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Research progress on the association between vaginal *Lactobacillus iners* and cervical cancer

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Abstract. Persistent infection with high-risk Human Papillomavirus (hrHPV) is the central etiological factor in cervical cancer, while the host vaginal microenvironment plays a critical role in disease progression. *Lactobacillus iners* is one of the most widely distributed lactobacilli in the vagina. Because of its unique biological features, including exclusive production of L-lactic acid and a small genome, it occupies a transitional state within the vaginal ecosystem. Recent studies have shown that *Lactobacillus iners* (*L. iners*) plays dual and paradoxical roles in cervical carcinogenesis and progression. In the vaginal microenvironment, *L. iners* is associated with persistent hrHPV infection and an increased risk of Cervical Intraepithelial Neoplasia (CIN) progression; its protective effects are limited and often coexist with unfavorable inflammatory states. In contrast, within the tumor microenvironment, intratumoral colonization by *L. iners* can markedly increase L-lactate production, induce chemoradiotherapy resistance in tumor cells, and serve as an independent risk factor for poor prognosis. This review systematically summarizes the biological characteristics of *L. iners*, its roles and mechanisms in cervical cancer initiation, progression, and treatment resistance, and its translational value as a novel biomarker and potential therapeutic target. Current controversies, limitations, and future directions are also discussed.

Keywords: cervical cancer, vaginal microenvironment, tumor microenvironment, *Lactobacillus iners*

1. Introduction

Cervical cancer is one of the most common malignancies among women worldwide. Persistent infection with high-risk Human Papillomavirus (hrHPV) is a necessary but not sufficient condition for cervical carcinogenesis. HPV DNA can be detected in 99.7% of cervical cancer tissues; however, 85%-90% of hrHPV infections are naturally cleared, and only 10%-15% develop into persistent infection and subsequently progress to Cervical Intraepithelial Neoplasia (CIN) and invasive cancer [1]. These observations indicate that host genetic background, immune function, and the local microenvironment are key determinants of disease outcome.

The vaginal microbiota is a core ecological barrier of the female reproductive tract. Under healthy conditions, *Lactobacillus* spp. are predominant and maintain an acidic environment through acid production, hydrogen peroxide generation, and bacteriocin secretion, thereby inhibiting pathogen colonization [2]. Lactobacilli were traditionally considered uniformly protective, but recent evidence has confirmed marked

functional differences among *Lactobacillus* species. Among them, *Lactobacillus iners* is one of the most prevalent vaginal lactobacilli among women of reproductive age worldwide. However, it has a small genome, depends heavily on host-derived nutrients, produces only L-lactic acid, lacks hydrogen peroxide synthesis capacity, and shows Gram-variable staining. During microbial dysbiosis, it can coexist with pathogenic bacteria and therefore exhibits an intermediate-state phenotype [3].

An increasing number of studies suggest that *L. iners* has complex and contradictory roles in the initiation, progression, and treatment response of cervical cancer. Its metabolite L-lactic acid may inhibit cervical cancer cell proliferation in the vaginal microenvironment; however, when *L. iners* colonizes the tumor microenvironment at high abundance, it can mediate chemoradiotherapy resistance and shorten recurrence-free survival and overall survival [4]. In addition, *L. iners* is associated with reduced hrHPV clearance, CIN progression, Bacterial Vaginosis (BV), and other adverse reproductive health outcomes. At present, the causal relationship and molecular mechanisms linking *L. iners* to cervical cancer remain unclear. Ethnic differences, strain heterogeneity, and microecological interactions also limit clinical translation. Based on current evidence, this review systematically summarizes the biological features of *L. iners* and its association with cervical cancer, providing a basis for microecological screening, prognostic assessment, and targeted therapy in cervical cancer.

2. Biological characteristics and ecological niche of *L. iners*

L. iners is among the most common vaginal colonizers in women of reproductive age. Within the Lactobacillus genus, its biological characteristics exhibit a typical pattern of genome reduction, specialized metabolism, and dual functionality, which gives it a unique ecological niche in the vaginal microenvironment. At the genomic level, *L. iners* has one of the smallest known genomes among lactobacilli, approximately 1.3 Mbp and encoding about 2,300 genes, nearly half the size of the *L. crispatus* genome. This genome reduction mainly results from large-scale gene loss, including the absence of the D-lactate dehydrogenase gene, which causes *L. iners* to produce only L-lactic acid. Morphologically, its cell wall peptidoglycan layer is extremely thin, leading to Gram-variable staining; it can be identified with the aid of transmission electron microscopy. Although this structure may contribute to clinical misclassification, it also enables efficient material exchange. In terms of metabolism, the very small genome limits the abundance of metabolic enzymes, restricts carbohydrate fermentation capacity, and makes *L. iners* highly dependent on exogenous amino acids and host-derived nutrients, for example through hemolysin-mediated membrane perforation. These features indicate a strong host-associated and parasitic tendency. Such intrinsic metabolic defects directly determine its ecological role in the vaginal microbiome. In the classification of Community-State Types (CSTs), the *L. iners*-dominated CST III is regarded as a typical transitional state. Unlike CST I, which is dominated by *L. crispatus* and characterized by strong acid production and high stability, or CST IV, which is dominated by anaerobes and reflects dysbiosis, CST III has low community stability because *L. iners* has insufficient acidification capacity and high sensitivity to environmental fluctuations. It may occur transiently in healthy individuals, but it is also frequently observed during recovery from BV or in the early phase of dysbiosis and can readily shift toward the high-diversity CST IV state [3]. Therefore, *L. iners* is not a stable microecological guardian in the traditional sense; rather, it is an opportunistic core bacterium with both colonization resistance and conditional pathogenic potential. This ecological oscillation, determined by its genomic and metabolic properties, provides a mechanistic basis for understanding its contradictory behavior in cervical cancer, including its involvement in HPV clearance failure and tumor microenvironment-mediated drug resistance.

3. Complex roles of *L. iners* in cervical cancer initiation and progression

In the cervicovaginal microbiota, *L. iners* is not a typical protective *Lactobacillus* species. Its role remains controversial and is generally more closely associated with adverse reproductive and tumor-related outcomes. The paradoxical nature of its biological behavior is rooted in its metabolic defects, unstable ecological niche, and complex interactions with the host and pathogens, making it a key link between vaginal microecological dysbiosis and cervical cancer development.

3.1. Limited protective effects and academic controversies of *L. iners*

Under ideal microecological conditions, *L. iners* may exert partial barrier functions, but its protective efficacy is significantly weaker than that of protective lactobacilli such as *L. crispatus* and is accompanied by prominent functional deficiencies. Its potential protective effects are mainly reflected in three aspects. First, by synthesizing L-lactic acid, it can help maintain vaginal acidity and, to some extent, inhibit colonization by exogenous pathogens; L-lactic acid also has stereochemistry-dependent antiviral activity [3]. Second, *L. iners* can secrete the bacteriocin inecin L, which has significant antimicrobial activity against common vaginal pathogens and drug-resistant strains, including Gardnerella vaginalis and group B Streptococcus [5]. Third, it has strong epithelial adhesion capacity and can competitively block pathogen binding sites [3]. In addition, *L. iners* is highly adaptable to environmental changes and may become dominant during menstruation, after antimicrobial intervention, or during mild microecological imbalance.

However, these protective effects have significant limitations and remain widely debated. Four core deficiencies are particularly important. First, *L. iners* lacks hydrogen peroxide synthesis capacity and therefore cannot inhibit anaerobic bacterial proliferation through the pyruvate oxidation pathway, which is a key functional difference from protective lactobacilli. Second, its ability to maintain acidity is insufficient because it produces only L-lactic acid and lacks the D-lactic acid synthesis pathway. Studies have shown that D-lactic acid is more effective in inhibiting bacteria, increasing cervical mucus viscosity, and trapping viral particles. Third, *L. iners* may indirectly promote viral invasion. Exclusive production of L-lactic acid can cause an imbalance in the L/D lactate ratio, activate matrix metalloproteinases, disrupt cervical epithelial integrity, and facilitate HPV entry into basal cells. Fourth, *L. iners*-dominated microenvironments are highly associated with local proinflammatory states, often accompanied by elevated levels of IL-1α, IL-18, TNF-α, and other proinflammatory factors, which may initiate chronic inflammation and weaken mucosal defense [3]. Meanwhile, *L. iners* shows a significant negative correlation with *L. crispatus* and has low colonization stability, existing mainly as a transitional state [6]. In the healthy vagina, its activity is limited, and it cannot effectively resist pathogen invasion; in some contexts, it may even indirectly increase infection risk. Therefore, *L. iners* should not be classified as a uniformly beneficial bacterium. Its protective effect is context dependent and unstable.

3.2. Association between *L. iners* and adverse tumor outcomes and potential mechanisms

A large body of clinical and basic research has shown that *L. iners* is an important risk factor for persistent hrHPV infection, CIN progression, invasive cervical cancer, and multiple reproductive tract infections. By disrupting the mucosal barrier, shaping a proinflammatory microenvironment, and regulating oncogenic signaling pathways, *L. iners* may participate in the entire process of cervical carcinogenesis.

At the level of persistent hrHPV infection and CIN progression, women with *L. iners*-dominant microbiota have a three- to five-fold higher risk of HPV infection than women with *L. crispatus*-dominant microbiota. The probability of hrHPV progression, cervical dysplasia, or cancer is also two to three times higher.

Longitudinal cohort studies have confirmed that the relative abundance of *L. iners* is negatively correlated with HPV clearance within 12 months [7]. Persistent HPV infection can further reduce Lactobacillus abundance and promote a shift from CST III to CST IV, accompanied by enrichment of anaerobes such as *Prevotella* and *Peptostreptococcus*, forming a vicious cycle of microbial dysbiosis, HPV persistence, and lesion progression. At the same time, *L. iners* can reduce the function of the cervicovaginal mucus barrier and increase epithelial permeability, creating favorable conditions for HPV invasion and persistent infection. Increased abundance of *L. iners* is directly associated with CIN grade escalation and malignant transformation risk.

In terms of synergistic reproductive tract infections, *L. iners* is closely associated with BV, *Chlamydia trachomatis* infection, and vulvovaginal candidiasis. It is currently considered the only *Lactobacillus* species known to coexist with Gardnerella vaginalis and may even enhance pathogen adhesion, promote biofilm formation, and reduce antibiotic efficacy. Infection states such as BV further damage the cervical mucosal barrier, upregulate mucin-degrading and epithelial-degrading enzymes, and accelerate HPV invasion and immune escape. L-lactic acid produced by *L. iners* can disrupt cervical structure through the EMMPRIN-MMP-8 pathway, increase the risk of ascending pathogen infection, and indirectly promote the development of precancerous lesions [3].

At the molecular level, *L. iners*-mediated vaginal microenvironmental dysbiosis may promote malignant transformation through multiple pathways: (1) construction of a proinflammatory and immunosuppressive microenvironment, in which sustained activation of proinflammatory factors can upregulate HPV E6/E7 oncogene expression and suppress antitumor immune responses [8]; (2) activation of the TLR9 inflammatory pathway, where dysbiosis increases unmethylated CpG motifs that bind highly expressed TLR9 receptors, triggering the release of inflammatory factors and accelerating cell proliferation and malignant transformation [9]; and (3) involvement in metabolic and signaling remodeling, altering local amino acid and ketone body metabolism and affecting cell proliferation and DNA damage repair, thereby providing a metabolic basis for tumorigenesis [1].

Notably, high abundance of *L. iners* has been observed in some healthy populations and pregnant women, suggesting that strain-level genetic heterogeneity may lead to functional differentiation. A small number of strains may inhibit pathogens and maintain microecological balance [6], which is an important reason for current inconsistencies in research conclusions. Overall, however, within the risk framework of cervical cancer initiation and progression, adverse associations of *L. iners* predominate. Its ecological instability and metabolic defects jointly determine its central role as a marker of microecological dysbiosis and a potential promoter of lesion progression.

4. Key role of *L. iners* in treatment resistance and prognosis of cervical cancer

4.1. Intratumoral enrichment of *L. iners* as an independent risk factor for chemoradiotherapy resistance and poor prognosis

The effect of *L. iners* on cervical cancer cells is highly microenvironment dependent. In the normal vaginal microenvironment, its metabolite lactate can promote core fucosylation of epithelial cells through the lactate-GPR81-Wnt pathway, inhibit cervical cancer cell proliferation and migration, and exert a potential tumor-suppressive effect [10]. However, when *L. iners* colonizes the cervical tumor microenvironment, its biological function changes markedly, becoming a key risk factor that drives chemoradiotherapy resistance and shortens patient survival. Multiple clinical cohort studies have confirmed that intratumoral abundance of *L. iners* is closely associated with the efficacy and prognosis of Concurrent Chemoradiotherapy (CCRT) in cervical

cancer. Using 16S rRNA sequencing to analyze the cervical cancer tumor microbiome, Colbert et al. found that high colonization by *L. iners* was significantly associated with nonresponse to chemoradiotherapy, and its abundance was negatively correlated with recurrence-free survival. After adjusting for confounding factors such as tumor stage and gut microbiome diversity, multivariable Cox proportional hazards models further confirmed that high intratumoral abundance of *L. iners* was an independent predictor of shortened recurrence-free survival and overall survival, whereas other tumor-resident bacteria and microbial diversity parameters were not independently associated with prognosis. This study minimized interference from microecological background and clinical stage and established a robust association between *L. iners*, treatment resistance, and poor prognosis in cervical cancer. In addition, the abundance of *L. iners* was significantly increased in the vagina and tumor tissues of patients with recurrent cervical cancer, suggesting that it may serve as a microbial biomarker for predicting recurrence risk before chemoradiotherapy [4]. Unlike its transitional function in the vagina, intratumoral *L. iners* directly reduces the sensitivity of cervical cancer cells to radiation and chemotherapy through specific metabolic and signaling mechanisms, making it a key microecological factor that limits therapeutic efficacy.

4.2. Core mechanism by which *L. iners* mediates chemoradiotherapy resistance: the L-lactate metabolic axis and signaling remodeling

The core effector molecule mediating treatment resistance by *L. iners* is its specific metabolic product, L-lactic acid. This metabolic feature is determined by its unique genome and undergoes further adaptive evolution in the tumor microenvironment, forming a regulatory cascade of genomic features, metabolic advantage, and signaling remodeling, ultimately conferring strong chemoradiotherapy tolerance on cervical cancer cells.

4.3. Genomic features and lactate metabolic reprogramming of tumor-derived *L. iners*

L. iners lacks the D-LDH gene and therefore cannot synthesize D-lactic acid, making it an exclusive L-lactic acid-producing bacterium. This genetic deficiency constitutes its metabolic basis. Compared with Normal vaginal *L. iners* strains (NC-*L. iners*), Cervical Cancer-derived *L. iners* strains (CC-*L. iners*) exhibit significant adaptive genomic changes. Approximately 81% of genes are shared by the two strain types, whereas CC-*L. iners*-specific genes account for as much as 16%, far higher than the 2% observed in NC-*L. iners*. A key difference is that CC-*L. iners* carries an additional lacG gene encoding 6-phospho-β-galactosidase, which enables efficient utilization of lactose and galactose through the Leloir pathway and the tagatose-6-phosphate pathway. This significantly enhances galactose metabolic flux and thereby promotes substantial L-lactic acid production. Untargeted metabolomics has shown that galactose metabolism is the only upregulated metabolic pathway in CC-*L. iners*, confirming the specific enhancement of its lactate-synthesizing capacity [4].

This tumor-derived metabolic reprogramming enables *L. iners* to continuously secrete high concentrations of L-lactic acid within the tumor microenvironment. Inactivated bacteria lack this effect, indicating that active L-lactic acid synthesis by live bacteria is necessary for mediating resistance. In vitro experiments have confirmed that cell-free supernatants of *L. iners* can induce significant resistance of cervical cancer organoids to radiotherapy and CCRT, and L-lactic acid alone can fully reproduce this resistance phenotype, directly establishing L-lactic acid as the core effector molecule mediating chemoradiotherapy resistance [4].

4.4. L-lactic acid regulates tumor cell signaling pathways and systematically mediates chemoradiotherapy resistance

L-lactic acid reduces the sensitivity of cervical cancer cells to chemoradiotherapy from multiple dimensions by regulating hypoxia, oxidative stress, DNA damage repair, and cell-cycle-related pathways.

4.4.1. Activation of HIF-1 signaling and establishment of a hypoxia-tolerant phenotype

L-lactic acid can significantly stabilize Hypoxia-Inducible Factor 1 (HIF-1), upregulate transcription of its downstream target genes, and mimic a hypoxic microenvironment (Figure 1). Activation of the HIF-1 pathway further reduces the sensitivity of tumor cells to radiation-induced oxidative injury and enhances cell survival, which is one of the core mechanisms of radiotherapy resistance.

4.4.2. Disruption of reactive oxygen species homeostasis and attenuation of radiation damage

CC-*L. iners* can increase ROS levels in the tumor microenvironment while activating antioxidant response pathways, placing cancer cells in a preadapted oxidative stress state (Figure 1). This significantly reduces radiation-induced ROS accumulation and oxidative DNA damage, thereby weakening the cytotoxic effects of radiotherapy.

4.4.3. Suppression of DNA damage repair and checkpoint function and maintenance of genomic instability

Treatment with *L. iners* supernatant can significantly downregulate DNA damage response pathways, DNA replication initiation programs, G2/M and S-phase checkpoints (Figure 1), and E2F transcriptional targets, impairing cellular repair of DNA double-strand breaks induced by chemoradiotherapy. Although this checkpoint suppression aggravates genomic instability, it enhances the tolerance of cancer cells to lethal injury and promotes survival and clonal expansion.

4.4.4. Upregulation of pro-survival and invasion signaling pathways to accelerate post-treatment repair

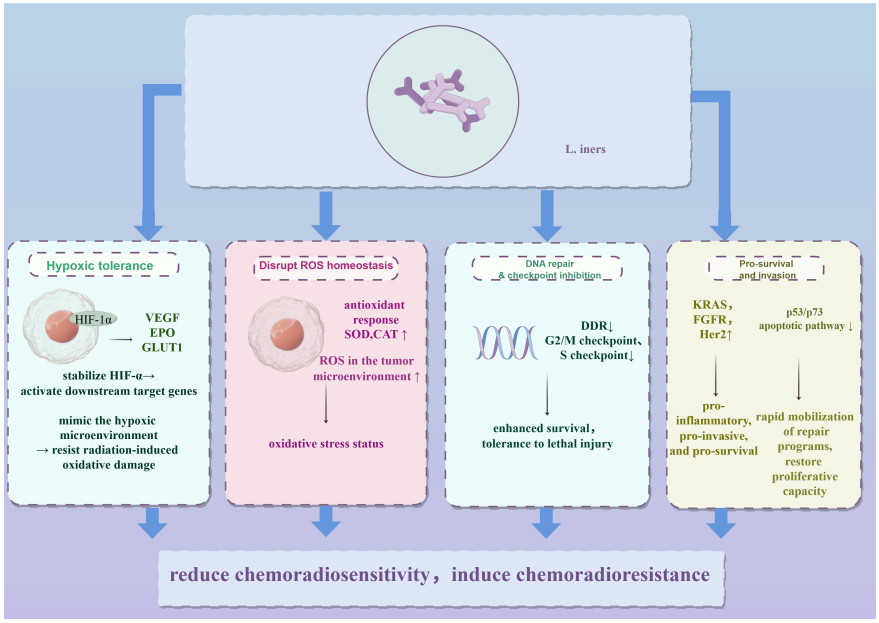

Figure 1. L-lactic acid regulates tumor cell pathways and systematically mediates chemoradiotherapy resistance

L-lactic acid can induce G2/M-phase arrest, upregulate pro-invasive, proinflammatory, and pro-survival signals such as NF-κB, KRAS, FGFR, and HER2/ERBB2, and suppress p53/p73-dependent apoptotic pathways. These changes help cancer cells rapidly initiate repair programs after therapeutic injury and regain proliferative capacity (Figure 1).

5. *L. iners* as a biomarker for cervical diseases

L. iners may serve as a predictive indicator for BV onset and intermediate vaginal states. However, because the vaginal microbiota is complex and *L. iners* is widely distributed, its value as an independent biomarker for cervical cancer is limited. Predictive models constructed by combining *L. iners* with other bacterial species or metabolites have greater clinical significance. A study of reproductive-age women in Xinjiang, China, suggested that *L. iners*-dominant colonization combined with the presence of Shuttleworthia may represent a characteristic microecological pattern in HPV-infected women with Low-grade Squamous Intraepithelial Lesions (LSIL) [11]. Oh et al. reported that the absence of *L. crispatus*, dominance of Atopobium vaginae, and secondary infection with *G. vaginalis* and *L. iners* can increase the risk of Low-Grade and High-Grade Squamous Intraepithelial Lesions (LGSIL/HGSIL) by approximately six-fold, while combinations involving *L. iners* and *Atopobium* spp. may serve as signature indicators of severe cervical lesions [12]. Using a random forest model, Lee et al. identified a 33-bacterium signature that could efficiently distinguish CIN2+ from CIN1- (AUC = 0.952), with *L. iners* being the most influential predictor [13]. In terms of prognosis, a 2023 study by Colbert et al. demonstrated that intratumoral colonization by *L. iners* significantly shortened recurrence-free survival in patients with locally advanced cervical cancer receiving chemoradiotherapy. By producing lactate, *L. iners* mediated chemoradiotherapy resistance and served as an independent predictor of poor prognosis [4]. Related markers have also been associated with shorter recurrence-free survival in other tumors, such as lung cancer and colorectal cancer, suggesting a potential pan-cancer prognostic value that warrants further investigation.

6. *L. iners* as a potential target for prevention and therapy

The position of *L. iners* in the cervicovaginal microenvironment remains controversial. Clinically, *L. crispatus*-dominant colonization is currently more often regarded as a feature of a healthy microenvironment. The vaginal microbiota is influenced by multiple factors, including diet, hormone levels, and sexual behavior. Healthy dietary patterns, such as reducing alcohol and animal protein intake and increasing alpha-linolenic acid intake, together with behavioral interventions, may promote the growth of *L. crispatus* and prevent *L. iners* from becoming dominant, thereby helping maintain vaginal microecological balance and reduce gynecological disease risk. Intervention strategies targeting *L. iners* have shown potential in related diseases. In the treatment of BV, the K7 bacteriocin can specifically inhibit *L. iners* with an inhibition rate of 100% while having minimal effects on other beneficial lactobacilli. Combined use with metronidazole can completely inhibit the co-growth of *L. iners* and *G. vaginalis* without affecting *L. crispatus* colonization. The combination of cysteine inhibitors and metronidazole can promote *L. crispatus* growth and inhibit *L. iners* proliferation, offering a new strategy for the treatment of BV and hrHPV infection [14]. In the field of cervical cancer, targeting *L. iners* and its signaling network may optimize combined treatment strategies. Phage therapy may reduce tumor lactate and restore the sensitivity of cancer cells to cisplatin. Targeting L-lactate metabolism in *L. iners* with LDH inhibitors such as FX11 can reduce L-lactate production and enhance therapeutic efficacy when combined with radiotherapy. Engineered bacteria, such as *Escherichia coli* Nissle

1917 expressing lactate oxidase, may also decrease intratumoral lactate and improve chemoradiotherapy outcomes, showing promising clinical potential [15].

7. Conclusion and perspective

Existing studies have preliminarily revealed the complex roles of *L. iners* in cervical cancer initiation, progression, and treatment resistance. In the vaginal microenvironment, *L. iners* often acts as a marker of microecological dysbiosis, whereas in the tumor microenvironment it is a key factor mediating poor prognosis. Targeted intervention strategies related to *L. iners* have also shown potential for clinical application.

Nevertheless, several limitations remain. First, most studies are still limited to correlation analyses, and the causal relationship and specific molecular mechanisms linking *L. iners* to cervical cancer have not been fully clarified. Second, detection methods are not standardized, and the generalizability of *L. iners*-based biomarkers requires validation in large multicenter clinical cohorts. Third, the influence of ethnicity, lifestyle, and other factors on the cervicovaginal microbiota and cervical cancer risk has not been sufficiently considered. Fourth, strain-level heterogeneity and interactions between *L. iners* and other microbial taxa have often been overlooked; studies focusing on a single species cannot fully reflect the overall characteristics of the microbiota. Fifth, clinical translation still faces obstacles such as optimization of detection methods and safety validation of intervention strategies. Future research should first clarify the causal mechanisms by which *L. iners* participates in cervical cancer initiation and progression. It should then standardize testing procedures and validate biomarker performance across diverse populations. Personalized prevention strategies should be developed by integrating ethnic background and individual lifestyle differences, while strain heterogeneity and microbial interaction networks should be systematically analyzed. In addition, multi-omics approaches are needed to map the cervical microecological network and advance clinical trials of intervention strategies, thereby promoting translation from basic research to clinical practice and providing support for precision prevention and treatment of cervical diseases to protect female reproductive health.

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