to persistent HPV infection and subsequent development of precursor lesions and cervical cancer. It is possible that certain species participate more in the initiation and progression of the disease than others. Early characterization of vaginal microbiota discriminates against women at risk of developing persistent HPV infection for close monitoring or treatment.

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