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肠道–阴道轴微生物组交互机制及其在妇科恶性肿瘤中的研究进展

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摘要 妇科恶性肿瘤是全球女性健康的重大威胁, 其发病机制尚未被完全阐明, 现有防治策略仍面临早期诊断困难、治疗耐药及预后不佳等挑战。近年来, 人体微生物组研究揭示了不同解剖部位微生物群落的跨部位动态交互是调控宿主健康和疾病进程的关键环节。其中, 肠道与阴道作为女性体内两大关键黏膜器官, 在妇科恶性肿瘤发生中的作用逐渐成为研究热点。然而, 现有研究多聚焦单一部位微生物的独立作用, 尚未系统整合肠道–阴道轴介导的跨部位微生物组串扰机制, 且缺乏对该轴通过多通路协同调控肿瘤发生发展的整体性认知, 导致肠道–阴道轴在妇科恶性肿瘤的核心调控作用与潜在机制仍未被充分揭示。该文旨在系统阐述肠道–阴道微生物组交互机制及其在妇科恶性肿瘤中的研究进展, 重点从免疫调节、代谢通路及内分泌信号等维度, 剖析其相互作用的网络机制, 以期为深入探究妇科恶性肿瘤的发生发展提供新的研究视角与理论支撑。

关键词 微生物组串扰; 肠道–阴道轴; 炎症; 妇科恶性肿瘤; 肿瘤微环境

The Interaction Mechanisms between Gut-Vaginal Axis Microbiome and Its Research Progress in Gynecological Malignant Tumors

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Abstract Gynecological malignant tumors pose a significant threat to woman's health wordwide. The underlying mechanism of these tumors has not yet been fully elucidated, and the existing prevention and treatment strategies still face challenges such as difficulties in early diagnosis, treatment resistance, and poor prognosis. In recent years, studies on the human microbiome have revealed that the cross-site dynamic interactions of microbial communities in different anatomical locations are a key link in regulating host health and disease progression. Among them, the gut and the vagina, as two crucial mucosal organs in the female body, have gradually become a research hotspot in the occurrence of gynecological malignancies. However, existing studies mostly focus on the independent effects of microorganisms in a single site, and have not systematically integrated the cross-site microbial group crosstalk mechanism mediated by the gut-vagina axis. Moreover, there is a lack of a comprehensive understanding of the overall regulation of tumor occurrence and development through multiple pathways of this axis, resulting in the core regulatory role and potential mechanisms of the gut-vaginal axis in gynecological malignancies

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still not being fully revealed. This article aims to systematically expound the interaction mechanism of the gut-vaginal microbiome and its research progress in gynecological malignant tumors. It focuses on analyzing the network mechanism of their interactions from dimensions such as immune regulation, metabolic pathways, and endocrine signals, with the expectation of providing new research perspectives and theoretical support for in-depth exploration of the occurrence and development of gynecological malignant tumors.

Keywords microbiome crosstalk; gut-vaginal axis; inflammation; gynecological malignant tumors; tumor microenvironment

妇科恶性肿瘤严重威胁女性健康, 其中以宫颈癌、卵巢癌和子宫内膜癌较为常见。从流行病学数据来看, 宫颈癌的发病率在我国女性恶性肿瘤中高居第二位, 仅次于乳腺癌[1]。在全球范围内, 宫颈癌是造成女性相关癌症死亡的第四大原因[2]。卵巢癌是女性生殖系统中最致命的肿瘤类型之一, 由于早期症状隐匿加之缺乏特异性筛查手段, 多数患者确诊时病情已发展至晚期, 导致疾病整体预后较差。从疾病特征来看, 卵巢癌具有易复发、化疗耐药性强的特点, 约75%的晚期卵巢癌患者在初始治疗后的两年内出现疾病反复, 这一问题严重制约了临床治疗效果的进一步提升[3]。与此同时, 子宫内膜癌近年来的发病率呈上升状态, 在经济发达区域尤为显著, 其发生与女性体内激素水平失衡密切相关[4], 肥胖[5]、绝经年龄延迟[6]等潜在危险因素会增加子宫内膜异常增殖及恶性转化的风险, 晚期或复发患者面临治疗反应不佳和预后较差的挑战。因此, 深入挖掘妇科恶性肿瘤发病机制, 探索新的防治靶点与策略, 已成为当前医学领域的迫切需求。

在此背景下, 人体微生物组研究为解析肿瘤发生发展机制提供新的视角。人体微生物组广泛分布于肠道、阴道、皮肤、口腔等多个部位, 其中肠道与阴道作为女性体内两大关键黏膜器官, 其微生物群落与宿主形成紧密的共生互作关系: 一方面, 它们在维持局部微环境稳定中发挥核心作用; 另一方面, 这些微生物群落深度参与机体免疫调节、代谢产物合成等关键生理过程[7-8]。微生物群落失衡已被证实与盆腔炎等多种妇科疾病的发生发展密切相关[9]。在这一背景下, 阴道微生态作为女性生殖健康的重要指标, 虽已被广泛研究并明确了其与流产[10]、细菌性阴道炎[11]等疾病之间的关系, 但其在妇科恶性肿瘤治疗及预后评估中的潜在作用尚未被充分探索。更为重要的是, 女性生殖系统与肠道并非相互独立的微生态单元, 二者可通过解剖毗邻、免疫网络及内分泌通路形成动态交互的肠道−阴道轴。肠道菌群紊乱可破坏阴道微生态平衡, 进而参与妇科恶性肿瘤的发生; 反之, 阴道菌群失调也可能通过上行感染、炎症因子扩散等途径影响远端菌群结构与功能, 这种跨生态位的微生物串扰可能通过代谢重编程、免疫逃逸及慢性炎症驱动的机制促进肿瘤进展, 并影响化疗敏感性和患者预后。

因此, 系统阐释肠道−阴道轴在妇科恶性肿瘤发生与发展中的微生物组串扰机制, 不仅有助于揭示新的致病通路, 也可为开发基于微生物组的早期预警、靶向干预及疗效改善策略提供新的思路。本文旨在从微生物组串扰的视角出发, 系统解析肠道−阴道轴在妇科恶性肿瘤中的作用机制, 为突破妇科恶性肿瘤防治困境提供理论依据。

1 人体微生物组概述

人体存在由细菌、真菌、病毒等亿万微生物构成的复杂生态系统, 该系统即为人体微生物组[12]。它们与宿主共生, 深度参与调节多项关键的生理功能, 包括免疫应答、神经认知功能、炎症及造血等, 因而被誉为人类的“第二基因组”[13]。这一生态系统的稳定对维持宿主健康至关重要, 当外界环境发生剧烈变动时, 宿主相关联的微生物组内在稳态可能发生失衡, 这种失调状态能够驱动局部或全身性的慢性炎症反应, 并成为恶性肿瘤发生与发展的重要潜在危险因素[14]。

人体微生物组的分布具有显著的组织特异性, 不同解剖部位微环境的差异塑造了各具特征的微生物群落结构与功能。例如, 口腔作为消化道与呼吸道的入口, 受饮食、唾液成分及咀嚼运动影响, 定植了包括变形链球菌、牙龈卟啉单胞菌在内的复杂菌群, 参与口腔局部免疫调节及机体营养代谢等[15]; 皮肤表面受角质层屏障结构、局部湿度及皮脂分泌水平的区域差异影响, 形成以葡萄球菌属、链球菌属为主

的微生物群落[16]。而在人体众多微生物定植部位中，肠道与阴道因其与宿主免疫代谢功能的紧密互动以及在女性生殖健康及代谢稳态中的核心地位，而成为研究的焦点。二者在解剖结构、免疫等功能上相互关联，构成了一个动态的“肠道–阴道轴”。理解这两大核心微生态区域的平衡与失调机制，对于揭示其在妇科恶性肿瘤中的作用具有根本性意义。

1.1 肠道微生物组：宿主代谢和免疫稳态的核心调控者

肠道微生物组是人体内规模最大、功能最为复杂的微生态系统，通过短链脂肪酸、次级胆汁酸等代谢产物的分泌及免疫信号的传递，系统性维持宿主免疫稳态与代谢平衡[17]。从群落构成的区域特异性来看，肠道从十二指肠至直肠的不同区段因消化液成分、营养供给、肠道蠕动频率及氧分压的差异，形成了梯度化的微环境特征，进而塑造了结构与功能高度特异的肠道微生物群落。健康成人肠道微生物以细菌为主导，其中厚壁菌门和拟杆菌门占据绝对优势，二者占比可达肠道总群的90%以上，辅以放线菌门、变形菌门等少量菌门[18]；在属水平上，结肠中双歧杆菌属、乳杆菌属等有益菌通过竞争性黏附肠道黏膜上皮细胞抑制致病菌定植，而拟杆菌属、梭状芽孢杆菌属等则通过分解复杂碳水化合物产生代谢底物，形成功能互补的群落网络，其动态平衡是维持肠道功能稳定的关键[19]。

从核心功能机制来看，肠道微生物组的作用远不止消化功能，其核心功能主要体现在三个方面。第一，代谢调控。肠道微生物能够发酵人体无法直接消化的膳食纤维，产生短链脂肪酸等关键代谢产物，其中丁酸不仅是结肠上皮细胞的主要能量来源，更可通过抑制组蛋白去乙酰化酶等机制，发挥抗炎、诱导肿瘤细胞凋亡等作用，对维持肠道屏障完整性与预防恶性肿瘤至关重要[20]。第二，免疫调节。一方面，肠道是人体最大的免疫器官，肠道微生物的结构成分(如脂多糖、肽聚糖)激活宿主Toll样受体(Toll-like receptor, TLR)信号通路，诱导树突状细胞成熟、调节性T细胞(regulatory T cell, Treg)分化；另一方面，肠道微生物代谢产物可通过激活G蛋白偶联受体(G protein-coupled receptor, GPCR)，抑制辅助性T淋巴细胞17(T helper cell 17, Th17)极化，减少促炎因子释放，从而维持机体正常的免疫监视功能；若发生菌群失调，则免疫监视功能下降，这成为肿瘤发生的重要诱因[21]。第三，屏障维护。健康的肠道菌群能促进黏液分泌与紧密连接蛋白表达，构成坚实的物理化学屏障，防止病原体内移及内毒素入血，一旦屏障受损，将导致全身性的慢性低度炎症状态，为肿瘤生长创造有利的条件[22]。尤为重要的是，肠道微生物组的这些局部作用可通过代谢产物进入循环系统或免疫细胞迁移产生远程调控效应，具备影响远端生殖道微环境的潜力。肠道微生物组类型及核心特征见表1。

1.2 阴道微生物组：女性生殖健康的“黏膜防线”

阴道作为女性生殖系统的核心黏膜部位，与肠道微生态的多样性不同，健康的阴道微生物组以其低多样性和乳酸杆菌属的优势定植为显著特征[11]。健康育龄期女性阴道内pH值维持在3.8~4.5的酸性范围，这一环境主要由乳杆菌属通过发酵阴道上皮细胞分泌的糖原产生乳酸所构建，同时乳酸杆菌分泌细菌素、过氧化氢等抗菌物质，构成抵御病原微生物入侵的第一道防线[23]。从群落构成看，健康阴道微生物组的优势菌高度集中，其中以卷曲乳杆菌、

表1 肠道微生物组类型及核心特征

Table 1 Types and core characteristics of the intestinal microbiome

菌群类型 Microbial community type	核心优势菌群 Core beneficial bacterial flora	核心生理功能 Core physiological functions	失调后的核心影响 The core impact after the imbalance
Symbiotic strains	*Bacillota* *Bacteroidetes*	Promote nutrient digestion and absorption	Digestive system disease
Conditioned pathogen	*Escherichia coli*	Maintain the function of the intestinal barrier	Systemic diseases caused by impaired intestinal barrier function
Pathogenic bacteria	*Salmonella* *Shigella*	Regulators of the immune system	Immune-related diseases
		Anti-inflammatory	Chronic inflammation
		Anti-cancer	Increase the risk of tumor formation
		Regulate estrogen metabolism	Metabolic-related diseases
		Regulating emotions and brain functions	Nervous system disease

表2 阴道微生物组类型及核心特征

Table 2 Types and core characteristics of the vaginal microbiome

菌群类型 Microbial community type	核心优势菌 Core beneficial bacteria	pH值范围 pH value range	核心特征 Core feature	与女性生殖健康/妇科恶性肿瘤关联 Associated with female reproductive health/gynecological malignancies
Lactobacillus dominant strain	*Lactobacillus crispatus* *Lactobacillus acidophilus* *Lactobacillus casei* *Jian's Lactobacillus*	3.8-4.5	Low diversity of the microbial community; the proportion of beneficial bacteria is 80% to 95%; secretion of lactic acid and H_2O_2; antibacterial and anti-inflammatory	Maintain the reproductive mucosal barrier, inhibit persistent HPV infection, and reduce the risk of gynecological tumors
Microbial community mixture type	Decrease in *lactobacilli* The number of facultative anaerobes has increased	4.6-5.0	Increase in microbial diversity; weakening of acidic environment; the opportunistic pathogen begins to multiply	Local mucosal immunity declines, increasing HPV susceptibility, thereby raising the potential risk of cervical lesions
Anaerobic dominant type	*Gardnerella* *Prevotella* *Bacteroides*	＞5.0	The lactobacillus significantly decreased; pathogenic bacteria are dominant; the increase in amine substances; compared with chronic inflammation	Disrupting the local immune microenvironment, hindering the clearance of HPV, inducing pelvic inflammatory disease, and increasing the risk of cervical, endometrial and ovarian cancers

格氏乳杆菌、詹氏乳杆菌及惰性乳杆菌为核心菌种, 占比可达80%~95%, 其余少量菌群为肠球菌属、葡萄球菌属等兼性厌氧菌, 以及加德纳菌等条件致病菌, 正常状态下条件致病菌丰度被乳杆菌严格抑制[24]。阴道微生态系统具有动态调节性, 其菌群结构会因妊娠、月经周期等内在生理因素及不洁卫生习惯、无保护性行为等行为因素, 以及细菌性阴道病等病理状态而产生适应性改变, 但阴道乳酸杆菌主导的状态是健康的标志[25]。阴道乳酸杆菌能够调节局部黏膜免疫应答, 促进免疫耐受与有效防御之间的平衡。另外乳酸杆菌产生的乳酸, 尤其是L-异构体, 不仅维持酸性环境, 还能直接促进宫颈阴道上皮的屏障修复、抑制病原体增殖并调节免疫细胞功能[26]。值得注意的是, 阴道微生态的紊乱并非一个孤立事件, 其影响可通过免疫炎症循环或代谢扩散波及肠道, 这构成了“肠道−阴道轴”双向互调的核心逻辑。阴道微生物组类型及核心特征见表2。

2 肠道−阴道轴微生物组交流机制

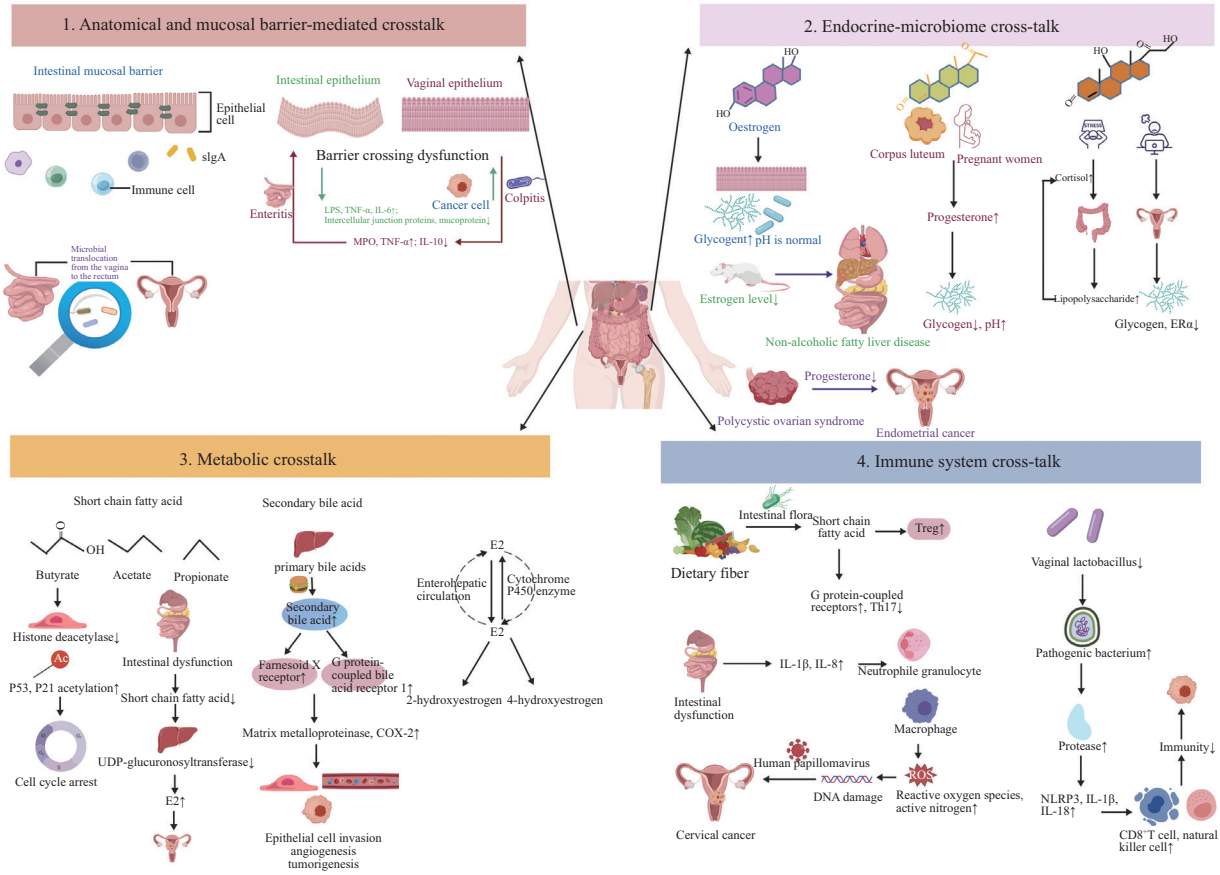
肠道与阴道微生物组之间的双向串扰由解剖、免疫、代谢和内分泌网络介导, 构成了肠道−阴道轴的核心调节逻辑, 实现了持续动态的信号交流。这种串扰的失调破坏了两个微生态系统的共生平衡, 创造了一个促炎和促肿瘤的微环境, 从而驱动了妇科恶性肿瘤的发生和进展。为了充分解析肠道−阴道轴在肿瘤生物学中的作用, 需系统地剖析双向串扰每个维度背后的作用机制。肠道–阴道轴微生物组交流机制见图1。

2.1 解剖学和黏膜屏障介导的串扰: 微生物组溢出的直接途径

肠道与女性生殖道在解剖上的毗邻性与保守的黏膜屏障特性, 为微生物及其信号分子的直接易位提供了物理基础[27]。在健康状态下, 肠道黏膜屏障由黏液层、抗菌肽、分泌性免疫球蛋白A以及固有层的免疫细胞等多种组成要素共同构成, 形成物理、化学和免疫三重防御体系[28]; 阴道上皮屏障主要由复层鳞状上皮及其细胞间连接构成, 其防御功能在很大程度上依赖于优势菌群乳酸杆菌的功能性强化[29-30]。肠道黏膜屏障与阴道上皮屏障形成双重防线, 有效抑制微生物过度生长与迁移。

2.1.1 *微生物易位* 研究发现, 共在阴道或直肠部位检出63种细菌, 其中44%的细菌物种在两个器官中均有分布, 且68%的物种在基因型层面完全一致[31]。近年发表的一项研究结果显示, 基于物种级Spearman相关系数分析, 研究者对孕妇直肠与阴道内的微生物群落进行分离与检测, 揭示了非乳酸杆菌主导的孕妇阴道和直肠中特定细菌共存特征[32]。

2.1.2 *屏障交叉失调* 既往相关横断面研究已证实, 肠道是乳酸菌菌株的重要储存库[33]。当肠道功能受损时, 阴道中乳酸菌水平随之下降, 影响阴道屏障功能完整性。此外, 当肠道屏障受损时, 脂多糖(lipopolysaccharide, LPS)进入循环并诱导促炎因子



向上箭头: 上调; 向下箭头: 下调。

Upward arrow: upregulation; downward arrow: downregulation.

图1 肠道–阴道轴微生物组串扰与妇科恶性肿瘤的关联机制

Fig.1 The mechanism of the microbiome cross-talk between the gut and vaginal axes and its association with gynecological malignancies

如肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、白介素-6(interleukin-6, IL-6)产生, 促炎因子可下调紧密连接蛋白表达、减少黏蛋白分泌, 进而破坏阴道上皮屏障完整性[34]。这会形成一个正反馈病理循环, 即阴道屏障受损会让阴道病原体如阴道加德纳菌上升到子宫或输卵管, 从而可能诱发盆腔炎, 而盆腔炎恰好是子宫内膜癌和卵巢癌的明确风险因素[35-36]。

值得注意的是, 肠道与阴道的串扰是双向的。已有研究表明, 阴道加德纳菌诱导的阴道病可以引起结肠髓过氧化物酶(myeloperoxidase, MPO)活性升高、TNF-α表达上调、IL-10表达下调, 导致全身炎症反应, 特别是结肠炎等胃肠道炎症。这种双向屏障功能障碍使得慢性炎症状态长期维持, 为微生物组驱动的肿瘤发生奠定了基础[37]。

2.2 内分泌–微生物组串扰: 激素信号作为双向通信的关键调节因子

肠道–阴道轴受宿主内分泌系统动态调节, 性激素和应激相关激素将微生物组的结构与功能和宿主生殖健康联系起来。这些激素调节肠道和阴道中的微生物群落结构和功能, 而微生物组反过来又调节激素代谢, 从而形成一个相互的内分泌–微生物组反馈循环, 这对于维持体内平衡至关重要。这一循环的破坏会影响微生物平衡和激素信号转导, 增加妇科恶性肿瘤的发生风险。

2.2.1 *雌激素介导的肠道–阴道交叉调节* 雌激素是女性的主要性激素, 对肠道和阴道微生物组都具有组织特异性作用, 其水平决定了微生物群落结构的关键特征。①阴道微生物组调节: 雌激素促进阴道上皮细胞的增殖和分化, 上调糖原的合成和分泌[38]。糖原是阴道乳酸杆菌的重要营养来源, 青春期及妊娠期女性在高水平生理性雌激素的作用下, 阴道糖原富集, 乳酸杆菌利用糖原发酵产生乳酸, 从而维持酸性阴道微环境[30]。相反, 绝经后女性在雌激素水平下降的状态下, 阴道上皮萎缩会降低糖原的可用性, 导

致乳酸杆菌丰度显著下降和机会性病原体如阴道加德纳菌的过度生长[39]。②肠道微生物组调节: 人类志愿者数据表明, 肠道微生物群影响全身雌激素水平[40]。与此同时, 雌激素可通过调控肠道上皮的生理功能及局部免疫活性, 参与肠道微生物群落的组成与稳态维持[41]。一项动物实验表明, 手术或自然更年期相关的生殖激素缺乏与非酒精性脂肪肝的高风险相关, 雌激素可以通过调节肠道微生物群组成预防绝经后非酒精性脂肪肝的发生[42]。

2.2.2 *黄体酮和皮质醇: 肠道−阴道轴串扰的次级内分泌调节剂* 黄体酮是另一种关键的性激素, 主要在黄体期和怀孕期间调节肠道−阴道串扰。在月经周期的黄体期, 黄体酮水平上升, 抑制阴道上皮细胞增殖和糖原分泌, 导致乳酸杆菌丰度短暂降低, 阴道pH值轻度升高[43-45]。这种生理波动通常耐受性良好, 但在已有阴道生态失调的女性中, 它会促进致病菌过度生长, 增加周期相关阴道炎的风险。在妊娠期间, 黄体酮水平急剧上升, 一方面通过增强阴道上皮屏障功能支持乳杆菌定植以降低感染风险, 另一方面有研究认为, 若黄体酮介导的免疫抑制过度, 可能导致致病菌过度增殖, 间接增加早产和宫内感染风险[46-47]。同时, 相关研究表明黄体酮通过增强肠道屏障功能和抑制促炎反应来调节肠道微生物组, 这有助于降低怀孕期间炎症性肠病的发病率[48]。黄体酮介导的微生物调节机制若中断, 如多囊卵巢综合征女性常因排卵异常出现黄体酮缺乏, 导致肠道乳杆菌丰度下降、促炎菌群富集, 进而通过干扰雌激素代谢稳态, 增加子宫内膜癌风险[49]。

皮质醇是主要的应激激素, 是肠道−阴道轴的另一种关键内分泌调节剂。在心理压力、慢性疾病状态下, 机体循环皮质醇持续升高从而破坏两个部位的微生物稳态: ①在肠道中, 皮质醇通过下调紧密连接蛋白的表达和减少黏液分泌增加肠道通透性, 促进微生物易位和LPS释放, 这会引发全身炎症反应, 进一步提高皮质醇水平, 形成“压力−炎症−生态失调”循环[50-51]; ②在阴道中, 皮质醇通过抑制阴道上皮细胞中糖原合成和下调雌激素受体α(estrogen receptor alpha, ERα)表达来抑制乳酸杆菌的增殖, 从而降低阴道黏膜对雌激素营养作用的敏感性[52]。此外, 皮质醇激活阴道免疫细胞上的糖皮质激素受体, 抑制抗菌肽的产生并损害阴道免疫细胞的吞噬功能, 增加阴道感染的风险。流行病学研究已经将慢性压力及皮质醇升高与HPV感染后的免疫清除障碍、细菌性阴道炎复发和宫颈癌进展的风险增加联系起来, 这凸显了压力相关的内分泌功能障碍在破坏肠道−阴道轴串扰和促进肿瘤发生方面的作用[53]。

2.3 代谢串扰: 微生物组衍生的代谢物作为肿瘤代谢的远程调节剂

微生物代谢产物是介导肠道−阴道对话的一类关键信使, 它们由肠道微生物群产生, 并通过体循环远程调控远端器官。其中短链脂肪酸(short-chain fatty acids, SCFAs)、次级胆汁酸(secondary bile acid, SBA)和雌激素代谢物是肠道与阴道代谢串扰特征较为明确的介质, 对妇科恶性肿瘤的发展具有一定的影响。

2.3.1 *SCFAs: 保护性代谢物* SCFAs主要包括丁酸盐、乙酸盐和丙酸盐, 是通过肠道共生体如普氏粪杆菌、双歧杆菌发酵膳食纤维产生的, 在肠道菌群失调患者中, 它们的水平显著降低, 通过多种机制促进肿瘤发生。丁酸盐是最有效的SCFAs, 可降低阴道和子宫上皮细胞中的组蛋白脱乙酰酶(histone deacetylase, HDAC)活性, 增加*P53*和*P21*抑癌基因的乙酰化水平, 这种上调诱导细胞周期停滞和细胞灭亡, 阻止上皮细胞的恶性转化[54-55]。SCFAs增强肝脏UDP-葡萄糖醛酸转移酶(UDP-glucuronosyltransferase, UGT)的活性, UGT是将雌激素结合成非活性形式的酶, 促进其代谢清除[56]。在肠道生态失调状态下, SCFAs减少会降低UGT活性, 导致循环中生物活性雌激素水平升高。持续的高雌激素暴露会刺激子宫内膜上皮细胞增生, 这是子宫内膜癌的关键驱动因素。

2.3.2 *SBA: 双刃剑* 初级胆汁酸在肝脏中合成, 肠道细菌通过水解作用将其去结合, 进一步通过7α-脱羟基等反应将其转化为SBA[57]。高脂肪饮食或具有胆汁代谢能力的梭状芽孢杆菌过度生长会增加循环中的SBA水平[58]。胆汁酸可以激活法尼醇X受体(farnesoid X receptor, FXR)和G蛋白偶联胆汁酸受体1(G protein-coupled bile acid receptor 1, Gpbar1), 触发下游细胞内信号通路, 间接上调基质金属蛋白酶(matrix metalloproteinase, MMP)和环氧合酶2(cyclooxygenase-2, COX-2)的表达, 促进上皮细胞侵袭和血管生成, 加速癌症的发展进程[59-61]。肠道来源的SBA可能通过体循环等途径进入腹膜腔并在卵巢肿瘤微环境中积累, 在卵巢癌细胞中, 脱氧胆酸诱导线粒体功能障碍和氧化应激, 促进活性氧(reactive oxygen species, ROS)的产生和DNA损伤、突变, 推动肿

瘤的恶性演进[62]。

2.3.3 雌激素代谢物串扰: 与激素驱动癌症的关键联系 肠道微生物组是雌激素代谢的关键调节因子, 可直接调控激素依赖性妇科恶性肿瘤如子宫内膜癌、卵巢癌的发生。肠道微生物组对雌激素代谢的调控是双向串扰的关键环节, 除结合型雌激素的肠肝循环调控外, 肠道菌群还可通过细胞色素P450酶将雌激素代谢为不同活性产物, 如将雌二醇转化为弱雌激素(2-羟雌酮)或强雌激素(4-羟雌酮), 健康菌群以产生2-羟雌酮为主, 而菌群失调时4-羟雌酮积累, 进一步增强雌激素对子宫内膜的刺激作用[63-64]。

2.3.4 其他代谢物串扰 色氨酸是人体必需氨基酸, 无法自身合成, 需要通过膳食摄取, 既是宿主合成蛋白质、5-羟色胺等生物活性物质的核心底物, 也是肠道与阴道微生物组的重要代谢原料[65]。在人体微生态系统中, 肠道中的大肠杆菌、梭状芽孢杆菌等通过色氨酸酶催化色氨酸生成吲哚[66]。在健康状态下, 吲哚-3-甲醇及其主要代谢物3, 3'-二吲哚甲烷能够调节雌激素代谢, 降低雌激素驱动的恶性肿瘤风险[67]。

2.4 免疫学串扰: 调节肿瘤免疫监测的系统网络

免疫系统是肠道−阴道轴中至关重要的沟通桥梁, 它与代谢、内分泌等通路共同构成一个复杂的协同网络, 调控着女性生殖道的健康。肠道作为人体最大的免疫器官, 其菌群状态系统性塑造了宿主的免疫基调[68]。

2.4.1 肠道微生物群塑造阴道黏膜免疫 肠道菌群发酵膳食纤维产生的丁酸等SCFAs, 是诱导肠道中Treg分化和功能的关键信号[69]。凭借黏膜免疫的共同黏膜免疫系统特性, 这些肠道来源的Treg可进入全身循环, 分布至远端黏膜部位[70]。在阴道黏膜, 丁酸可激活上皮细胞和免疫细胞上的GPCR, 抑制促炎Th17细胞分化, 同时促进具有免疫抑制功能的Treg扩增, 从而维持阴道局部的免疫稳态, 防止过度炎症[71]。相比之下, 肠道菌群失调会打破阴道免疫微环境平衡, 使其向促炎表型偏移, 此时肠道与阴道局部的促炎细胞因子如IL-1β、IL-8水平显著升高, 招募中性粒细胞和活化的巨噬细胞聚集于阴道黏膜[72-73]。这些免疫细胞被过度激活后会释放ROS和活性氮, 进而诱导阴道和宫颈上皮细胞发生DNA损伤, 在HPV持续感染的背景下, 这种损伤会进一步加剧, 增加宫颈癌的发生风险[74-75]。此外, 肠道驻留树突状细胞可捕获肠道共生细菌抗原, 其迁移到肠系膜淋巴结并诱导抗原特异性T细胞分化, 这些活化T细胞可通过体循环被运输到包括阴道在内的远处黏膜部位[76-77]。例如肠道鼠李糖乳杆菌激活的树突状细胞, 可诱导局部分泌IL-10的Treg分化[78]; IL-10作为关键抗炎细胞因子, 既能维持宿主对阴道共生菌的免疫耐受, 又能抑制过度炎症反应。当肠道菌群失调时, 树突状细胞反而被致病抗原激活, 诱导促炎Th1细胞分化, 后者随循环迁移至阴道并驱动慢性炎症, 从而创造有利于妇科肿瘤进展的微环境[79]。

2.4.2 阴道微生物群调节全身抗肿瘤免疫 阴道乳酸杆菌作为优势菌群, 其数量耗竭会导致病性细菌过度增殖。这些致病菌会分泌蛋白酶、毒素等物质, 诱导阴道上皮细胞坏死, 坏死细胞释放的损伤相关分子模式(damage-associated molecular pattern, DAMP)会激活阴道局部巨噬细胞中的NLRP3炎症小体, 进而触发IL-1β、IL-18等促炎因子的大量分泌[80]。这些促炎细胞因子进入全身循环后, 可促进髓源性抑制细胞向肿瘤微环境募集并活化, 活化的髓源性抑制细胞又可进一步抑制全身的$CD8^+$ T细胞和自然杀伤细胞(natural killer cell, NK)的功能, 进一步削弱全身抗肿瘤免疫应答[81]。

3 肠道−阴道轴微生物组串扰与妇科恶性肿瘤的关联机制

3.1 宫颈癌: HPV感染的土壤塑造与清除抑制协同效应

高危型人乳头瘤病毒(high-risk human papillomavirus, HR-HPV)持续感染是宫颈癌发生的始动因素, 但肠道−阴道轴微生物组串扰通过调控HPV感染微环境及宿主免疫清除能力, 决定病变进展走向[82]。当轴系串扰紊乱时, 双重病理效应加速致癌进程。机体阴道微生态平衡被打破, 诱发细菌性阴道病等疾病时, 加德纳菌、普雷沃菌等厌氧菌过度增殖, 其代谢产生的腐胺、尸胺等胺类物质中和乳酸, 使阴道pH升至5.0以上, 为HR-HPV附着创造适宜微环境[83]。有学者研究证实, 阴道菌群失衡还与病毒清除延迟有关, 细菌性阴道炎有助于HPV感染的持续存在[84]; 且宫颈上皮内肿瘤的严重程度与阴道微生物多样性的增加具有一定相关性[85]。分泌型免疫球蛋白A(secretory immunog lobulin A, sIgA)是肠道黏膜组织中最丰富的抗体类型, 可调节肠道菌群的组成比例, 维持肠道内微生物的稳态。一项临床研究表明, 阴道微生态可影响sIgA的分泌效率, 宫颈病变程度与sIgA的表

达呈负相关, 当sIgA表达水平降低时机体对宫颈的保护作用也会相应下降[86]。当肠道−阴道轴串扰正常时, 乳酸杆菌占据优势, sIgA分泌增多, 高浓度的sIgA通过免疫排斥机制清除病毒颗粒并将病原体阻挡在黏液层外, 从而提高HR-HPV的清除率, 使病变消退概率增大[87]。当HR-HPV持续感染并引发微生态紊乱时, 细菌性阴道病相关的厌氧菌可分泌唾液酸酶, 其可切割sIgA末端的唾液酸, 使糖残基暴露在外, 加速sIgA被阴道加德纳菌、普雷沃菌属等分泌的蛋白酶水解, 最终导致sIgA的非特异性抗菌功能受损[88]。另外, 目前的诸多研究证实, 结肠癌、宫颈癌等多种癌细胞表达并分泌免疫球蛋白G(immunoglobulin G, IgG)[89-90]。WANG等[91]研究表明, 在人宫颈HeLa细胞中, 癌源IgG在体内及体外低水平诱导ROS产生以促进癌细胞生长和增殖。该团队后续研究进一步揭示, IgG通过与TLR4相互作用并增强其表达, 促进LPS诱导的促炎因子产生, 从而推动宫颈癌细胞的生长和增殖[92]。

3.2 子宫内膜癌: 激素失衡与微生物组串扰的双重驱动

子宫内膜癌尤其是I型雌激素依赖性子宫内膜癌的核心致病因素是持续性雌激素暴露, 而肠道−阴道轴微生物组串扰通过调控雌激素代谢、局部炎症和免疫平衡, 成为激素失衡与肿瘤发生代谢桥梁。近期研究表明, 菌群失调导致肠道屏障受损, 通过激活TLR引起慢性炎症状态, 并使得代谢和雌激素水平失调, 这些效应会作用于妇科肿瘤的癌变过程[93]。肠道菌群失衡时, 部分结合型雌激素可随胆汁进入肠道, 经肠道菌群产生的β-葡萄糖醛酸酶(β-glucuronidase, GUS)分解为游离型雌激素, 进而重吸收进入血液循环, 造成体内雌激素蓄积, 靶向作用于乳腺、子宫内膜等组织器官, 从而促进子宫内膜癌、乳腺癌等雌激素依赖性肿瘤的发生与进展。此外, 雌激素水平升高还会引发阴道微生物组的结构改变, 扰乱肠道−阴道微生物组轴的稳态, 进而间接推动子宫内膜癌的发生与进展[94]。

3.3 卵巢癌: 腹膜微环境重塑与转移潜能增强的病理枢纽

卵巢癌因早期症状隐匿且转移迅速, 预后极差, 肠道−阴道轴串扰通过重塑腹膜微环境及增强肿瘤侵袭性参与其发病。相关研究通过16S rRNA基因的高通量测序技术对比分析卵巢癌患者样本与健康卵巢组织后发现, 卵巢癌患者的肠道微生物群落多样性显著降低, 且群落结构发生紊乱, 潜在致病菌的丰度上升[95]。NENÉ等[96]研究发现, 近期确诊卵巢癌以及BRCA1胚系突变携带者(尚未患癌)的女性与健康女性的宫颈−阴道菌群相比, 卵巢癌的存在或已知的疾病风险因素(年龄、BRCA1胚系突变等)与低乳酸杆菌比例的阴道菌群具有相关性。既往研究显示, 卵巢癌女性的阴道与肠道微生物群呈现共同的失调特征, 乳酸杆菌比例下降, 而普雷沃特菌相对丰度增加, 这些结果表明, 微生物组结构的变化与卵巢癌疾病状态有关; 此外, 化疗也被证实会影响阴道菌群的组成[97]。当轴系串扰紊乱时, 多重病理改变推动卵巢癌发生发展。阴道微生态失调导致的致病菌可通过生殖道上行侵入腹膜, 与肠道移位的致病菌共同形成腹膜菌群污染, 其释放的LPS激活腹膜间皮细胞NF-κB通路, 分泌CCL2、CXCL8等趋化因子, 招募髓源性抑制细胞, 形成免疫抑制的腹膜微环境[98-99]; 肠道菌群紊乱引发的代谢性内毒素血症则通过血液循环增强卵巢癌细胞侵袭能力。

4 结语与展望

肠道−阴道轴微生物组在妇科恶性肿瘤中的研究取得一定进展, 但仍面临以下挑战。①现有研究多基于动物模型和横断面临床研究, 对“微生物组−宿主−免疫−代谢”多系统互作网络的解析停留在相关性层面, 缺乏大规模、多中心的前瞻性队列研究以明确微生物紊乱与肿瘤发生发展的动态因果链。②微生物临床干预策略的疗效受宿主遗传背景、基础微生态、饮食生活方式等多重因素的影响。目前缺乏能够精准预测疗效的生物标志体系, 导致无法实现患者的有效分层, 从而制约了个性化干预方案的制定与应用。③虽然已有研究指出SCFAs、SBA、雌激素代谢物等在宫颈癌、子宫内膜癌、卵巢癌中的潜在作用, 但缺少大规模随机对照试验验证微生物干预对生存率、复发率或化疗耐药的直接影响。基于当前研究瓶颈, 未来研究可聚焦以下方向, 推动肠道−阴道轴微生物组在妇科恶性肿瘤领域的相关进展。①开展多中心、长周期的微生物组–肿瘤进展纵向队列研究, 构建“微生物扰动−肿瘤演化”的动态因果网络。②致力于构建基于多组学整合分析的患者分型系统, 通过定义不同的“微生态–肿瘤”亚型, 为设计联合益生菌、靶向抗生素的个性化、标准

化方案提供理论依据，并开展相应的临床试验以验证其有效性与安全性。③探索将微生物组调节与现有标准疗法联合应用，有效逆转免疫抑制、克服治疗耐药，从而改善患者预后，特别是晚期及复发患者，开辟新的治疗途径，以期肠道−阴道轴微生物为妇科恶性肿瘤的机制解析及相关临床转化提供新视角。

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