Thieme

Dysbiotic Co-Factors in Cervical Cancer. How the Microbiome Influences the Development of Cervical Intraepithelial Neoplasia (CIN)

Dysbiotische Co-Faktoren des Zervixkarzinoms. Der Einfluss des Mikrobioms auf die Entstehung zervikaler intraepithelialer Neoplasien (CIN)

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ABSTRACT

Human papillomavirus (HPV) infection is a necessary but not sufficient condition for the development of cervical cancer. The dysbiotic shift in the cervicovaginal microbiome appears to be a major co-factor in carcinogenesis. New analytical methods, such as next-generation sequencing (NGS), can be used to detect all of the vaginal microorganisms present and therefore identify individual therapeutic options. The relationship of bacterial vaginosis and carcinogenesis, as well as possible indications for the use of microbiome analysis, will be discussed.

ZUSAMMENFASSUNG

Die Infektion mit humanen Papillomaviren (HPV) ist für die Entstehung des Zervixkarzinoms eine notwendige, aber nicht hinreichende Bedingung. Die dysbiotische Verschiebung des zervikovaginalen Mikrobioms stellt offensichtlich einen wesentlichen Co-Faktor in der Karzinogenese dar. Neue Analysemethoden, wie das Next-Generation-Sequencing (NGS), erlauben die Bestimmung der Gesamtheit der vaginalen Mikroorganismen und damit die Ableitung individueller Therapieoptionen. Der Zusammenhang von bakterieller Vaginose und Karzinogenese sowie mögliche Indikationen für den Einsatz der Mikrobiom-Analyse werden diskutiert.

Introduction

Following the introduction of organized cancer screening for cervical carcinoma ("CC") in 2020, a so-called co-test is performed on all women from the age of 35 every three years as part of cervical cancer screening. This means that a cervical smear sample is assessed cytologically and laboratory testing is performed for the genetic detection of the various high-risk types of human papillomavirus (HPV). Annual cytology screening continues to be performed in women under 35 years of age who are screened. In all women with cytological findings of confirmed or suspected high-grade dysplasia, a colposcopy is mandatory, irrespective of the HPV test result. In the majority of cases, tissue is removed from the cervix for histological examination [1].

Genetic material, particularly from high-risk types of HPV, is detectable in tumor tissue in almost all cases of cervical carcinoma. In this context, HPV-mediated carcinogenesis is mainly induced by the two viral oncoproteins E6 and E7. These oncoproteins drive the infected cells into an unregulated cell cycle and cause cell proliferation with the accumulation of genetic abnormalities in the epithelium [2].

However, HPV infection is not sufficient for the development of cervical cancer, because more than 90% of these infections are transient and resolve on their own (known as "clearance") [3]. Of course, other factors are required for cancer or precancer to develop in the infected epithelium. An important prerequisite is a persistent HPV infection in the mucosal epithelia for many years. In recent years, the microbiome has been shown to be another important factor in the persistence of HPV infection and the development of cervical intraepithelial neoplasia (CIN).

It is therefore useful to test the vaginal microbiome – in addition to testing for HPV – if certain clinical questions or constellations of findings arise from the cervical cancer screening examination.

Bacterial Vaginosis Predisposes to HPV Infections and CIN Lesions

It has long been known that abnormal cytological findings are more common in women with disturbed vaginal flora [4], suggesting a link between bacterial vaginosis (BV) and the development of cervical cancer. In about half of cases, a disturbance of the vaginal environment leads to symptoms such as discharge that smells like ammonia and signs of inflammation, such as redness, itching, and a burning sensation. The vaginal pH is elevated and there are characteristic "clue cells" in the smear preparation [5]. BV is the most common vaginal disease in women of childbearing age and may be associated with gynecologic and obstetric complications, for example the spread of inflammation to the upper genital tract ("pelvic inflammatory disease [PID]"), cervicitis, premature birth, and chorioamnionitis.

Although scientific studies use different criteria to diagnose BV, several meta-analyses still show a clear association between the occurrence of bacterial vaginosis and CIN lesions [6, 7]. In addition, it has also been confirmed that the prevalence of HPV is significantly higher in women with BV than in women without the disease [7].

New Technical Possibilities

It is not always easy to detect BV. In addition to microscopy, the cultivation of potential pathogens traditionally plays a major role in detecting possible pathogens with antibiotic testing (sensitivity testing) [8].

However, not all pathogens associated with BV can be grown in standard culture media. As a result, relevant microorganisms in bacterial vaginosis, such as Atopobium or Mobiluncus, usually cannot be detected. These pathogens must be detected by molecular genetic analysis, for example by means of polymerase chain reaction ("PCR").

In addition, microorganisms are cultured in conventional medical microbiology with the aim of isolating, if possible, one or more potentially pathogenic agents from the microbial colony. The growth of other remaining microbes is deliberately suppressed by the selective media used. In the process, information about other pathogens, such as the protective lactobacillus species, is usually lost.

However, culture and PCR do not in any case provide information on the relative quantitative composition of the mucosal flora, i.e. the microbiome. This is only possible through the use of next-generation sequencing (NGS), in which genes from all given microorganisms can be sequenced simultaneously. For this purpose, the microbial gene sequences obtained are compared with extensive databases, which makes it possible to determine the percentage ("abundance") of individual species.

The Vaginal Microbiome

NGS data obtained from the vaginal microbiome revealed that it is organized into so-called "community state types" (CST) [10]. Among them, four CSTs are dominated by single Lactobacillus species: L. crispatus (CST I), L. gasseri (CST II), L. iners (CST III), and L. jensenii (CST V). For example, L. crispatus dominance is associated with a healthy vaginal microbiome, high production of lactate, and the formation of protective peptides.

CST IV, on the other hand, is characterized by the extensive loss of lactobacilli, with mostly anaerobic bacteria, such as Gardnerella, Atopobium, Mobiluncus, or Prevotella being detected in larger or dominating quantities. As a result, the microbiome becomes more diverse, i.e., the lactobacilli disappear or lose their dominance and are replaced by numerous other bacterial species. This increase in diversity can be calculated mathematically and is expressed as alpha diversity or the Shannon index.

In more recent studies, this medically important group is further subdivided into A–C, depending on the predominant constellation of pathogens, although it can be assumed that there are many more subgroups [11, 12] – see ▶ **Table 1**.

▶**Table 1** Differentiation of community state type (CST) IV, according to the "Valencia" classification [11].

CST IV-A: high/moderate relative abundance of G. vaginalis and BVAV1*
CST IV-B: high/moderate relative abundance of G. vaginalis and A. vaginae
CST IV-C: low relative abundance of G. vaginalis, BVAB1*, and Lactobacillus spp., and C0: relatively similar proportion of Prevotella spp. C1: dominated by Streprococcus spp. C2: dominated by Enterococcus spp. C3: dominated by Bifidobacterium spp. C4: dominated by Staphylococcus spp.

* BVAV1: bacterial vaginosis associated bacterium 1

Loss of Lactobacillus dominance signals a medically relevant miscolonization or dysbiosis, as group IV is also associated with an altered vaginal pH and an increased Nugent score as an indication of the presence of bacterial vaginosis [10].

CST III is also medically significant because L. iners has some peculiarities: it produces only small amounts of lactate and apparently few or no protective peptides. That is why it is also called the "poisoned apple", which mostly indicates a microbiome in transition: out of or into a dysbiosis or CST IV [13].

The menstrual cycle is considered to be a significant factor in the change of the colonization type: during ovulation, CST stability is the greatest, whereas with menstruation, it decreases the most. In addition, sexual activity is a factor in microbiome change, as is hygiene behavior (alkaline soaps, etc.).

Dysbiotic Factors for Viral Persistence and the Development of CIN Lesions

The previously described association of dysbiosis or BV and HPV infection or cervical intraepithelial neoplasia (CIN) has now been substantiated and clarified by numerous robust NGS studies [6, 14].

Lactobacillus dominance apparently goes hand in hand with natural clearance of HPV. The main species found is L. crispatus [15]. In a longitudinal study, L. gasseri also showed increased clearance of HPV [16]. A lactobacillus-dominated microbiome also showed a higher likelihood of regression of CIN2 lesions in a follow-up study; slower regression was seen with lactobacillus loss, typically with an increase in BV pathogens [17]. Dominance of L. crispatus demonstrated the most rapid regression of CIN lesions [17]. Thus, while Lactobacilli are protective, Gardnerella and increased microbial diversity are associated with CIN2 progression [18]. L. iners, on the other hand, is an exception among lactobacilli: it was found in increased numbers in HPV-positive women and in women with dysplasia [19].

Thus, for both HPV infection and persistence as well as the development and progression of CIN lesions, the vaginal microbiome exhibits a typical pattern similar to that of bacterial vaginosis: Loss of Lactobacillus dominance, increased microbial diversity with evidence of typical anaerobic bacteria (CST IV)[17]; in addition, L. iners (CST III) is associated with the development of CIN lesions [19], possibly also because it indicates a transient microbiome that can cross over into CST IV [13].

Potential Mechanisms of the Vaginal Microbiome in Viral Infection and the Development of CIN Lesions

The complexity of the cervicovaginal microenvironment in HPV infection or CIN lesion is determined not only by the local microbiome but also by its interplay with the patient's epithelial and immunologic defenses.

Lactobacilli produce numerous protective peptides and metabolites. The focus is on lactic acid (lactate), which is produced by metabolizing glycogen. This inhibits the attachment and growth of pathogenic bacteria, especially BV-associated pathogens [20]. D- or L-lactate isomers are produced; the D-form is mainly produced by L. crispatus, L. jensenii, and L. gasseri, whereas the L-form is produced by L. iners and anaerobic pathogens. Thus, in patients with predominant L. iners colonization, L-lactate predominates, leading to the activation of metalloproteinase 8 (MMP8) and thereby facilitating the entry of HPV into basal keratinocytes [21]. In contrast, if L. crispatus dominates, the viscosity of the cervicovaginal mucus increases, which in turn promotes the attachment of HP viruses [20, 22].

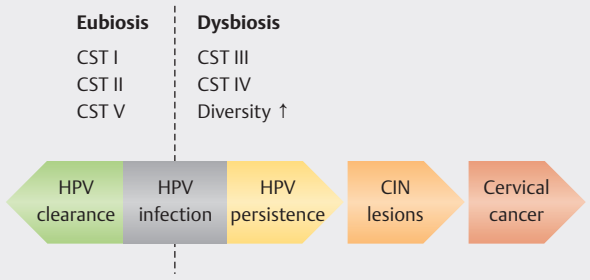
Other factors expressed by lactobacilli to defend against pathogenic bacteria are bacteriocidal and bacteriostatic peptides. Bacteriocin, for example, exerts an inhibitory effect on typical pathogens, especially Gardnerella vaginalis [20]. Hydrogen peroxide (H_2O_2) attacks bacteria such as Prevotella and Gardnerella, which themselves do not produce protective enzymes to degrade this molecule. Such mechanisms thus provide protection of the cervical epithelium and prevent pathogens such as HPV from accessing basal keratinocytes [23].

Due to the decline of lactobacilli with bacterial vaginosis or CST IV, not only do pathogenic anaerobic bacteria become predominant, but the aforementioned defense mechanisms (lactate, bacteriocin, etc.) also stop working. This allows pathogenic microorganisms to colonize the epithelium and promote inflammation through the synthesis of proinflammatory cytokines [24]. In this way, the integrity of the epithelium is damaged and the susceptibility of HPV infection is significantly increased; thus, the persistence of inflammation fosters HPV persistence. When the associated inflammation becomes chronic, this enables the development and persistence of CIN lesions and promotes their progression. In this context, the development of cervical cancer is apparently accompanied by a similar dysbiotic microbiome shift as occurs in the development of CIN lesions [14] – see ▶ **Fig. 1**.

Towards Individualized Therapy

Microbiome analysis allows not only the detection of a possible dysbiosis, but also helps to determine an individualized therapy.

In cases of severe dysbiosis or bacterial vaginosis, antibiotic therapy is often recommended [25]. This can be modified according to the prevailing spectrum of pathogens (see ▶ **Fig. 1**).



▶ **Fig. 1** Schematic representation of the influence of dysbiotic miscolonization on HPV infection, CIN progression and the development of cervical cancer. While the normal Lactobacillus-dominated vaginal microbiome (CST I, II, and V – "eubiosis") allows clearance of HPV infection, loss of Lactobacillus dominance (CST IV) – and an increase in diversity – or dominance with L. iners (CST III) are associated with persistence of HPV, development and progression of CIN lesions, and the development of cervical cancer.

In contrast to classical microbiology, microbiome analysis provides information on the percentage of individual pathogens: hence Gardnerella dominance is treated with different antibiotics than a high abundance of enterococci.

However, antibiotic therapy is associated with a high relapse rate [25]. Administration of L. crispatus after antibiotic treatment with metronidazole can significantly reduce the recurrence of bacterial vaginosis [26]. Therefore, restoration or normalization of the vaginal microbiome is considered a promising strategy. The administration of live vaginal lactobacilli (probiotics) has been shown to be effective in the treatment of bacterial vaginosis: longer treatments (1–3 months) have even been shown to be superior to antibiotics in recent meta-analyses [27]. Because L. iners indicates a transient microbiome, probiotic stabilization may be advisable in CST III, another individualized, therapeutically useful result of microbiome analysis. Other preclinical studies have demonstrated the anti-tumorigenic effects of probiotics [28]. In addition, there is also clinical evidence that probiotics promote the regression of CIN lesions [29].

Other studies have also demonstrated the efficacy of prebiotics. These are mostly carbohydrates that support the growth of beneficial microorganisms in the vagina as selectively as possible. Examples are fructo-oligosaccharides (FOS) or gluco-oligosaccharides (GOS), which promote the growth of lactobacilli, whereas G. vaginalis cannot use these sugars as an energy source [30]. Intravaginally administered GOS significantly improved the Nugent score in BV patients after metronidazole administration [23].

An interesting perspective is offered by the administration of lactoferrin, a human peptide secreted on various mucous membranes. This molecule plays an important role in fighting off bacteria as well as numerous viruses. Interestingly, lactoferrin is also active against HPV [31]. An intravaginal application study demonstrated that the composition of the microbiome changes in BV patients: there is a decline in Gardnerella and Prevotella and an increase in Lactobacilli [32].

Indication for Analyzing the Microbiome

From a clinical point of view, there are two main indications for microbiome analysis, the aim being to reduce the cancer risk by restoring the cervicovaginal flora.

The first is a **persistently positive HPV test result**, which is detected during a screening examination with the co-test in women 35 years of age and older, in cases where neither a positive smear test nor a dysplastic or malignant lesion can be detected colposcopically and/or histologically. The goal is to downregulate HPV expression in the epithelium by normalizing (through eubiosis or lactobacillus dominance) the resident bacterial flora and to prevent new infection or the development of dysplastic epithelial changes.

At the same time, it is reasonable to undertake microbiome analysis in cases of HPV-induced **low-grade epithelial lesions or equivocal findings** in women under 35 years of age where surgical treatment by excision ("conization") is not (yet) indicated. In such cases, the tendency of epithelial lesions to regress is high and current studies suggest that the elimination of existing dysbiosis is likely to have a positive preventive and protective effect. The curtailment of sometimes prolonged HPV persistence in the absence of histo- or cytomorphologic correlates, or the persistence of low-grade HPV-induced epithelial lesions may therefore shorten the surveillance period and the number of repeat colposcopies. This would improve the quality of life of the affected patients and save valuable resources for the healthcare system.

Conclusion

Persistent HPV is a necessary but not sufficient prerequisite for the development of cervical cancer. The dysbiotic shift in the vaginal microbiome appears to be a major co-factor in carcinogenesis. A systematic review of the literature and meta-analysis examined the association between cervicovaginal lactobacilli and genital high-risk HPV infections, CIN, and cervical cancer. Eleven studies with 1230 female patients were evaluated [33]. The results of this meta-analysis confirm the role of lactobacilli in preventing high-risk HPV infection and the resulting cervical preneoplasia and neoplasia.

Analysis of the vaginal microbiome by modern NGS methodology identifies the entire microbial community and the percentages of individual pathogens, which in turn assists with the selection of individualized therapy and may serve as a prophylactic measure against progressive cancerous epithelial transformation.

Conflict of Interest

The authors declare that they have no conflict of interest.

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