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Gut and oral microbiota in gynecological cancers: interaction, mechanism, and therapeutic value

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Jian Wu[1,3], Jiarui Li[2,3], Meina Yan[1] & Ze Xiang[2]

Gynecologic cancers develop from the female reproductive organs. Microbial dysbiosis in the gut and oral cavity can communicate with each other through various ways, leading to mucosal destruction, inflammatory response, genomic instability, and ultimately inducing cancer and worsening. Here, we introduce the mechanisms of interactions between gut and oral microbiota and their changes in the development of gynecologic tumors. In addition, new therapeutic approaches based on microbiota modulation are discussed.

Cancer is one of the leading causes of premature death all around the world and a huge threat to public health[1]. Due to the strong influence of demographic changes such as population aging and growth on different trends in cancer incidence in different regions, the number of cancer patients worldwide is expected to double in the next 50 years[2]. National cancer incidence rates from the GLOBOCAN database of the International Agency for Research on Cancer within the Global Cancer Observatory estimate that the six most commonly diagnosed cancers worldwide are currently: stomach, colorectal, lung, breast, cervical and prostate cancers[1], among which cervical cancer (CC) is the most common type of gynecological cancer. In addition, gynecological cancers also include endometrial cancer (EC) and ovarian cancer (OC) commonly, vaginal cancer and vulvar cancer rarely[3].

Different part of the human body (gut, skin, lungs, oral cavity) is colonized by a variety of commensal, symbiotic and pathogenic microbiota, including bacteria, archaea, fungi, protists, and viruses[4,5]. Additionally, the human microbiota, commonly referred to as "the hidden organ," contributes more genetic data than the total human genome by a factor of over 150[6]. The community of microbes in a particular environment is called microbiota, while the microbes, their genomes, and the surrounding environment are called microbiome[7]. In the past two decades, due to the rapid development of the technology of cultivating independent genomes, a lot of related research has been carried out, and studies such as the Human Microbiome Project (HMP) provide insights into the composition of a typical healthy microbiome[8]. Recent advances in microbiome research have demonstrated that the microbiome is not just a passive bystander, but plays an important role in altering the immune, metabolic and endocrine systems, which in turn affects the physiological functions of the host[9–11]. More importantly, microbes have shown a complex relationship with cancer development. Although cancer is generally considered to be caused by a combination of host genetic and environmental factors, microbes have been implicated in ~20% of human malignancies[12].

As one of HMP's five research priorities (oral cavity, nasal, vaginal, intestinal, skin), the gut microbiome is considered the most important microbiome for maintaining human health. It is estimated that the human gastrointestinal tract harbors as many as 100 trillion microbes, with 200–1000 species of bacteria, numbering around 40 trillion[13]. The exact number of bacterial species shared within the digestive system or among individuals remains undetermined. For instance, a study of 124 European individuals revealed a total of approximately 1150 bacterial species, with most individuals harboring around 160 species[14]. Another study identified 632 bacterial species in a cohort of 1135 Dutch individuals[15]; and at least 1235 species-level phylotypes (SLPs) were found in the gut microbiota of 120 Chinese individuals[16]. Bacteria in the gut microenvironment are divided into seven major phyla (Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia, and Cyanobacteria), among which Bacteroidetes and Firmicutes accounting for over 90%[17]. The differences in microbial composition among different individuals can be categorized into three clusters, known as enterotypes, characterized by Bacteroidetes, Prevotella, and Firmicutes[18]. There are significant functional variations between different enterotypes. Crosstalk between microbial species also influences cancer pathology, acting on DNA stability, microenvironment composition, tumor promotion, and activation or avoidance of cancer immunity[19]. The rich gut microbiota not only affects cancer progression systemically, but also modulates response to cancer chemotherapy, radiation therapy, and immunotherapy[20].

The microbiome of oral cavity is the second largest and most diverse microbiome after the gut, with more than 700 species of bacteria[21]. The normal average temperature of the mouth at 37 °C and the stable pH of

[1]Department of Clinical Laboratory, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Gusu School, Nanjing Medical University, Suzhou, Jiangsu, China. [2]Zhejiang University School of Medicine, Hangzhou, Zhejiang, China. [3]These authors contributed equally: Jian Wu, Jiarui Li.
e-mail: wujianglinxing@163.com; zexiang@zju.edu.cn

saliva at 6.5–7 provide a stable environment for bacteria. Some periodontal microbes have now become the focus of a developmental association between oral microecosystems and cancer[22]. Microbes of oral cavity can be divided into 12 main phyla: Firmicutes, Fusobacteria, Proteobacteria, Actinobacteria, Bacteroidetes, Chlamydiae, Chloroflexi, Spirochaetes, SR1, Synergistetes, Saccharibacteria (TM7) and Gracilibacteria (GN02)[23]. Oral cavity microecological disorders are closely related to many systemic diseases[24]. Microbiota of oral cavity can invade the intestine or enter the blood circulation through tissues, and then affect the whole body[25]. Oral microbiota mediated carcinogenic effects have been found, as represented by *Porphyromonas gingivalis*, *Tannerella forsythia* and *Prevotella intermedia*[26].

Previous studies have reviewed the potential relationships between the gut microbiome and CC, EC, and OC[27], but research on the complex role of oral microbiome and the interaction between oral-gut microbiome in gynecologic cancer is still lacking. Thus, this review focuses specifically on the relationship between intestinal and oral microbiota and their interactions with gynecological cancers. We highlight the interactions between host and bacterial communities and discuss how the gut-oral cavity microbiome plays an important role in the development and progression of gynecological malignancies. Finally, we also summarize the possible role of the microbiome in the etiology, prevention, therapeutic efficacy and toxic effects of gynecological cancer.

The role of gut, oral microbiota and their interaction in carcinogenesis

Gut microbiota

The gut is not only a major site for digesting and absorbing nutrients, but also a natural immune barrier against pathogens. The paracacellular pathway regulated by tight junction (TJ) plays a crucial role in the generation of this selective barrier[28]. TJ is a class of protein complexes that occurs only in vertebrates and is the junction complex at the very top of epithelial and endothelial cells[29]. The core structure and function of TJ depend on occludin, claudins, the intracellular adapter proteins (ZO proteins) and junctional adhesionmolecule (JAM)[30]. Damage to the integrity of the intestinal barrier can lead to a rupture of the intestinal barrier TJ, resulting in a "leaky gut" that allows the lumen contents to interact abnormally with the intestinal mucosal immune system[31]. It has been reported that there is a strong link between intestinal microbiota imbalance and leaky gut. Excessive production of bacterial metabolites by overgrown bacteria can affect the barrier function of the intestinal wall, acting on zonulin (currently the only known physiological regulator of tight junctions between cells), and ZO-1 dissolves from TJ, increasing intestinal permeability[32].

After promoting leaky gut, bacterial antigens themselves can migrate throughout the body, known as microbial translocation, and produce autoreactive immune cells within lymphatic junctions in peripheral organs. Nucleotide-binding oligomerization domain receptors (NODs) and toll-like receptors (TLRs) were used for pattern recognition receptor systems (PRRs)[33], where immune cells recognize microbial or pathogen-associated molecular patterns on pathogens (MAMP or PAMP)[34]. At the same time, bacterial antigens can stimulate intestinal immune cells to produce autoreactive cells, which then migrate throughout the body to their target peripheral organs and begin to attack[35]. Mammalian native immune cells, including macrophages, dendritic cells, etc., can be activated by microbial components (non-self) represented by endotoxins or lipopolysaccharides of Gram-negative bacteria[36]. Subsequently, a variety of intracellular signaling pathways are activated, and immune cells express pro-inflammatory and anti-microbial cytokines, chemokines and immune receptors[34,37], which induce gene mutation, change the expression and transformation of oncogenes and tumor suppressor genes, inhibit cell apoptosis, induce angiogenesis, and result in abnormal inflammatory signaling pathways[38]. Chronic inflammation can also promote the establishment of immunosuppressive tumor microenvironment (TME) by recruiting a variety of immunosuppressive cells (M2-TAMs, MDSC, Treg, etc.), and promote the occurrence and development of tumors[38].

In addition, metabolites of the gut microbiota have been shown to be associated with alteration of the host immune system and cancer incidence. Short-chain fatty acids (SCFAs) and bile acids (BAs) produced by the gut microbiota are critical in cell homeostasis because they help influence cell attachment, immune cell migration, cytokine production, chemotaxis, and programmed cell death[39]. SCFAs, also known as volatile fatty acids, are the products of anaerobic bacteria in the colon that ferment undigested dietary fiber[40]. The receptors for SCFAs belong to the G-protein-coupled receptors (GPCRS), which play roles in a variety of cellular pathways[41]. Various GPCRS, including GPR109A[42], GPR41[43], and GPR43[43], affect the carcinogenic outcome by assisting T cell differentiation, promoting the formation of anti-pro-inflammatory cytokines, activating mitogen-activated protein kinases (MAPK) p38, and altering the cell cycle[39]. BAs are a key metabolic component of gut bacteria that link the gut to the liver, thereby affecting gastrointestinal motility, intestinal permeability, and cancer development[44]. BAs are a ligand for G protein-coupled bile acid receptor 1 (TGR5) and nuclear hormone receptor farnesoid X receptor (FXR). Studies have found that FXR expression levels are reduced on the mRNA of colon polyps, and the intestinal barrier is impaired and immune cell infiltration is increased in FXR-deficient mice[45]. TGR5 signaling controls the complex balance between pro-inflammatory and anti-inflammatory cytokines in tumor-associated macrophages[46]. Therefore, the regulation of SCFAs and BAs plays an important role in tumor prevention and treatment.

Oral microbiota

Microbiota of oral cavity can directly affect the disease status of dental caries and periodontal diseases. At the same time, oral microbiota reflects immune and metabolic information and status through dynamic interaction with the whole body organs of the host. In 1891, Willoughby D. Miller, the first oral microbiologist, wrote in the Lancet that "the human mouth is the focus of infection" and proposed the theory of focal oral infection, which believed that infections from the mouth were closely related to systemic diseases[47]. A focal infection of oral origin may come from an open or closed site. Open lesions included caries, periodontal pockets, and extractive cavities, while closed lesions included periapical infections, unerupted teeth, and infected pulp tissue[48]. From this, microorganisms and their metabolites can pass through connective tissues, muscles and fascia, enter blood vessels or lymphatic vessels or the nervous system, and eventually cause various systemic or degenerative changes[49]. Thus, oral microbiota plays an important role in tumor proliferation, invasion and metastasis.

Radiotherapy is the most effective cytotoxic method against local solid tumors. Compared with healthy controls, the α-diversity of oral bacteria increased with disease intensification, and changes in oral microbiota can also affect the therapeutic effect and prognosis of liver metastasis radiotherapy for primary rectal cancer and colorectal cancer (CRC)[50]. *Porphyromonas gingivalis* has been shown to evade the host immune response by invading host cells, directly degrading cytokines and mediating receptor loss[51,52]. Previous studies have shown that a history of periodontal disease and the presence of circulating antibodies against specific oral pathogens are associated with an increased risk of pancreatic cancer[53]. Fan et al., in the first assessment between oral microbiome and risk of pancreatic cancer, found that *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* were associated with an increased risk of pancreatic cancer, phylum *Fusobacteria* and its genus *Leptotrichia* were associated with a reduced risk of pancreatic cancer[54].

Interaction between gut and oral microbiota in carcinogenesis

The mouth and gut are the most complex microbial habitats, exhibiting unique microbiota associated with the unique microenvironmental characteristics of these two physiological niches. The interactions between the oral and intestinal microbiota are complex, unstable, and interconnected. Regarding the transmission of oral bacteria to the intestine, two hypotheses have emerged: the hematogenous route, that is, oral bacteria enter the lesion and circulate to the gastrointestinal mucosa and colonize; And the enteral route, where bacteria in the mouth travel through the stomach to the intestines[55]. Given the anatomical connection between the two organs, alterations in the gut microbiome may also exert an influence on the oral microbiome. Oral to gut and gut to oral microbial transmission can shape and reshape microbial ecosystems in both habitats, thereby regulating the pathogenesis of different diseases[56]. Typically, the taxa associated with environmental communities are part of the natural microbiome of healthy humans, and although pathogenic genera are widely present in the normal human microbiome, their abundance is comparatively lower[57]. The potential for colonization of the gut by oral microbiota via the enteral route under healthy conditions is a topic of considerable controversy. Rashidi et al. demonstrated distinct ecological niches between the saliva and fecal microbiomes of healthy adults, challenging the hypothesis that oral bacteria can colonize the distal gut[58]. However, Schmidt et al. provided evidence supporting widespread transmission and colonization of oral microbiota in healthy individuals despite intestinal barriers[59]. Notably, microbial transmission between the mouth and gut is more pronounced in patients than in healthy individuals. In disease states, compromised chemical or immunological barriers and reduced colonization resistance may exacerbate the invasion and overgrowth of oral pathogens within the gut environment. The enrichment of oral bacterial communities observed in pancreatic cancer underscores the significance of the oral microbiome[60]. It is noteworthy that *Fusobacterium nucleatum* is present both in saliva and colon samples from CRC patients[61]. Thus, perturbations to the oral/gut microbiome occur under diseased conditions with increased prevalence of pathogenic bacteria and specific alterations to microbial composition depending on disease state.

Numerous studies have shown that the gut microbiota from the mouth is enriched in the context of disease[60–62]. 16S rRNA analysis of gastric mucosal samples from gastric cancer (GC) patients at different stages of development showed that five bacterial taxa were enriched in GC and showed significant centrality in their ecological networks, which were *Peptostreptococcus stomatis*, *Streptococcus anginosus*, *Parvimonas micra*, *Slackia exigua* and *Dialister pneumosintes*[63]. Flemer et al. found similar enriched bacterial networks on the oral and colonic mucosal surfaces of patients with CRC and developed a CRC screening criterion that combines oral and fecal microbiota profiles with high specificity and sensitivity, and is particularly suitable for detecting colorectal polyps[64]. Principal-coordinate analysis (PCoA) revealed that the intestinal ecology shaped by total abdominal irradiation (TAI) could be remodeled by the regulation of oral microorganisms. The relative abundance of *Lachnoclostridium* and *Akkermansia* in fecal samples of mice receiving oral microbiota transplantation (OMT) after TAI increased and decreased respectively at the genus level, but the relative abundance of both *Lachnoclostridium* and *Akkermansia* in the oral samples was reduced at the genus level, suggesting that oral microorganisms may migrate and transfer to the lower digestive tract[50]. Ectopic colonization of the colon by orally derived *Klebsiella* is associated with abnormal activation of the immune system, inducing Th1 enrichment and driving severe intestinal inflammation (Fig. 1)[65].

Gut and oral microbiota in gynecological cancer

Vaginal microbiota

With the development of modern molecular biology technology, especially the application of amplicon and metagenomic sequencing technology, it is increasingly recognized that even regions previously considered sterile, such as the uterus and fallopium, can harbor unique microbial communities[66,67]. The healthy vaginal microbiota of most women of childbearing age is characterized by low microbial diversity and only one or a few dominant *Lactobacillus* spp., which maintain an acidic vaginal environment through colonization resistance, bioantagonism, and decomposition of glycogen in vaginal epithelial cells to produce lactic acid. Vaginal "self-purification" is maintained by the secretion of hydrogen peroxide (H_2O_2), bacteriocins, bacteriocins, and biosurfactants and by stimulating the body's immune defense against the growth of other bacteria and pathogenic bacteria[68]. Vaginal microecological imbalance is closely related to the occurrence and development of female reproductive tract infectious diseases. Using 16S rRNA sequencing analysis, Ravel et al. firstly divided the vaginal microbiota of asymptomatic women of childbearing age into five community state types (CST), among which, the species diversity of CSTI (26.2%), CSTII (6.3%), CSTIII (34.1%) and CSTIV (5.3%) were dominated by *L. crispatus*, *L. asseri*, *L. inners* and *L. Jensenii*, respectively, with low species diversity. In contrast, CSTIV (27.3%) typically contained little or no *Lactobacillus* and was rich in anaerobes and bacteria associated with bacterial vaginosis, including *Streptococcus*, *Prevotella*, *Sneathia*, and others[69].

Studies have revealed the possibility that vaginal microbiota is influenced by gut and oral microbiota. Petricevic et al. found that 80% of pregnant women and 40% of postmenopausal women had the same *Lactobacillus* isolates in the vagina and rectum, and 53% of pregnant women and 33% of postmenopausal women had the same *Lactobacillus* strains in oral and rectal specimens. The presence of simultaneous oral, vaginal, and rectal custom *Lactobacillus* spp. in up to 30% of postmenopausal women reveals the potential role of the gut and oral cavity as reservoirs for vaginal colonization of *Lactobacillus*[70]. Meanwhile, the gut and oral cavity may also be sources of extra-vaginal pathogens. Vaginal dysbiosis is characterized by a decrease in the number of *Lactobacillus*, and the most common form of vaginal dysbiosis is bacterial vaginosis (BV). *Gardnerella vaginalis* and *Leptotrichia/Sneathia* spp. were detected in oral or anal samples and anal samples of BV patients, respectively. The concentrations of these bacteria and *Megasphaera* were also higher at each site than in the 30 controls. In contrast, *L. crispatus* was more detected in anal samples from controls[71]. Therefore, extrapaginal colonization of vaginosis associated bacteria may be a risk factor for inducing disease.

Cervical cancer

CC is the fourth most common female cancer worldwide[72], affecting about 8–30 women per 100,000 women per year worldwide[73]. The main causes of CC are human papillomavirus (HPV) infection, environmental hygiene and dietary habits[74], and low- and middle-income countries face a significantly greater burden than high-income countries due to the lack of prevention and treatment programs. Persistent infection with high-risk HPV types, including HPV16 and HPV18, is a major cause of CC and its precancerous lesions. At the same time, it can also lead to high-grade lesions of the vagina, vulva and anus, and even invasive cancer in the corresponding parts[75].

The integration of HPV DNA into the genome of cervical epithelial cells results in the persistent expression of viral oncogenes E6 and E7. The products of these oncogenes stimulate the cellular ubiquitin-proteasome system (UPS), leading to the degradation of retinoblastoma protein (pRb) and facilitating entry into the S (synthesis) phase, thereby providing a foundation for viral replication[76]. Concurrently, HPV E6 disrupts p53 function, thus interfering with normal cell apoptosis mechanisms and promoting unregulated cell proliferation. It also includes the involvement of other biomolecules such as proteins that affect gene splicing and epigenetic inheritance, ultimately leading to abnormal cell proliferation and carcinogenic induction[77].

Gut and oral microbiota in CC

One of the sites where HPV establishes itself is the respiratory tract, which is anatomically directly linked to the oral cavity. The epithelium of the mucous membrane of the upper aerodigestive tract (UADT) is similar to the epithelium of the outer layer of the cervix and vagina, so it is sufficient in both sites for HPV to colonize. Carcinomas of the oropharynx, particularly Waldeyer's tonsillar ring, contain more than 50% HPV DNA, and evidence of HPV colonization in the mouth has been obtained through epidemiological and molecular studies[78–80]. Simultaneously, the presence of identical cancer-causing HPV types in CC has also been observed in head and neck squamous cell carcinoma (HNSCC), thereby reinforcing the correlation between oral microbiota and CC[81]. Sexual activity is the main route of HPV transmission in the oral cavity. Gillison et al.'s comparative epidemiology of HPV-associated HNSCC and CC showed that both oral and cervical HPV infection are closely related to sexual behavior, and oral-genital contact may be a major mode of HPV exchange and transmission between the two sites[82]. Recent research on oral HPV infection also supports non-sexual contact, including the transmission of saliva through behaviors such as deep kissing[83]. In addition to the oral cavity, studies have shown that HPV also occurs in the gut and may have

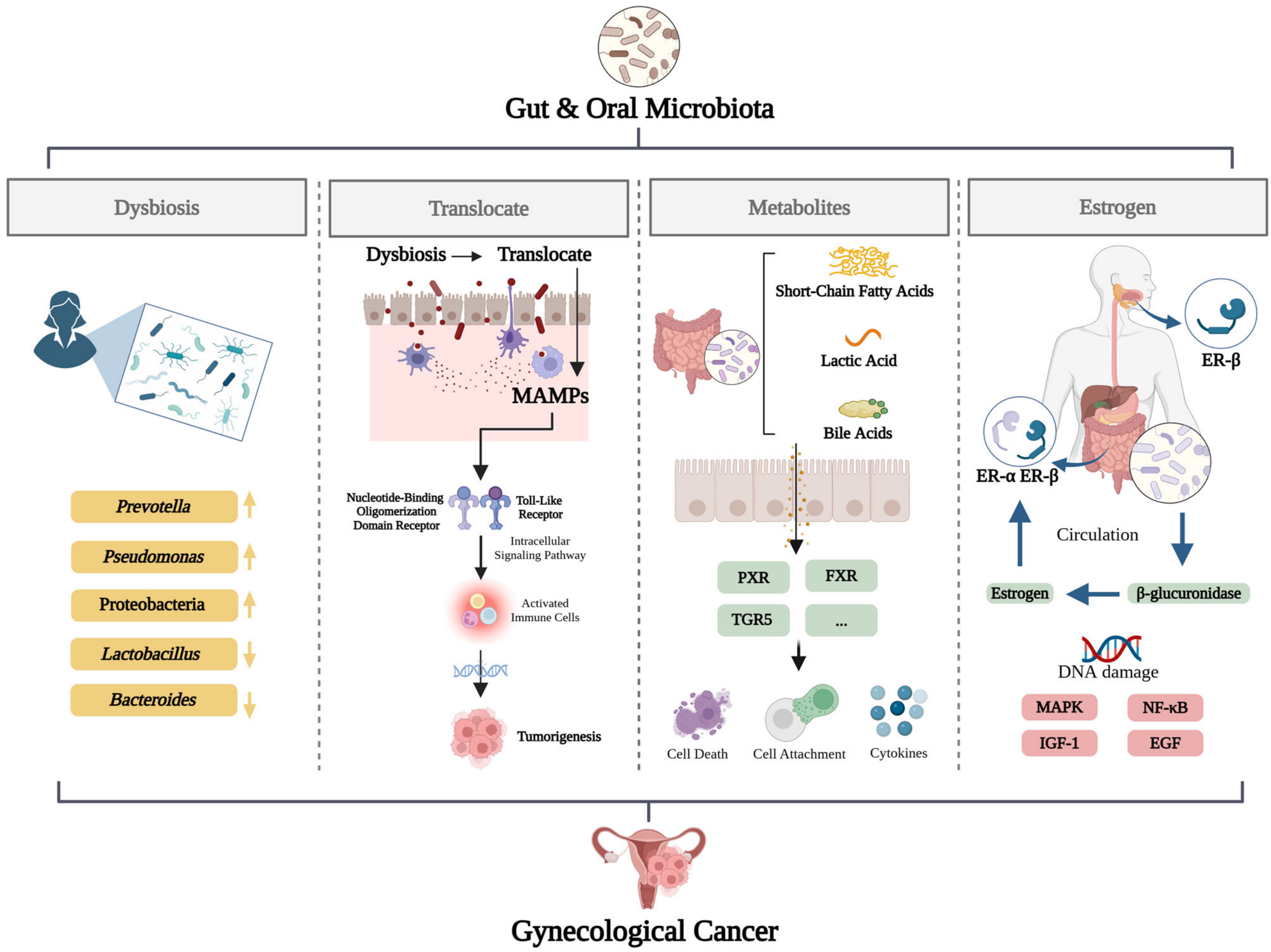

Fig. 1 | Gut and oral microbiota in the tumorigenesis. MAMP microbial-associated molecular patterns, PXR pregnane X receptor, FXR farnesoid X receptor, TGR5 Takeda G protein-coupled receptor 5, MAPK mitogen-protein kinases, NF-κB nuclear factor kappa-light-chain-enhancer in activated B cells, IGF-1 insulin-like growth factor 1, EGF epidermal growth factor. Alterations in oral/gut microbiota composition may impact the development of gynecological cancers via changes in pathogen translocation, metabolite release, and modulation of estrogen levels. Dysbiosis within the gut/oral microbiome represents a consistent hallmark among gynecological cancer patients; distinct diseases exhibit varying increases in specific bacterial species while universally displaying reduced levels of beneficial bacterium *Lactobacillus*. Anatomically, the mouth and gut are closely connected, and pathogens that colonize these two sites can migrate to various parts of the body. Immune cells recognize pathogens' MAMPs through NODs and LTRs, producing a strong inflammatory response that induces gene mutations. Metabolites produced by intestinal microbes, including short-chain fatty acids (SCFAs), bile acids (BAs), and lactic acids (LAs), are crucial for cellular homeostasis. SCFAs are ligands for GPCRs, while BAs are ligands for PXR, TGR5, and FXR, which play roles in various cellular pathways, controlling cell adhesion, cell apoptosis, and the formation of various cytokines. Furthermore, estrogen receptors are highly expressed in the mouth and intestines, where estrogen compounds can shape the gut and oral microbiomes. On the other hand, there are genes encoding β-glucuronidase in the human gut microbiome, which regulates endogenous estrogen metabolism and affects down-stream MAPK, NF-κB, IGF-1, and EGF pathways.

an impact on tumorigenesis. Cheng et al. used polymerase chain reaction (PCR) and Southern blot hybridization to detect specific types of HPV DNA in colorectal tumors and detected HPV DNA in 37 out of 70 patients with colorectal cancer (CRC), indicating that HPV may be associated with the development of CRC[84]. Consequently, HPV can gain entry into the body via oral transmission routes such as sexual activity and subsequently disseminate to lower anatomical regions, establishing residence in the respiratory and digestive tracts while readily infiltrating the uterus. However, there was no close relationship between HPV and sex, age, tumor stage, and tumor location, suggesting that viral infection is not retrograde transmission from the anus to the cecum. Therefore, whether HPV can be transmitted to the cervix through the anus also needs more research to fully confirm.

Apart from HPV infection, gut and oral microecological disorders caused by abnormal bacterial proliferation are also a major cause of CC. The reduction of *Lactobacillus* and the advantage of anaerobic bacteria are the characteristics of the microecology of CC patients[85]. Depletion of certain *Lactobacillus* species, including *L. crispatus*, *L. gasseri*, and *L. jensenii*, can trigger an inflammatory response that can lead to DNA damage and cancer-causing mutations[86,87]. HPV infection induced by reducing *Lactobacillus*, while increasing the abundance of *Sneathia* spp. and *Clostridiales*, which may also contribute to the pathogenesis of CC[88]. Wang et al. compared the gut bacteria of CC patients with healthy controls. The gut microbiota associated with CC showed an increasing trend in α-diversity, while the abundance of bacteria in seven genera, including *Escherichia-Shigella*, *Roseburia*, *Pseudomonas*, *Lachnoclostridium*, *Lachnospiraceae_UCG-004*, *Dorea* and *Succinivibrio*, were significantly enriched from healthy controls[89]. It can be seen that the disruption of the microbiome, represented by the abnormal reduction of beneficial bacteria *Lactobacillus*, has a potential relationship with the occurrence of CC. The increased α-diversity of oral microbiome has also been demonstrated in patients with many different types of cancer[90,91], which may hint at the role of oral-gut microbiome communication in CC. However, studies on changes in oral microbiome composition in patients with CC are still limited, and more studies are needed to verify the association between the two (Fig. 2).

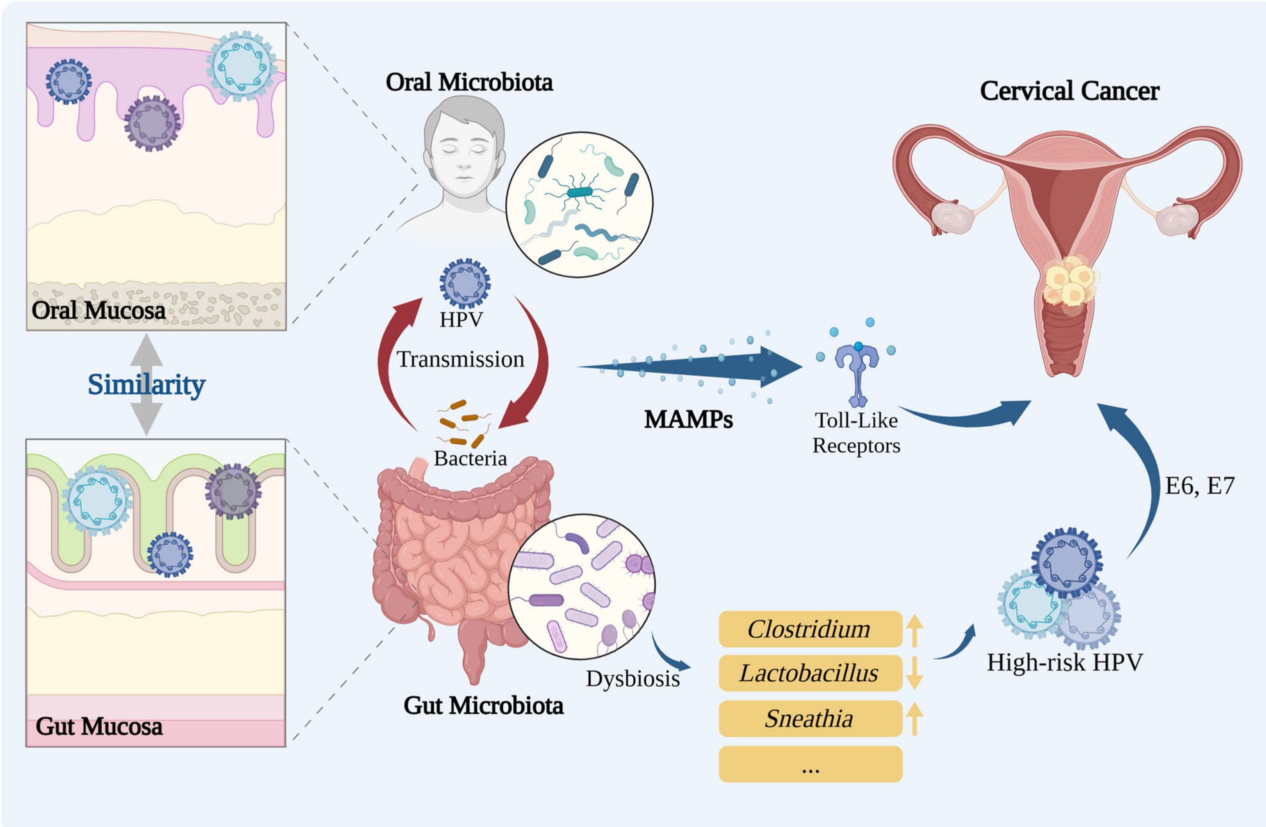

Fig. 2 | Gut and oral microbiota in the development of cervical cancer (CC). HPV is the main cause of CC, and evidence of HPV colonization has been found on the mucous membranes of the oral and gastrointestinal tracts. Integration of HPV DNA into the genome of cervical epithelial cells leads to sustained expression of viral oncogenes E6 and E7, ultimately leading to abnormal cell proliferation and carcinogenic induction. In addition to HPV infection, bacterial dysbiosis caused by abnormal bacterial proliferation in the gastrointestinal tract and oral mucosa is also a major cause of CC, with a reduction in *Lactobacillus* and an advantage of anaerobic bacteria being characteristic of CC patients' microbiome. Disruption of the microbiome triggers an inflammatory response, which can lead to DNA damage and carcinogenic mutations. HPV may also interact with the microbiome, with a reduction in Lactobacillus induced by HPV infection, and an increase in the abundance of *Sneathia* spp. and *Clostridium* also potentially contributing to the development of CC.

Therapeutic value of microbiota in CC

At present, the mainstream prevention method for CC is HPV vaccine, with ongoing enhancements in both their efficacy and safety as the vaccines themselves continue to advance. Folate and methionine are important components of DNA synthesis and methylation, and low red blood cell folate levels have been associated with hypomethylation of DNA in stunted tissues and an increased risk of HPV infection in women[92,93]. When the combined methylation level of the HPV 16 enhancer and the promoter site is ≥11%, the likelihood of being diagnosed with cervical intraepithelial neoplasia (CIN) 2+ is reduced by 55%. Oral supplementation of folic acid and vitamin B12 leads to a significant reduction in the methylation of HPV16, thereby inhibiting cervical dysplasia and ultimately lowering the risk of CIN[94,95].

Microbial regulation methods, particularly probiotics, have gradually shown surprising effects in the treatment of CC. *Lactobacillus* is found in the lower part of the female reproductive tract and protects vaginal epithelial cells from HPV by producing antibacterial products, blocking the production of harmful molecules adhering to cervical epithelial cells, and the production of lactic acid[96]. Taking the commercially available probiotic Yakult (containing *Lactobacillus casei* Shirota) was used to intervene in patients with low-grade squamous intraepithelial lesions. Women who received the probiotic were found to have twice the likelihood of clearing HPV-related cellular abnormalities compared to the control group (60% vs. 31%), and also exhibited a higher HPV clearance rate (29% vs. 19%)[97]. Furthermore, *L. paracasei*a and *L. casei* isolated from human milk have demonstrated exceptional antibiotic sensitivity, antioxidant activity, and robust resistance to low pH and high concentration bile salt, rendering them promising candidates as anti-cancer agents[98]. Probiotics can also affect the survival outcome of preclinical rat models by influencing cell cycle, oxidative stress, and inflammatory response[73]. Additionally, probiotic therapy can alleviate side effects during cancer treatment. The co-administration of *Lactobacillus acidophilus* LA-5 and *Bifidobacterium animalis* subsp. *lactis* BB-12 significantly reduced radiation-induced diarrhea (53.8% vs. 82.1%), thereby contributing to the shortened overall treatment duration and mitigating the risk of tumor cell regrowth[99].

Endometrial cancer

EC is the second most common gynecological malignancy, with 417,000 new cases worldwide in 2020, posing a serious threat to women's reproductive health and life safety[100]. The overall incidence of EC has increased by 132% in the last 30 years, and obesity and metabolic syndrome-related diseases, including diabetes and polycystic ovary syndrome (PCOS), are risk factors for developing EC[100–103]. In addition, estrogen-secreting tumors and hormone replacement with unopposed estrogen therapy also increase the risk of EC in women[104,105]. In recent years, although the incidence has increased across all age groups, cases in women under 40 have doubled[106]. The traditional treatment methods of EC are mainly surgery and chemoradiotherapy, and the treatment methods are relatively single, and the patients have insufficient or excessive treatment. Therefore, it is very important to explore the pathogenesis and new diagnosis and treatment methods of EC.

Gut and oral microbiota in EC

Microbiome disturbances represent a significant risk factor for developing EC. Compared to healthy controls, there was a notable decrease in α-diversity within the gut microbiome among individuals with EC; additionally observed were reduced abundance of *Firmicutes*, *Clostridia*, *Clostridiales*, *Ruminococcaceae*, *Faecalibacterium*, and *Gemmiger_formicis* alongside an increased prevalence of *Proteobacteria*, *Gammaproteobacteria*, *Enterobacteriales*, *Enterobacteriaceae* and *Shigella* as predominant members within their gut microbial community[107]. This indicates that the abundance, diversity, and dominant microbiota of the gut microbiome in EC patients have undergone significant changes. Further research has strengthened the tight connection between dysbiosis of the gut microbiome and various health problems, especially estrogen metabolism disorders and PCOS, which are considered strong risk factors for EC. Most *Porphyromonas* species reported in the literature are found in the oral microbiota of mammals and are closely related to oral cancer[108]. However, recent studies have found that *Porphyromonas somerae* is overrepresented in the uterus of EC patients, and *P. somerae* can invade host uterine endometrial cells and may interfere with normal cell function by producing succinic acid[109]. In the lower genital tract, the diagnostic sensitivity of *Atopobium vaginae* and *Porphyromonas* sp. for EC ranges from 73% to 93%, with a specificity of 67% to 90%[110]. This research indicates a potential translocation of oral pathogens to the uterus leading to carcinogenesis.

Recent advances in sequencing technology have shown that estrogenic compounds can shape the vaginal and distal microbial communities, including the gut and mouth[111–113]. Estrogen promotes the proliferation of endometrial cells through the action of estrogen receptors, which may cause the accumulation of carcinogenic mutations and lead to cancer[114]. Estrogen receptor-β is highly expressed in the oral mucosa and salivary glands, which explains the effect of estrogen on oral tissues[115]. Estrogen metabolites are excreted from the urine or bile after binding by sulfonation or gluconalidation, while estrogen inactivated in the intestine can be accidentally reactivated and absorbed by the intestine[116]. In contrast, the gut and oral microbiota also affect women's sex hormone levels and thus alter the development of cancer[117]. It has been shown that estrogen levels are directly related to the α-diversity of the gut microbiome, which is significantly associated with three genera of the Ruminococcaceae family, and the gut microbiome can also participate in the reactivation of estrogen[118]. β-glucuronidase regulates endogenous estrogen metabolism. In the gut, the most important gene encoding β-glucuronidase activity is the β-glucuronidase (GUS) gene. The atlas for the characterization of β-glucuronidase in the human gut microbiota identified 112 GUS coding genes, and they were expressed in four phyla: Bacteroidetes, Firmicutes, Verrucomicrobia, and Proteobacteria[119]. While little is known about the oral microbiome and EC, there are studies that have revealed the potential of *Porphyromonas gingivalis* in the carcinogenesis process[109]. In summary, we can speculate that oral-gut microbes may alter cancer progression through pathogen translocation and perturbation of estrogen levels.

Studies have shown that women diagnosed with PCOS had a 2.7-fold increased risk of EC[120], and that gut microbiome dysbiosis was associated with the onset of both PCOS and EC. Comparative analysis of insulin resistance PCOS (PCOS-IR), PCOS alone (PCOS-NIR) and healthy control (HC) showed no significant difference between α-diversity and β-diversity in three types of samples. However, the relative abundance of *Rothia*, *Ruminococcus* and *Enterococcus* in PCOS-IR group was significantly increased[121]. Another study also revealed higher abundance of *Lachnospira* in the gut microbiota of PCOS-IR patients, along with lower abundance of *Prevotella* compared to the PCOS-NIR group. In the latter group, there was a relatively higher abundance of *Lactobacillus* and *Akkermansia*[121]. *Enterococcus. fasecalis*produces GelE, which can degrade the intestinal incretin hormone glucagon-like peptide-1 (GLP-1), leading to abnormal insulin secretion and disruption of host metabolism. Thus, *Enterococcus*may impact the development and progression of PCOS-IR by modulating the GLP-1 signaling pathway[122]. Similarly, various bacteria associated with endometriosis (EMS), endometrial polyps (EP), dysfunctional menstrual bleeding[123] and pelvic inflammatory disease[124] also cause endometrial inflammation and can lead to endometrial malignancies. Limited data from animal models have demonstrated a robust correlation between the gut microbiome and EMS. These findings indicate a decrease in both diversity and abundance of the gut microbiome in EMS mice, alongside an increase in the levels of fecal goosedeoxycholic acid and ursodeoxycholic acid[125]. Lan et al. prospectively revealed the biomarker role of gut microbes in EP. Compared to infertile and healthy subjects, infertile EP patients had higher proportions of *Prevotella*, *Streptococcus*, *Fusobacterium*, *Fenollaria*, and *Porphyromonas*[126].

Therapeutic value of microbiota in EC

Regulation of microorganisms by probiotics, fecal microbial transplantation (FMT) and antibiotics have opend up potential avenues for improving care of EC and endometrium-related diseases. Given the limited research on EC microbiome regulation therapy, we have supplemented the microbiome treatment related to gynecological diseases associated with EC, hoping to provide more insights into cancer treatment. As a preferred strain for optimizing the female reproductive tract environment, *Lactobacillus rhamnosus* BPL005 is often selected in most studies, with its ability to effectively lower pH levels in the external environment while secreting organic acids such as lactic acid, thereby assisting in inhibiting the growth of pathogenic bacteria[127]. Chenoll et al. found that the *L. rhamnosus* BPL005 (CECT 8800) strain could be protective against endometrial infection in an in vitro model of primary endometrial epithelial cells with *Atopobium vaginae*, *Gardnerella vaginalis*, *Propionibacterium acnes*, and *Streptococcus agalactiae* colonization. In this model, BPL005 was shown to reduce pH and produce organic acids when co-cultured with these pathogens, with lactic acid being most relevant[128]. After treating PCOS rats with *Lactobacillus* and FMT from healthy rats, it was observed that the estrus cycle improved in all the eight rats in the FMT group and 75% of the rats in the *Lactobacillus* group. Additionally, there was a reduction in androgen biosynthesis. The intestinal microecology of the FMT and *Lactobacillus* treatment groups recovered with the increase of *Lactobacillus* and *Clostridium*, and the decrease of *Prevotella*[129].

In addition to FMT, manipulating the microbiota using antibiotics or probiotics represents a potential approach for treating chronic diseases that may progress to EC. Modifying the composition of the gut microbiome with broad-spectrum antibiotics (vancomycin, neomycin, metronidazole, and ampicillin) has been shown to decelerate the proliferation and inflammation of endometriosis in mice; targeting *Bacteroides* with metronidazole can reduce the growth of endometriosis[130]. Simultaneous administration of vitamin D and probiotics containing *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *L. reuteri* and *L. fermentum*) has demonstrated significant improvements in hirsutism and total testosterone concentration, as well as reductions in inflammation and oxidative stress[131].

Ovarian cancer

OC is an uncommon but serious threat to women's health of the malignant tumor, called by "silent killer" because of its difficulty to detect, treat and easiness to relapse[132,133]. More than 70% of OCs are not diagnosed until the disease has progressed to stage III or IV, and more than 50% of OC patients survive less than 5 years[134]. The enhancement of clinical diagnosis and treatment for OC, as well as the improvement of patient survival prognosis, is a matter of urgency. OC can be subdivided into different histological subtypes, of which 90% are epithelial cancers, including serous, endometrioid, clear-cell and mucinous carcinomas, and the remaining 10% are non-epithelial cancers[135]. Genes have been identified that are associated with a higher risk of developing OC, such as BRCA1 or BRCA2[136]. Standard treatments for newly diagnosed cancers include cell reduction surgery and platinum-based chemotherapy. For recurrent cancer, chemotherapy, anti-angiogenic drugs, and poly (ADP-ribose) polymerase inhibitors are the main means[135]. With the development of microbiome, the potential of microbiome in diagnosis, treatment and prognosis of OC remains to be explored.

Gut and oral microbiota in OC

The role of infection and inflammation in the pathogenesis of OC has not been fully elucidated. As hormone levels change, inflammation and ovulation may lead to oxidative stress leading to DNA damage. Ovarian synthesis and secretion as well as estrogen, progesterone and a small amount of androgens, estradiol level changes are associated with the development of OC[137]. As mentioned before, the gut microbiome not only alters the hepatoenteric circulation of estrogen, but also interferes with the secretion of β-glucuronidase, thereby altering the regulation of estrogen metabolism[138]. A comparative analysis of epithelial ovarian cancer (EOC), epithelial benign ovarian tumor (EBOT) patients, and HC revealed that in EOC the relative abundance of beneficial bacteria *Bifidobacterium* and *Ruminococcaceae_Ruminococcus* is decreased, and its distribution is related to EOC stage and subtype, while microdysbiosis promotes EOC progression through Hedgehog (Hh) signaling pathway[139]. Amico et al. analyzed the gut microbiome of patients with EOC and documented fluctuations in changes from adjuvant chemotherapy to postoperative follow-up. Gut microbiota of platinum-resistant patients exhibited a significant decrease in diversity and an increase in the proportion of *Coriobacteriaceae* and *Bifidobacterium* while that of platinum-sensitive patients appear to be more diverse and stable overall, and are rich in lactic acid users from the Veillonellaceae family[140]. D'Amico et al. also demonstrated a similar correlation between the dynamics of the intestinal microbiome during chemotherapy and treatment outcomes in EOC patients, suggesting that the microbiome during chemotherapy can serve as a prognostic biomarker for EOC[141]. Malregulated oral microbes may be ectopic to the gut, or interact with estrogen to trigger an inflammatory response, and then affect the development of OC through MAMP. However, the relevant research is still very limited and needs to be carried out.

Therapeutic value of microbiota in OC

Existing studies have hinted that balancing the composition of microecology is a feasible strategy for the treatment of OC. The proportion of Proteobacteria, Firmicute, *Brucella*, Chlamydia and Mycoplasma was significantly increased in OC tissues[67,142,143]. Nene et al.'s analysis of the cervix and vagina of patients with OC showed that a reduction in the relative abundance of the beneficial *Lactobacillus spp*. increased the risk of cancer development[144]. Rats with PCOS that underwent FMT or *Lactobacillus* transplant exhibited reduced serum androgen levels, increased granulosa cells in the ovaries, and the formation of corpora lutea, indicating amelioration of ovarian cysts[129]. It may be feasible to modulate the microbial composition in the female reproductive tract and fallopian tube by using antibiotics, suppository containing viable *Lactobacillus spp*. or performing FMT from healthy people in patients. But whether this modulation can directly transform into reduced OC incidence still needs to be investigated.

Vaginal cancer

The incidence of primary vaginal cancer is relatively rare, accounting for only 1% to 2% of female reproductive tract malignancies and 10% of vaginal malignancies[145]. Most vaginal malignancies are metastatic cancers that can originate from tumors of the cervix, vulva, or other sites. Guidelines from the International Federation of Gynecology and Obstetrics (FIGO) state that cases should be classified as vaginal cancer only after the possibility of metastasis has been ruled out[146]. Previous vaginal cancer is most common in older, postmenopausal women[147]. Young vaginal malignancies are often associated with CC and are particularly associated with persistent HPV infection[148]. With numerous number of women who continue to be infected with high-risk types of HPV, there is an increasing trend of young vaginal cancer patients, especially in areas with high incidence of human immunodeficiency virus (HIV) infection.

Gut and oral microbiota in vaginal cancer

The homeostasis of vaginal microbiota is directly linked to the development of vaginal cancer. Several studies have reported that the healthy vaginal microbiota is dominated by species represented by *Lactobacillus* spp., which includes *L. crispatus*, *L. gasseri*, *L. iners*, *L. jensenii*[149,150]. The normal average vaginal pH value for a woman is 3.80 ± 0.20, with an average lactic acid concentration of $0.79\% \pm 0.22\%$w/v. This concentration demonstrates efficacy in deactivating BV-associated bacteria, HIV-1, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae*[151]. Disruption of the oral/gut microbiome may perturb the equilibrium of the vaginal microbiome, impact vaginal pH, and contribute to the development of vaginal diseases, potentially progressing to cancer. In comparison to adolescent women with a Lactobacillus-dominated vaginal microbiome, those with an unfavorable vaginal microbiome exhibited a higher prevalence of bacteria linked to periodontal disease in their supragingival microbiome, including *Prevotella intermedia* and *Porphyromonas endodontalis*, Saliva showed enrichment of *Pseudomonas aeruginosa* and *P. intermedia*[152]. These findings imply a correlation between dysbiosis in the oral and vaginal microbiomes. 16S rRNA sequencing of patients with BV revealed that gut microbiome was dominated by Firmicutes followed by Bacteroidetes and Proteobacteria[153]. Another study found that BV-positive patients harbored higher α-diversity and had lower abundance of *L. helveticus*. Meanwhile, *Prevotella copri*, an intestinal microbe associated with healthy microecology, was only abundant in vaginal samples from women without BV, which reveals a possible cross-talk between gut-vaginal microbiota[154]. A study by Antonio et al. evaluated the association between vaginal and/or rectal colonization of the genus *Lactobacillus* and the presence of BV and found that the rectum may act as a vaginal *Lactobacillus* reservoir. Co-colonization of the vagina and rectum with H_2O_2-producing *Lactobacillus* was associated with a lower prevalence of BV compared with vaginal colonization alone[155]. Besides, additional relationships between the vaginal and gut microbiome have been proposed: for example, gut β-glucuronidase activity can affect vaginal microbiome homeostasis by modulating circulating estrogen levels[156].

Therapeutic value of microbiota in vaginal cancer

The balance of microecology and prevention of BV may be an effective way to prevent and treat vaginal cancer. A randomized trial involving 64 patients revealed that oral administration of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 caused microbial transfer from the rectum to the vagina, increased the vaginal load of *Lactobacillus*, and reduced the occurrence and recurrence of BV in nonpregnant women[157]. After oral administration of probiotics in women with BV, the abundance of *Prevotella copri* was significantly increased, while that of *Gardnerella vaginalis* was significantly decreased, suggesting that probiotics may play a role in the regulation of vaginal microbiota[154].

Vulvar cancer

Vulvar cancer is also a rare malignancy of the reproductive system that pretends to occur in postmenopausal women, accounting for 3–5% of all gynecologic cancers in economically developed countries[158]. At present, there is no specific screening method for vulvar cancer, and the most effective way to reduce its incidence is to treat vulvar precancerous lesions related to its occurrence and development in time[159]. Most patients with vulvar cancer will have symptoms of pruritus or pain, lumps, or ulcers in the vulva[160]. Therefore, any suspected vulvar lesion must be biopsied to rule out invasive carcinoma. The pathological causes of vulvar cancer include HPV infection, chronic inflammation and immunosuppression. The most common pathological type of vulvar cancer is squamous cell carcinoma, and the treatment is mainly based on tissue type and surgical stage[159].

Gut and oral microbiota in vulvar cancer

Gut and oral microbiota may enhance inflammatory responses through the activation of MAMP and its pattern recognition receptor (PRR)[161]. Toll-like receptors (TLRs) are one of the most widely studied PRRs. Interactions between the lipopolysaccharide (endotoxemia) and TLRs can trigger an inflammatory response that leads to disruption of intestinal impermeability and altered carbohydrate metabolism and absorption[162]. TLRs are thought to be involved in the response to HPV infection, and several lines of evidence suggest that they may play a role in HPV clearance[163]. A large study involving 876 cases of CC, 517 cases of vulvar cancer, and 1100 controls showed that genetic variation in TLR was associated with an increased risk of developing cervical and vulvar tumors[164]. Due to the scarcity of clinical cases, the current research on the microbiome of vulvar cancer mainly focuses on the vaginal microbiome, while the research on the intestinal and oral microbiome of patients is very scarce.

Table 1 | Changes of gut and oral microbiota in gynecological disorders

Disease Type	Colonization site	Name of Microbiota	Changes	Reference
CC and HNSCC	Oral cavity	HPV	Increase	82
Colorectal cancer	Gut	HPV	Increase	84
CC	Gut	*Escherichia-Shigella*, *Roseburia*, *Pseudomonas*, *Lachnoclostridium*, *Lachnospiraceae_UCG-004*, *Dorea* and *Succinivibrio*	Significant different from healthy controls	89
Endometrial cancer	Gut	*Faecalibacterium prausnitzii* and *Gemmiger formicilis*	Decrease	107
Endometrial cancer	Gut	*Bifidobacterium adolescentis*	Increase	107
Endometrial cancer	Oral cavity	*Porphyromonas somerae*	Increase	109
PCOS	Gut	*Lactobacillus*, *Ruminococcus* and *Clostridium*	Decrease	129
PCOS	Gut	*Prevotella*	Increase	129
PCOS	Gut	*Rothia*, *Ruminococcus* and *Enterococcus*	Increase	121
Endometriosis	Gut	*Lachnospiraceae_NK4A136_group*, *Lactobacillus* and *Bacteroides*	Decrease	125
Endometriosis	Gut	*Allobaculum*, *Akkermansia*, *Parasutterella* and *Rikenella*	Increase	125
Endometrial polyps	Gut	*Prevotella*, *Streptococcus*, *Fusobacterium*, *Fenollaria*, and *Porphyromonas*	Increase	126
OC	Gut	Actinobacteria	Decrease	139
OC	Gut	Proteobacteria	Increase	139
OC	Gut	Coriobacteriaceae and *Bifidobacterium*	Increase	141
BV	Oral	*Prevotella intermedia*, *Porphyromonas endodontalia* and *Pseudomonas aeruginosa*	Increase	152
BV	Gut	Firmicutes, Bacteroidetes and Proteobacteria	Increase	153
BV	Gut	*L. helveticus* and *Prevotella copri*	Decrease	154
BV	Gut	*L. crispatus* and *L. jensenii*	Decrease	155

CC cervical cancer, *HNSCC* head and neck squamous cell carcinoma, *PCOS* polycystic ovary syndrome, *OC* ovarian cancer, *BV* bacterial vaginosis.

Therapeutic value of microbiota in vulvar cancer

The lack of preclinical or clinical trials demonstrating a therapeutic relationship between vulvar cancer and the microbiota in the available literature limits further deliberation in this review.

Insights into shared pathogenic mechanisms among gynecologic cancers

Despite the distinct pathological features of various gynecological cancers, all gynecological cancers originate from the Müllerian duct and are located within the female reproductive system, regulated by female hormones such as estrogen and progesterone. Molecular sequencing has revealed common processes in the development of different types of gynecological cancers. For example, there are 193 differentially expressed genes between CC, EC, and vulvar cancer, with apoptosis regulation genes enriched in all three cancers[165]; CC and EC have extensive similarities in differentially expressed genes, affected biological processes, and transcription factor binding sites[165]; while CC, EC, and OC share a dMMR-signature, four recurrent CNV events, and extensive alterations in PI3K-Akt-mTOR signaling and cilium component genes[166]. Due to the related pathway and gene features among gynecological cancers, multiple networks or cascades can lead to the malignant transformation of ovarian-uterine-vaginal tissues, and these cancers may share common pathogenic factors.

Disturbances in the oral and gut microbiome are one of the causative factors of gynecological cancer. In different gynecological cancers or precancerous gynecological conditions, an increase in anaerobic bacteria and a decrease in beneficial bacteria *Lactobacillus* have been found. Elevated pathogens may disseminate to various parts of the female reproductive system, triggering a strong autoimmune response and causing cellular malignant mutations. Meanwhile, a decreased *Lactobacillus* is associated with an abnormal elevation in vaginal pH. Furthermore, estrogen receptors display high expression characteristics in both the oral and gut mucosa, revealing the interaction between estrogen and its receptors in maintaining microbial stability in these two sites. Estrogen shapes the oral and intestinal microbiome through complex mechanisms. Estrogen compounds can interact with the gut microbiome to promote the growth and proliferation of beneficial bacteria, while preventing the excessive proliferation of harmful bacteria[167]. It is worth noting that the human gut microbiome contains the gene GUS, which encodes β-glucuronidase. β-glucuronidase is a key enzyme that catalyzes the hydrolysis reaction of bound estrogen (such as estradiol glucuronate), generating biologically active free estrogen. These free estrogen can then activate estrogen receptors in the gut and surrounding tissues, triggering a series of downstream signaling pathways, including MAPK, NF-κB, IGF-1, and EGF, which play important roles in regulating endometrial[168], ovarian epithelial[169], and vaginal mucosal[170] cell proliferation and differentiation.

Outlook

People's understanding of the microbiome is changing from "affecting human health and disease" to "seeing the human microbiome as an organ." For example, the gut microbiome is closely related to the occurrence and development of diseases in various systems throughout the body, so concepts such as "gut-brain axis" and "gut-liver axis" have been proposed successively. Current research focuses on the signaling pathway and metabolite transfer between the microbiome and tissues and organs such as brain, liver and lung, and analyzes the interaction mechanism. The study of microbes and human health and disease has gradually increased from "correlation" to "causal mechanism".

Gynecological malignancies pose a great threat to women's health, and the application of microorganisms is a promising therapeutic target. The microbiome composition of cancer tissue and adjacent reproductive tract different from that of normal patients. Besides, microorganisms in distal organs such as the gut and mouth interact, migrate to the female reproductive tract to interfere with the microecological balance. *Lactobacillus* was found to play a crucial role in maintaining reproductive health, and the relative abundance of *Lactobacillus* was significantly reduced in patients with gynecological cancer. At the same time, metabolites produced by the microbiota, such as SCFAs and BAs, can affect the inflammatory response, the absorption of nutrients, and also have an impact on the development of cancer (Table 1).

Table 2 | Modulation of microbiota in the treatment of gynecological cancer and disorders

Disease Type	Method	Specific ingredients/ Taeget microbiota	Result	Reference
CIN	Folate and vitamin B12 intake	HPV 16	Higher folate and vitamin B12 intake could lower the risk of HPV16 infection and CIN.	95
Cervical lesions	Probiotics	HPV	Probiotics increased the chance of clearance of HPV and cytological abnormalities.	97
CC	Probiotics	*L. casei* and *L. paracasei*	Probiotics had acceptable anticancer effects on cervix cancer.	98
CC	Probiotics	*L. acidophilus* LA-5 and *Bifidobacterium animalis subsp. lactis* BB-12	Probiotics reduced the incidence and severity of side effect radiation-induced diarrhea.	99
Endometrial infection	Probiotics	*L. rhamnosus* BPL005	*L. rhamnosus* BPL005 showed a protective role on endometrial infections with no signs of cytotoxicity.	128
Endometriosis	Antibiotics	Vancomycin, neomycin, metronidazole and ampicillin	Antibiotic therapy reduces endometriosis progression in mice, possibly by reducing specific gut bacteria.	130
PCOS	Probiotics and vitamin D	*L. acidophilus*, *Bifidobacterium bifidum*, *L. reuteri* and *L. fermentum*	Co-administration of vitamin D and probiotic significantly improved the health state of PCOS patients.	131
Bacterial vaginosis	Probiotics	*L. rhamnosus* GR-1 and *L. fermentum* RC-14	Probiotics reduced the occurrence and recurrence of BV in nonpregnant women.	157
Bacterial vaginosis	Probiotics	*L. rhamnosus* GR-1 and *L. fermentum* RC-14	Probiotics restored the abundance of Prevotella copri in BV patients.	154

CIN cervical intraepithelial neoplasia, *PCOS* polycystic ovary syndrome.

The relationship between the human microbiome and nutrition and medicine provides new ideas for personalized nutrition interventions and the development of new therapies, and has become another revolutionary innovation point in the pharmaceutical, food and health products industry, with great potential to trigger fierce global competition (Table 2). The main ways to regulate the human microbiome in clinical practice are: microbiome detection and health guidance, antibiotics and other microecological drugs, probiotics and prebiotic, FMT, etc.

Currently, the microbiological research in the field of gynecologic oncology is still in its early stages, with insufficient depth and breadth of exploration, which to some extent limits our understanding of the complex mechanisms of gynecologic cancer. Because of this, this article collects typical cases of microbial regulation in closely related gynecologic basic diseases, intending to provide new perspectives and insights into the pathogenesis and treatment of gynecologic cancer through these examples. More extensive and in-depth research is needed in the future to develop more precise and effective diagnostic tools and treatment methods, in order to provide comprehensive services for the prevention, early diagnosis and comprehensive management of gynecologic cancer, and ultimately benefit the health and well-being of female patients.

Data availability

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

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Author contributions

J.W., J.L., and Z.X.: writing–original draft preparation; J.W., M.Y., and Z.X.: writing–review & editing; Z.X. and J.L.: references collection, tables and figures organization; J.W.: acquisition of funds, J.W. and Z.X.: visualization, investigation. All authors have agreed to its publication.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Jian Wu or Ze Xiang.