Review Article

Role of Vaginal microbiota and Human Papillomavirus infection in cervical Oncogenesis: where do we stand?

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Abstract

Vaginal Microbiota has emerged as an important contributing factor for viral persistence, which can lead to the process of oncogenesis. The female reproductive system has a unique microbiome that helps keeping health maintenance and protects against infection. Contrary to other mucosal sites, the vaginal microbiota often exhibits limited diversity and contains few *Lactobacilli* species, which were categorized into five distinct community state types using high-throughput 16S rRNA gene sequencing. According to current research, Human Papillomavirus (HPV) acquisition, persistence, and cervical cancer development are influenced by increasing vaginal microbiome diversity and decreased *Lactobacillus spp*. This review explores the intricate relationship between vaginal microbiota and HPV in the context of cervical cancer development. It discusses the impact of microbiota diversity and dysbiosis on the acquisition, persistence, and clearance of HPV. The review also emphasizes the role of vaginal microbiota in maintaining a healthy female reproductive system and explores the potential of various interventions, such as probiotics and prebiotics, in restoring a healthy vaginal environment. Challenges and future directions for a healthy vaginal environment are also revealed in the article.

Keywords

Cervical oncogenesis, Vaginal Microbiota, High- risk Human papillomaviral infection, community state types, *Lactobacillus* species, bacterial vaginosis, dysbiosis

Introduction

The word Microbiota is in boom nowadays, and vaginal microbiota is one of them influencing the process of cervical oncogenesis. Cervical cancer continues to pose a significant global health challenge, particularly in developing nations. While the primary cause of cervical cancer is High-Risk (HR) Human Papillomavirus (HPV) infection, growing attention has been paid to the involvement of other factors, including the vaginal microbiota[(1)]. This article emphasizes the relationship between persistent viral infections and the interplay with the microbiome. It discusses the distinctive composition of the cervicovaginal microbiome, its essential protective mechanisms, and the factors influencing its balance.

According to a global public health report in 2020, there were 570,000 new cases of cervical cancer worldwide, with 342,000 deaths attributed to the disease[(2)]. Persistent infection with HR-HPV remains the leading cause of cervical cancer and its precursor lesions. Although HPV infection is common, approximately 80% of cases are transient and clear within two years, while the remaining 20% lead to persistent infection and disease progression[(2)]. While prolonged infection with these viruses can lead to various malignancies, other co-factors are also crucial for tumor development. The microbiota appears to significantly contribute in viral persistence, as recent studies highlight its role in various viral infections and cancers[(3)]. The cervicovaginal microbiome has been well studied and is associated with various gynecologic diseases. Advances in Deoxyribonucleic Acid (DNA) sequencing technologies and bioinformatics have led to an increased understanding of the diversity and dynamics of the microbiota over the past two decades. The microbiota comprises a range of microorganisms, some of which can be detrimental, while others are commensal or symbiotic. Dysbiosis, a disruption of microbiota homeostasis, can compromise health, rendering the host more susceptible to infections. Knowing the relationship between the microbiota and HPV persistence, as well as the variables that influence the vaginal microbiota and how they interact with immuno-regulatory molecules is crucial. Understanding these correlations may make it easier to pinpoint key targets that influence HPV persistence. The review talks about how vaginal microbiome can be used in clinical therapy and predictive diagnostics to cure and prevent HPV persistence and the subsequent development of Cervical Intraepithelial Neoplasia (CIN) and Cervical Cancer (CC).

Materials and Methods

Data was obtained from database searches (Scopus, Embase, EBSCO, PubMed, and Google Scholar) using keywords cervical cancer, vaginal microbiota and cervical precancerous lesions, and digital imaging and cross-references were searched.

Results and Discussion

1. Microbiota of the Female Reproductive System

Microbiota, mainly comprised of *Lactobacillus* species [species depends upon Community State Types (CST) I-V], prevent entry of pathogens. However, dysbiosis can lead to pathological conditions that enhance the persistence of pathogens like HPV. Key protective mechanisms employed by Lactobacillus species safeguard the female reproductive system[1,2]. The vaginal microbiota changes significantly during a woman's life, often coinciding with transitional reproductive periods that impact the host reproductive system's general physiology. It has been discovered that vaginal microbiota is essential for preserving a wholesome vaginal environment, halting the colonization of pathogenic microorganisms, and eliciting a potent immune response – all of which are signs of improved genital tract functions. A healthy vaginal microbiota may shield against a variety of infectious agents, including bacteria, yeast fungi, and viruses such as *Escherichia coli* and *Gardnerella vaginalis*. Viruses like HPV and Human Immunodeficiency Virus (HIV) are among the many infectious agents that can be prevented. Thus healthy microbiota plays an essential role in the development of proper vaginal immunity.

2.1 Bacterial Vaginosis and Vaginal Diseases

The significance of bacterial vaginosis as a form of dysbiosis creates its impact on the vaginal microbiota and the associated health risks. There is a proven correlation between increased microbiota diversity and susceptibility to sexually transmitted infections, including HPV.

The microbiota of the female reproductive system is unique, with its composition varying throughout the menstrual and female life cycles. The vaginal microbiota in a healthy state is limited in diversity, with *Lactobacillus* species predominating. Various *Lactobacillus* species, including *Lactobacillus gasseri*, *Lactobacillus crispatus*, *Lactobacillus iners*, *Lactobacillus jensenii*, and *Lactobacillus vaginalis*, play a defensive role in preventing pathogens from taking hold in the vagina[4,5]. Lactic acid production results in a low pH, which can be used as a marker to track the survival of vaginal microorganisms. Furthermore, the production of bacteriocin by the vaginal microbiota inhibits the growth of several competing harmful microorganisms. The gut-vagina axis also influences the vaginal microbiota through the oestrobolome, a group of gut bacteria modified to metabolize estrogen. Dysbiosis can lead to immune and metabolic signaling changes, which may contribute to cancer-related pathophysiological changes[6].

2.2 HPV and Cervical Cancer

This section provides an overview of the role of the microbiota in preventing HPV entry and highlights how dysbiosis can promote infection. Over 220 HPV genotypes have been identified to date, with 40 capable of infecting the anogenital region. Among these, 14 HR-HPV genotypes, including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68, are linked to various human cancers. Cervical cancer is the most significant malignancy associated with HPV, and HR-HPV infection is prevalent among sexually active women[7]. Cervical lesions are categorized into CIN1, CIN2, and CIN3, with Low-grade Squamous Intraepithelial Lesion (LSIL) and High-grade Squamous Intraepithelial Lesion (HSIL) being precancerous lesions according to the Bethesda System. While HPV infection can lead to cervical cancer, other risk factors such as race, smoking, long-term hormonal and contraceptive use, multiple pregnancies, multiple sexual partners, genetic mutations, epigenetic changes, a weakened immune system, and the vaginal microbiome also play a major role.

2.3 Dysbiosis and Its Impact

Dysbiosis disrupts the homeostasis of the cervicovaginal microbiota, leading to various pathological conditions, including cancer. The impact of dysbiosis influences epithelial barrier integrity, inflammation, and other hallmarks of cancer development. HPV is prevented from entering the host cell through mucus production and thickening of the epithelium. Studies have shown that the oestrobolome can adversely affect the composition of the vaginal microbiome due to decreased gut microbiota diversity. *Lactobacillus* species primarily defend the female reproductive system by competing for adhesion to the vaginal epithelium, inhibiting pathogen migration, preventing pathogen growth through acid production, promoting autophagy in infected cells, modulating local defense, and eliminating infections[8,9,10]. The vaginal microbiota's diversity is significantly altered by HPV infection, which increases the anaerobic bacteria *Prevotella* and *Sneathia* and decreases *Lactobacillus*, *Gardnerella*, and *Atopobium*. In the end, severity of CIN and CC is increased. Numerous studies have reported the importance of the vaginal microbiota and discovered that reducing the amount of Lactobacillus species, which predominate in the vagina, can significantly increase the persistence of HPV infection and its eventual progression into cancerous outcomes. This finding supports the beneficial

role of *Lactobacillus* species, so as to prevent HPV persistence[10,11].

Several factors, including race, menstrual cycle-related hormonal changes, age, pregnancy, vaginal douching, sexual activity, and antibiotic usage, can influence the composition of the vaginal microbiota. One significant factor influencing vaginal microbiota composition is ethnicity[12]. Significantly, research indicates that the production of cytokines linked to cancer, including Macrophage Inflammatory Protein-1 Beta (MIP-1β), Regulated upon Activation, Normal T cell Expressed and Secreted (RANTES), Interferon-gamma-induced Protein 10 (IP-10), Interleukin-2 (IL-2), Interleukin-4 (IL-4), Fms-like Tyrosine Kinase 3 Ligand (Flt-3L), and CD40L, may be influenced by the makeup of the vaginal microbiota. This is due to the presence of these cytokines that are significantly reduced in vaginas with a *lactobacilli*-dominant microenvironment. Besides, the vaginal metabolites have a direct impact on inflammation and susceptibility to vaginal diseases. However, this has yet not been used as biomarkers to determine the association between HPV infection and CC.

The most prevalent vaginal disease in women of reproductive age, Bacterial Vaginosis (BV), represents a form of dysbiosis and is characterized by an imbalance and an increase in diversity of microbiota[13-15]. BV is associated with various symptoms and complications, including an elevated risk of sexually transmitted infections like Herpes simplex Virus (HSV-2), HPV, and HIV[16,17]. Studies have indicated an association between increasing vaginal microbiota diversity and advancing CIN disease severity, suggesting a potential role in regulating viral persistence and the progression of the disease. Smoking has been identified as a significant risk factor for BV, likely due to its anti-estrogenic effects[18-22]. A study done by Lee et al. in 2013 reported higher levels of pathogenic microbes namely *Anaerococcus tetradius*, *Sneathia sanguinegens*, and *Peptostreptococcus anaerobius* in patients with high-grade CIN than low-grade CIN patients[13]. The vaginal microenvironment may become more colonized by the fungal community due to the lower quantity of *Lactobacillus,* and as a result, the growth of *Lactobacilli* is inhibited. Present study also discovered fungal biomarkers, such as *Malassezia* for high-risk HPV infections and *Saccharomyces* and *Sporidiobolaceae* for Atypical Squamous Cells of Undetermined Significance (ASCUS)[23,24].

In one study, the treatment of an HPV 16-infected cervical cell line with *Bifidobacterium adolescentis* SPM1005-A led to reduced synthesis of E6 and E7 mRNA, suggesting the potential of *Bifidobacterium adolescentis* SPM1005-A as a unique therapeutic agent for virally tarnsformed cells[25-27]. Cancer therapies can impact the microbiota, or microbiota composition can influence the effectiveness and side effects of cancer treatments, as well as the quality of life after treatment[23,24]. Vaginal toxic effects of the treatment of CC can be reduced through vaginal probiotics, probiotics and microbiome implants[19,20].

Conclusion

In conclusion, the acquisition, persistence, and clearance of HPV in the human vagina are significantly influenced by the vaginal microbiota. Vaginal dysbiosis can facilitate the spread of Sexually Transmitted Infections (STIs). Additionally, HPV infection has been shown to increase the diversity of vaginal bacteria in women, thereby increasing the risk of cervical cancer. Treating vaginal dysbiosis can improve the health of the female reproductive system. Modulating the microbiome through probiotics or microbiota transplants may enhance response to cancer treatment and quality of life.

Future directions and challenges

A healthy local microenvironment especially of the vaginal microbiome can be restored through vaginal probiotics, prebiotics, biofilm disruptors, novel antimicrobials, and microbiome implants. This will decrease or the vaginal toxic effects of treatment of cervical cancer. Potential risk factors should be considered during microbiome implant with strict inclusion and exclusion criteria.

Whole-genome Next-generation Sequencing (NGS) helps in precise characterization of HPV sequences more accurately. This includes variants and subvariants. It also provides information about HPV-associated diseases such as identifying this includes information about the high-risk sublineages that are linked to cancer and specific genetic factors that influence viral persistence are identified .

Cancer screening awareness should be implemented in health education syllabus to decrease the incidence of cervical precancer changes induced by human papillomavirus. HPV vaccine for young girls (11-14) should be encouraged to generate immunity.

There is the need of more longitudinal studies that can provide insights about the contribution of vaginal microbes in the clearance of acute HPV infection. This information will further assist in the understanding of interplay between microbiota and HPV persistence, clearance, and progression to CC.

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