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The Importance of the Microbiota in Cervical Cancer Pathogenesis and Therapy

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ABSTRACT

Background. Cervical cancer remains a significant public health challenge despite advances in screening and HPV vaccination. Persistent infection with oncogenic human papillomavirus (HPV) is the primary etiological factor; however, additional components of the cervical microenvironment, including the cervicovaginal microbiota, may influence disease development.

Aim. This review aims to summarize current knowledge on the role of the cervicovaginal microbiota in cervical cancer pathogenesis and its potential clinical relevance in diagnosis, prognosis, and treatment.

Material and methods. A narrative review of the literature was conducted, focusing on studies investigating the composition, function, and clinical significance of the cervicovaginal microbiota in relation to HPV infection and cervical cancer.

Results. Under physiological conditions, the vaginal microbiota is dominated by *Lactobacillus* species, which maintain an acidic environment and provide protection against pathogenic microorganisms. Dysbiosis, characterized by reduced *Lactobacillus* abundance and increased microbial diversity, is associated with HPV persistence, chronic inflammation, and progression of precancerous lesions. Certain microorganisms, including *Lactobacillus iners*, may be associated with poorer treatment outcomes and resistance to chemoradiotherapy. Moreover, specific microbiota profiles may serve as potential diagnostic and prognostic biomarkers.

Conclusions. The cervicovaginal microbiota plays a significant role in cervical cancer pathogenesis and represents a promising target for future diagnostic and therapeutic strategies. However, further research is required to better understand microbiota–host interactions and to develop effective microbiome-based interventions.

Keywords: cervical cancer, vaginal microbiota, microbiome, HPV Virus, *Lactobacillus*

Contents:

1. Introduction

Cervical cancer remains one of the most significant public health challenges in gynecological oncology, despite advances in prevention, screening, and HPV vaccination programs [1–3].

Persistent infection with oncogenic types of human papillomavirus (HPV) is considered the primary etiological factor; however, the presence of HPV alone is insufficient for the development of intraepithelial lesions and invasive cancer, indicating the involvement of additional modifiers of the cervical microenvironment [4–7].

In recent years, increasing evidence suggests that one such factor may be the cervicovaginal microbiota, which influences the integrity of the mucosal barrier, local immune responses, and the course of chronic HPV infection [2,4,8,9].

Under physiological conditions, the vaginal microbiota is typically dominated by bacteria of the genus *Lactobacillus*, which maintain an acidic pH, produce protective metabolites, and limit colonization by potentially pathogenic microorganisms [2,9,10].

Disruption of this balance, referred to as dysbiosis, is associated with a reduction in lactic acid bacteria and an increase in microbial diversity, which may promote HPV persistence, enhance local inflammation, and contribute to the progression of precancerous lesions [1,7,8,11,12].

Studies on cervical cancer have reported an increased prevalence of bacteria associated with bacterial vaginosis, such as *Gardnerella vaginalis*, *Atopobium vaginae*, and other anaerobes, suggesting their possible role in shaping a microenvironment conducive to carcinogenesis [1,12–14].

Importantly, the role of the microbiota is not limited to disease initiation and progression. Increasing attention is being paid to its impact on treatment response, particularly to chemoradiotherapy and radiotherapy, as well as its potential role as a prognostic biomarker [15–17].

Of particular interest is the observation that the presence of specific microorganisms, including *Lactobacillus iners*, may be associated with poorer treatment response and a higher risk of disease recurrence, possibly through modulation of tumor metabolism and local immune interactions [15,16].

Concurrently, the concept of therapeutic microbiota modulation is being developed, including the use of probiotics, prebiotics, and other strategies aimed at restoring cervicovaginal eubiosis, which may support HPV clearance, reduce inflammation, and improve oncological treatment outcomes [9,18,19].

Therefore, the cervicovaginal microbiota is currently regarded not only as a passive marker of disease but also as an active component of cervical cancer pathogenesis and a potential target for novel diagnostic and therapeutic interventions [8,11,19].

The aim of this review is to present current knowledge on the composition and function of the cervicovaginal microbiota, its role in cervical cancer pathogenesis, and its potential clinical significance in prevention, diagnosis, and treatment of this disease [2,11,19].Research Objective: The objective of this study is to analyze the role of the cervicovaginal microbiota in cervical cancer development, diagnosis, and treatment. Research Problem: How does the composition of the cervicovaginal microbiota influence HPV persistence and cervical cancer progression?

2. Materials and Methods

This study is a narrative review of the literature. A comprehensive search was conducted in electronic databases, including PubMed, Scopus, and Web of Science, to identify relevant studies on the role of the cervicovaginal microbiota in cervical cancer.

The search included articles published in recent years, with particular emphasis on studies addressing microbiota composition, its role in HPV persistence, and its clinical significance in diagnosis, prognosis, and treatment.

Keywords used in the search included: "cervical cancer", "vaginal microbiota", "microbiome", "HPV", and "Lactobacillus".

Articles were selected based on relevance to the topic, scientific quality, and contribution to understanding microbiota–host interactions. Both experimental and clinical studies, as well as review articles, were included.

3. Cervicovaginal microbiota – composition and functions

The cervicovaginal microbiota constitutes a complex ecosystem of microorganisms that plays a crucial role in maintaining the homeostasis of the lower female reproductive tract [2,10].

Under physiological conditions, this environment is typically dominated by *Lactobacillus* species, which maintain a low vaginal pH through lactic acid production and inhibit colonization by pathogenic microorganisms [2,10,19].

Lactic acid bacteria are also capable of producing hydrogen peroxide, bacteriocins, and other antimicrobial metabolites, further enhancing the protective function of the microbiota [19].

These mechanisms not only inhibit pathogenic bacteria but may also limit HPV persistence by influencing local immune responses and maintaining epithelial barrier integrity [4,5].

Several community state types (CSTs) of the vaginal microbiota have been described, differing in dominant bacterial species [3,8].

The most commonly observed communities are dominated by *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus jensenii*, or *Lactobacillus iners*, although their biological properties and clinical significance may differ substantially [2].

Particular attention has been given to *Lactobacillus iners*, which, despite belonging to lactic acid bacteria, exhibits distinct functional characteristics and is often present in microbiota associated with increased

instability [15,17].

Some studies suggest that dominance of this species may be associated with increased susceptibility to microbiological imbalance and poorer treatment response in cervical cancer [15,17].

In cases of microbial imbalance, there is a reduction in *Lactobacillus* species and an increase in anaerobic microorganisms such as *Gardnerella vaginalis*, *Atopobium vaginae*, *Prevotella*, and *Sneathia* [1,8,14].

This condition, referred to as dysbiosis or bacterial vaginosis, may lead to enhanced inflammatory processes and alterations in the cervical microenvironment [8,11].

Increased vaginal microbial diversity has been repeatedly observed in women with persistent HPV infection as well as in patients with dysplasia and cervical cancer [6,7,12].

These changes may promote viral persistence through modulation of immune responses, disruption of the mucosal barrier, and production of pro-inflammatory metabolites [1,6].

Thus, the cervicovaginal microbiota is currently considered a key component of the cervical microenvironment, influencing both susceptibility to HPV infection and the progression of neoplastic processes [3,11].

4. The relationship between microbiota, HPV infection, and cervical cancer pathogenesis

Persistent infection with oncogenic HPV types is the primary etiological factor of cervical cancer; however, tumor development is influenced by multiple factors modulating the cervical microenvironment [4–6].

Recent studies indicate that the cervicovaginal microbiota may play a significant role in this process by affecting both viral persistence and local immune mechanisms [8,19].

A healthy vaginal microbiota dominated by *Lactobacillus* species exerts protective effects by maintaining low pH and producing metabolites that inhibit pathogenic microorganisms [13,19]. This acidic environment and the presence of lactic acid help maintain epithelial barrier integrity and may reduce the ability of HPV to persist in cervical epithelial cells [5,7].

Microbial imbalance, or dysbiosis, leads to decreased *Lactobacillus* abundance and increased diversity of anaerobic microorganisms [1,8].

Such conditions may promote chronic inflammation and impair mucosal barrier function, facilitating HPV persistence and increasing the risk of precancerous lesion development [7,8,12].

Molecular studies have demonstrated that women with persistent HPV infection often exhibit increased abundance of bacteria associated with bacterial vaginosis, including *Gardnerella vaginalis*, *Atopobium vaginae*, *Prevotella*, and *Sneathia* [1,14].

These microorganisms may influence the cervical microenvironment through the production of mucus-degrading enzymes, pro-inflammatory metabolites, and modulation of host immune responses [6,14].

Increased microbial diversity has also been associated with cervical dysplasia and cancer compared to healthy individuals [12].

This diversity may contribute to a pro-inflammatory microenvironment, which is a known factor promoting carcinogenesis [11].

Additionally, certain bacterial species may modulate immune responses to HPV, affecting cytokine production and immune cell activity, thereby facilitating viral persistence and disease progression [5].

Particular attention has been paid to *Lactobacillus iners*, which is frequently found in unstable vaginal microbiota and dysbiotic states. Some studies suggest that its presence may be associated with increased susceptibility to HPV infection and tumor microenvironment alterations influencing disease progression [15,17].

Therefore, the cervicovaginal microbiota is increasingly recognized as a key factor influencing both HPV infection and the progression of cervical cancer [3,19].

5. The role of microbiota in diagnosis and prognosis of cervical cancer

In recent years, there has been growing interest in the use of the cervicovaginal microbiota as a potential diagnostic and prognostic tool in cervical cancer [2,19].

Advances in microbiome sequencing technologies have enabled a more detailed characterization of the microbial composition of the cervical environment and its alterations in neoplastic diseases. Studies indicate that specific microbial profiles may be associated with different stages of cervical disease progression, from HPV infection through cervical intraepithelial neoplasia to invasive cancer [1,14].

Patients with more advanced disease often exhibit increased microbial diversity and reduced abundance of *Lactobacillus* species. Higher microbial diversity has been identified as a potential marker of pathological changes and is associated with cervical cancer and advanced precancerous lesions [8,12].

Beyond diagnostic value, the microbiota may also influence prognosis. Some studies suggest that tumor microbiome composition may affect response to oncological treatments, including radiotherapy and chemoradiotherapy [16].

In particular, the presence of *Lactobacillus iners* has been linked to treatment response through modulation of tumor metabolism. It has been shown that these bacteria may contribute to chemoradiotherapy resistance via lactate-related metabolic pathways [17].

Moreover, the intratumoral microbiome may serve as a potential biomarker of treatment response. Microbial analyses indicate that the presence of specific microorganisms in tumor tissue may correlate with treatment efficacy and clinical outcomes [16].

Thus, analysis of the cervicovaginal microbiota and tumor microbiome may complement existing diagnostic and prognostic tools in cervical cancer [3,9].

6. Therapeutic potential of microbiota modulation in cervical cancer

An increasing number of studies suggest that the cervicovaginal microbiota may represent a potential target for novel therapeutic strategies in cervical cancer [3,19].

Microbial imbalance (dysbiosis) may promote HPV persistence and disease progression; therefore, restoration of a healthy microbiota may be beneficial in prevention and treatment [5,8].

One of the most promising approaches involves the use of probiotics containing *Lactobacillus* species. These microorganisms may help restore physiological vaginal microbiota through the production of lactic acid, hydrogen peroxide, and bacteriocins. Studies have shown that *Lactobacillus* strains isolated from healthy women can inhibit the growth of pathogens associated with bacterial vaginosis and cervical cancer [9,19].

In addition, probiotics may modulate host immune responses, potentially enhancing HPV clearance and reducing disease progression [5,18].

The microbiota may also influence the effectiveness of oncological treatments by modulating metabolic processes and tumor–immune interactions.Notably, *Lactobacillus iners* has been associated with metabolic alterations contributing to chemoradiotherapy resistance [16,17].

Future therapeutic strategies may include not only probiotics but also prebiotics, synbiotics, and advanced microbiome-targeting approaches [3,19].

7. Discussion

The present review highlights the significant role of the cervicovaginal microbiota as a key modifier of cervical cancer pathogenesis. Although persistent infection with oncogenic HPV

remains the primary etiological factor, the analyzed data indicate that additional elements of the cervical microenvironment, particularly the microbiota, play an essential role in disease development and progression.

The findings summarized in this study consistently demonstrate that a Lactobacillus-dominated microbiota exerts a protective effect by maintaining low vaginal pH, supporting epithelial barrier integrity, and modulating local immune responses. In contrast, dysbiosis, characterized by reduced Lactobacillus abundance and increased microbial diversity, appears to promote HPV persistence, chronic inflammation, and progression of precancerous lesions. These observations support the concept that microbiota composition is not only a marker of vaginal health but also an active participant in carcinogenic processes.

Particular attention should be given to the role of specific bacterial species, especially Lactobacillus iners, which has been associated with microbiota instability and unfavorable clinical outcomes. The presence of such microorganisms may influence tumor metabolism, immune responses, and treatment effectiveness, suggesting a more complex interaction between host, microbiota, and cancer biology than previously assumed.

The reviewed literature also emphasizes the growing importance of microbiota in the diagnostic and prognostic assessment of cervical cancer. Increased microbial diversity and specific microbial profiles have been associated with disease severity and may serve as potential biomarkers for identifying patients at higher risk of progression or poor therapeutic response. This highlights the potential of microbiome-based approaches as complementary tools in clinical practice.

Moreover, the therapeutic potential of microbiota modulation represents a promising direction for future research. Strategies such as the use of probiotics, prebiotics, and other microbiome-targeted interventions may contribute to restoring eubiosis, enhancing HPV clearance, and improving treatment outcomes. However, current evidence remains limited, and further well-designed clinical studies are necessary to establish standardized and effective therapeutic protocols.

This study has several limitations. As a narrative review, it is subject to potential selection bias, and the included studies differ in methodology, population characteristics, and analytical

approaches. These factors may affect the comparability of results and limit the generalizability of conclusions.

In summary, the cervicovaginal microbiota appears to play a crucial role in cervical cancer pathogenesis, influencing both disease development and response to treatment. A better understanding of microbiota–host interactions may contribute to the development of more precise diagnostic tools and innovative therapeutic strategies in the future.

8. Conclusions

The cervicovaginal microbiota has become an important focus of research in cervical cancer pathogenesis.

Growing evidence indicates that microbial composition and balance play a significant role in disease development [2,3,19].

A healthy *Lactobacillus*-dominated microbiota provides protective functions, while dysbiosis promotes HPV persistence and disease progression [7,8,12].

The microbiota may influence not only infection risk but also disease progression and treatment outcomes [5,6].

It may also serve as a diagnostic and prognostic biomarker and a target for novel therapeutic strategies. Further research is required to better understand microbiota–HPV–host interactions and to develop effective microbiome-based interventions [3,8,19].

Disclosure

Author Contributions

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