

肠道菌群与围绝经期妇科恶性肿瘤: 基于“三重调控轴”探讨其潜在关联与调控机制的叙述性综述

赵奕凌, 曹惠娟, 张红玉, 李雨峰*, 秦天生*

[兰州大学第二医院 (第二临床医学院), 甘肃 兰州 730030]

【摘要】 围绝经期是妇科恶性肿瘤的关键风险窗口, 其风险升高与激素失衡及肠道菌群紊乱密切相关。本综述首次提出“三重调控轴”框架, 阐述围绝经期女性肠道菌群通过肠道-激素轴、肠道-免疫轴、肠道-慢性炎症轴的协同作用, 从激素稳态、免疫功能、炎症状态三个核心维度调控妇科恶性肿瘤的发生发展进程。进一步总结益生菌干预、饮食调整、生活方式优化等菌群调控策略的临床效果, 并指出当前机制研究深度不足、临床转化局限、多轴协同复杂等挑战, 提出未来需聚焦“精准微生态干预”, 为围绝经期妇科恶性肿瘤防治提供新方向。

【关键词】 围绝经期管理; 肠道菌群; 三重调控轴; 妇科恶性肿瘤; 益生菌

中图分类号: R737.3

文献标识码: A

文章编号: 2096-8965 (2026) 01-0056-11

Gut microbiota and gynecological malignancies during perimenopause: A narrative review based on triple regulatory axis to explore their potential associations and regulatory mechanisms

Zhao Yiling, Cao Huijuan, Zhang Hongyu, Li Yufeng*, Qin Tiansheng*

(The Second Hospital & Clinical Medical School, Lanzhou University, Lanzhou 730030, Gansu, China)

【Abstract】 The perimenopausal period is a critical risk window for gynecological malignancies, and this increased risk is closely related to hormonal imbalance and gut microbiota dysregulation. This review proposes for the first time a "triple regulatory axis" framework, systematically elucidating how the gut microbiota in perimenopausal women regulates the initiation and progression of gynecological malignancies through the synergistic action of the gut-hormone axis, gut-immune axis, and gut-chronic inflammation axis, across three core dimensions: Hormonal homeostasis, immune function, and inflammatory status. This review further summarizes the clinical effects of gut microbiota regulatory strategies, including probiotic intervention, dietary adjustment, and lifestyle optimization, and highlights current challenges such as insufficient mechanistic insight, limitations in

收稿日期: 2025-09-22; 修回日期: 2025-11-17

基金项目: 兰州大学第二医院 (第二临床医学院) 引进人才计划项目 (YJRCKYQDJ-2024-02); 甘肃省自然科学基金项目 (24JRRA1103); 甘肃省联合科研基金项目 (24JRRA931); 兰州市科技发展计划项目 (2024-3-82); 陇南市科技计划项目 (2024CX12); 陇南市社会化出资项目 (2021-SZ-19)

通信作者: 李雨峰 (1988-), 男, 甘肃嘉峪关人, 副主任医师, 主要从事子宫腺肌瘤与妇科常见疾病的研究, E-mail: 2726166301@qq.com; 秦天生 (1976-), 女, 甘肃兰州人, 主任医师, 副教授, 博士研究生导师, 主要从事妇科肿瘤的靶向治疗与免疫治疗的研究, E-mail: ogqtsmile@yahoo.com

clinical translation, and the complexity of multi-axis synergy. It proposes that future research should focus on "precision microbiota intervention" to provide a new direction for the prevention and treatment of gynecological malignancies in perimenopausal women.

[Keywords] Perimenopause management; Gut microbiota; Triple regulatory axis; Gynecological malignancies; Probiotics

围绝经期作为女性从生殖期向非生殖期过渡的关键阶段, 年龄通常为45~55岁, 不仅伴随卵巢功能衰退引发的雌激素水平骤降与激素波动^[1], 更成为妇科恶性肿瘤的高发期。这一脆弱性的核心驱动因素除了传统认知中的激素失衡, 如无孕激素拮抗的持续雌激素暴露外, 肠道菌群也有可能成为围绝经期肿瘤发生发展的关键调节者。肠道菌群在围绝经期会经历显著的结构与功能重塑^[2]。本综述通过广泛检索和筛选相关文献, 对围绝经期肠道菌群与妇科恶性肿瘤之间的关系进行了梳理, 提示肠道菌群可能通过肠道—激素轴、肠道—免疫轴、肠道—慢性炎症轴“三重调控轴”在妇科恶性肿瘤进展中发挥重要作用, 基于现有研究, 本文以“三重调控轴”为核心框架, 进一步解析其如何从激素代谢、免疫应答、炎症状态三个维度打破机体稳态, 总结益生菌干预、饮食调整、生活方式优化等有前景的

菌群调控策略, 还对不同研究之间的结果进行了比较和分析, 揭示潜在的机制和联系。同时分析当前研究面临的挑战与未来方向, 旨在为围绝经期妇科恶性肿瘤的预防与辅助治疗提供理论依据与实践参考。

1 围绝经期肠道菌群的特征与变化

随着卵巢功能的衰退和雌激素水平的显著下降, 围绝经期女性的肠道菌群在组成和功能上均会经历一系列变化。具体表现为有益菌的丰度降低, 而条件致病菌的比例增加, 这种菌群失调通过多种调控通道, 如脑—肠轴、骨—肠轴等导致代谢功能异常, 或通过其代谢物异常, 导致围绝经期常见的体重增加^[3]、胰岛素抵抗^[4]、骨骼健康问题^[5]及情绪波动^[6]等症状出现, 由此对围绝经期女性健康产生深刻影响 (见表1)。

表1 围绝经期女性菌群结构改变及临床关联

Table 1 Changes in gut microbiota structure and clinical associations in perimenopausal women

菌群类别	丰度变化	临床关联
双歧杆菌 ^[7]	降低	作为“精神益生菌”可降低焦虑、抑郁发生率, 通过调节肠道—脑轴改善精神症状, 与绝经后女性失眠、抑郁相关 ^[8-10]
拟杆菌属	升高	与绝经后骨痛发生率呈正相关关系, 可能通过调控骨—肠轴代谢通路影响骨质疏松 ^[11-12]
布劳特氏菌属	升高	参与维持肠道稳态, 但丰度过高可能与抗炎菌减少相关 ^[13]
粪杆菌属	降低	产丁酸的核心菌属具有抗炎、保护肠黏膜功能; 其减少与绝经后肠道炎症风险升高、雌激素E2水平下降呈正相关关系 ^[14]
罗斯氏菌属、真杆菌属、 罕见小球菌属	降低	均为厚壁菌门下产短链脂肪酸 (Short-Chain Fatty Acids, SCFAs) 菌属, 其减少可能导致肠道抗炎能力下降, 且与促卵泡激素水平呈负相关关系
大肠杆菌-志贺氏菌属	升高	条件致病菌, 其丰度升高可能提示绝经后肠道屏障功能轻微受损

此外, 肠道菌群在年龄和性别中也存在差异: 未成年人肠道菌群无明显性别差异, 青壮年性别差异最明显^[15], 中老年随年龄增加性别差异逐步减弱, 绝大部分差异消失^[16]。了解这些特点有助于开发针对围绝经期女性的健康干预措施, 包括饮食调整、益生菌补充等, 以改善围绝经期女性的生活质量和健康状况。

2 “三重调控轴”的作用机制

2.1 肠道—激素轴: 双向调控失衡与肿瘤风险

围绝经期雌激素水平的剧烈变化是驱动子宫内膜癌、卵巢癌等激素依赖性妇科肿瘤的核心因素, 而肠道菌群通过调控雌激素代谢基因组 (Estrobolome, ESB) ^[17]及特定代谢物主导的肠道

—激素轴, 其核心失衡特征表现为 β -葡萄糖醛酸酶(β -Glucuronidase, β -GUS)介导的活性雌激素升高通路, 和肠道菌群调控雌马酚(Equol, EQ)生成的肿瘤保护通路。

2.1.1 β -葡萄糖醛酸酶介导的雌激素肠肝循环调控

肠道菌群编码的 β -GUS是ESB的关键功能分子, 其活性直接决定雌激素的生物利用度^[18]。卵巢分泌的雌激素在肝脏中经葡萄糖醛酸化修饰后, 转化为无活性的结合态雌激素, 随胆汁排入肠道; 正常肠道菌群中, 乳杆菌属等有益菌可抑制 β -GUS活性, 减少结合态雌激素的去结合。

2.1.2 特定菌群介导的雌马酚生成通路

雌马酚是大豆异黄酮(如大豆苷元)经肠道菌群代谢后生成的一种具有强雌激素活性的微生物代谢产物^[19]。人体自身无法合成雌马酚, 其生成完全依赖于肠道微生物的转化能力。膳食中的大豆异黄酮首先被细菌产生的 β -GUS水解为苷元形式, 随后在特定菌株, 如异黄酮转化斯莱克菌、产雌马酚菌、黏液肠杆菌的协同作用下, 经过多步还原反应生成雌马酚^[20]。雌马酚通过多种机制发挥其对雌激素依赖性疾病的保护效应, 包括竞争性抑制内源性雌激素与受体结合、并促进有害雌激素代谢物的解毒与排泄^[21]。个体能否产生雌马酚严格依赖于其肠道中是否存在上述特定菌株, 仅有少数成年人具备这种产雌马酚能力, 其余则为非产雌马酚者^[22]。

2.1.3 围绝经期女性特异性调控与妇科肿瘤的关联

围绝经期卵巢功能衰退导致雌激素水平骤降, 雌激素缺乏降低肠道黏液分泌, 增强相关菌群如拟杆菌门^[23]定植, 显著增强 β -GUS表达^[24], 通过调节上述过程导致外周血中活性雌激素水平异常升高。因此围绝经期女性易形成雌激素下降, 菌群失调, 进而活性雌激素升高的恶性循环^[25]。

子宫内膜癌是发达国家最常见的妇科癌症之一, 是全球女性第6大常见癌症^[26]。绝经后女性多见于60~70岁^[27]。绝经后女性发病率的增加取决于脂肪组织内源性雌二醇产生的子宫内膜增殖^[28], 肠道菌群与子宫内膜癌之间的进展已被广泛研究^[29]。子宫内膜癌患者肠道中拟杆菌属、大肠杆菌属等 β -GUS高活性菌株丰度显著升高^[30], 子宫内膜癌组织处富集拟杆菌属、普雷沃氏菌属、阿托波菌属等条件致病菌属^[31]增殖, 会使外周血中活性雌激素水平升高, 持续刺激子宫内膜上皮细胞增殖, 且与疾病严重程度和预后不良相关^[32]。癌症基因组图谱数据库分析发现, 子宫内膜癌组织中普雷沃菌属、卟啉单胞菌属丰度与局部雌激素受体 α (Estrogen

Receptor α , ER α)表达呈正相关关系, 这些菌群可通过分泌芳香化酶样物质, 在子宫内膜局部促进雄激素向雌激素转化, 形成局部高雌激素微环境, 加速癌变进程^[33]。一项孟德尔随机化研究^[34]证实, 肠道中 γ -变形菌门丰度与子宫内膜癌风险呈因果正相关关系。同时产雌马酚者的肠道中乳杆菌属、双歧杆菌属丰度更高, 而拟杆菌属、大肠埃希菌-志贺菌属等促炎菌群丰度更低^[24, 35]。这也暗示在肠道菌群介导的雌激素和雌马酚的调控作用在子宫内膜癌等雌激素依赖性疾病中可能发挥重要作用。

研究^[36]表明, 雌激素在体外可能刺激卵巢癌细胞的生长, 并进一步促进卵巢肿瘤的耐药性^[37]。过量的雌激素可能刺激卵巢上皮细胞的增殖, 并通过受体依赖性途径以及受体依赖性机制加速卵巢癌的进展^[38-39]。同时, 围绝经期女性因雌激素不足而出现的症状, 激素替代治疗是有效的治疗手段, 但长期使用雌激素替代疗法与卵巢癌风险增加显著相关^[40-41]。结合围绝经期女性中上述形成的低雌激素状态 $\rightarrow$ 菌群失调 $\rightarrow$ 活性雌激素升高恶性循环, 肠道菌群的改变可能会进一步促进卵巢癌的发生与发展。

宫颈癌是非典型的雌激素依赖性疾病, 人乳头瘤病毒(Human Papillomavirus, HPV)的持续感染是宫颈癌发展的主要危险因素之一。宫颈转化区的未成熟化生鳞状上皮细胞是HPV感染的主要靶点, 而围绝经期女性特殊的异常雌激素信号可能会通过双重途径为宫颈转化区的HPV感染癌变创造条件。一方面, 游离雌激素与宫颈上皮细胞的雌激素受体结合, 可直接刺激细胞增殖, 增加HPV病毒基因组整合入宿主细胞的概率^[42]。另一方面, 高雌激素状态抑制ER α 的正常表达, 促进其变体ER-36过度激活, 进而上调HPV E6/E7致癌蛋白的转录水平^[43], 该蛋白可分别降解抑癌基因p53和视网膜母细胞瘤蛋白, 阻断细胞凋亡, 推动癌前病变向浸润癌进展^[44]。

2.2 肠道—免疫轴: 通过免疫重塑调控肿瘤免疫监视与逃逸

围绝经期女性因卵巢功能衰退伴随雌激素水平骤降, 不仅具有免疫衰老的特征, 更通过重塑肠道菌群结构, 打破肠道—免疫轴的稳态平衡^[16]。肠道菌群的特异性改变, 如产SCFAs菌群减少、致病菌丰度升高, 直接调控全身及生殖道局部免疫应答, 成为妇科肿瘤免疫监视失效与免疫逃逸的关键驱动因素^[45-46]。

2.2.1 SCFAs代谢通路的菌群依赖性失衡

围绝经期女性肠道中产SCFAs的核心菌群丰度

较育龄期女性显著下降^[47], 且该下降趋势与雌激素水平呈正相关关系^[48]。这种菌群特异性减少直接导致肠道内丁酸、丙酸等 SCFAs 浓度降低^[49]。SCFAs 一方面通过促进闭合蛋白、紧密连接蛋白 1 的表达保证肠道免疫屏障功能; 另一方面, SCFAs 还可通过抑制组蛋白去乙酰化酶 (Histone Deacetylase, HDAC) 促进肠道固有层调节性 T 细胞 (regulatory T cell, Treg) 分化^[50], 其中丁酸作为核心效应 SCFAs, 可选择性抑制 HDAC1/2 亚型活性, 通过增强 *Foxp3* 基因座去甲基化维持 Treg 表型稳定, 同时诱导幼稚 CD4⁺T 细胞向功能性 Treg 分化, 上调 IL-10、TGF- β 等抗炎因子分泌^[51]。此外, SCFAs 可直接激活 Th17 细胞和固有淋巴细胞分泌 IL-22, 该细胞因子能强化肠道上皮细胞修复与抗菌肽合成, 进一步加固肠道屏障^[52-53]。同时 SCFAs 还可通过抑制哺乳动物雷帕霉素靶蛋白 (mammalian Target of Rapamycin, mTOR) 信号通路调控 T 细胞代谢重编程, 减少效应 T 细胞的促炎活性, 与 HDAC 抑制形成协同免疫调控效应^[54]。

围绝经期产 SCFAs 菌群不足还会致使肠道屏障完整性受损, 肠道通透性增加^[55], Treg 细胞占比降低, 且其分泌的抗炎因子 IL-10 水平下降^[56]。同时, SCFAs 不足以解除对巨噬细胞向 M1 型极化的抑制, 使外周血中 M1 型巨噬细胞比例升高, 过量分泌的肿瘤坏死因子 α (Tumor Necrosis Factor- α , TNF- α)、IL-6 进一步加剧免疫紊乱, 形成“炎症—免疫耗竭”恶性循环^[57]。

2.2.2 色氨酸代谢通路的菌群介导性紊乱

围绝经期肠道中可分解色氨酸生成吲哚-3-丙酸 (Indole-3-Propionic Acid, IPA) 的菌群丰度显著降低^[58], 而可产生吲哚胺 2, 3-双加氧酶 (Indole-amine 2, 3-Dioxygenase, IDO) 的促炎菌丰度升高^[59], 导致色氨酸代谢向促免疫抑制方向偏移。一方面, IPA 水平下降使树突状细胞 (Dendritic Cells, DCs) 成熟率降低, 无法有效递呈肿瘤抗原, 导致 CD8⁺T 细胞激活受阻^[60]; IPA 作为色氨酸代谢的关键保护性产物, 可通过抑制 mTOR 信号通路活性、下调核糖体生物合成相关基因表达, 直接抑制 Th17 细胞分泌 IL-17A, 从而减少促炎因子对肠道黏膜的损伤^[61-62]。同时, IPA 能增强 Treg 细胞对效应 T 细胞的抑制作用, 通过上调细胞毒性 T 淋巴细胞相关蛋白 4 表达强化免疫耐受^[63]。

另一方面, 促炎菌分泌的 IDO 可将色氨酸转化为犬尿氨酸, 后者通过激活 Treg 细胞的细胞毒性 T 淋巴细胞相关蛋白 4 信号, 进一步增强免疫抑制效

应, 使肿瘤细胞得以逃避 CD8⁺T 细胞的攻击, 形成免疫抑制微环境^[64]。

2.2.3 围绝经期特异性免疫紊乱与妇科肿瘤的关联

围绝经期女性肠道菌群紊乱通过上述及多种机制促进妇科肿瘤发展, 如 SCFAs 不足导致的肠道黏膜屏障受损, 使脂多糖 (Lipopolysaccharide, LPS) 入血激活 Toll 样受体 4/核因子 κ B (Toll-Like Receptor 4/Nuclear Factor- κ B, TLR4/NF- κ B) 信号通路, 外周血中自然杀伤 (Natural Killer, NK) 细胞的杀伤活性下降, 无法清除早期肿瘤细胞^[65]等。

DCs 成熟受阻使 HPV 感染的宫颈上皮细胞无法被 CD8⁺T 细胞识别, HPV 持续感染率升高, 显著增加宫颈癌前病变进展为宫颈癌的风险^[66]。同时, 围绝经期肠道菌群的特异性改变通过肠道—生殖道轴直接影响生殖道免疫稳态, 导致生殖道乳杆菌定植下降, 致病菌如加德纳菌、阿托波菌丰度升高^[67]。致病菌可通过激活生殖道上皮细胞的 TLR4 信号, 促进 IL-10、TGF- β 等免疫抑制因子分泌, 使生殖道局部 CD8⁺T 细胞浸润量减少^[66], 为 HPV 持续感染创造免疫赦免环境, 使 CIN 进展为宫颈癌的风险升高^[68]。

子宫内膜癌的肿瘤免疫微环境是一个动态且高度异质的生态系统, 在疾病进展、转移和治疗反应中发挥着核心和复杂的作用。其关键的细胞成分, 包括免疫抑制性肿瘤相关巨噬细胞 (Tumor-Associated Macrophage, TAMs)、骨髓源性抑制细胞和癌相关成纤维细胞, 以及细胞外囊泡和重塑的细胞外基质等非细胞成分, 会进行复杂的串扰, 以建立深刻的免疫抑制环境^[69]。围绝经期女性特异的肠道菌群在其中可能也会通过特异性菌群促进免疫抑制性细胞因子 (如 IL-10、TGF- β) 分泌, 增加 CD4⁺T 细胞在子宫内膜的浸润^[70], 从而扰乱子宫内膜癌的肿瘤微环境导致疾病进展, 未来可进一步进行深入研究。同时, 明确子宫内膜癌中涉及 TLR 的微生物相互作用^[30], 也可能更好地了解子宫内膜癌的进展。

卵巢癌的免疫治疗面临的挑战之一是其复杂且具有免疫逃逸特性的肿瘤微环境 (Tumor Micro Environment, TME), 据 T 细胞的浸润情况可以将肿瘤分为“热肿瘤”和“冷肿瘤”^[71-72], 耐药性卵巢癌的肿瘤微环境中肿瘤相关浸润细胞的减少使其表现为“冷肿瘤”的特点。围绝经期女性由于肠道菌群的改变, 激活 ER α 信号通路, 可能会通过上述机制, 解除对巨噬细胞向 M1 型极化的抑制, 使外周血中 M1 型巨噬细胞比例升高, 促进 TAMs 向 M2

型极化^[39,73];减少CD8⁺T细胞浸润,不仅促进卵巢肿瘤进展,同时在卵巢肿瘤的免疫治疗进展中发挥抑制作用。

2.3 肠道—慢性炎症轴:通过炎症信号通路驱动肿瘤进展

慢性低度炎症是围绝经期女性的典型生理特征,肠道菌群通过肠道—慢性炎症轴释放促炎因子、激活炎症信号通路,进一步放大炎症效应,为妇科肿瘤的进展提供“炎症土壤”。

2.3.1 LPS-TLR4-NF- κ B 信号通路激活与炎症放大

围绝经期女性肠道菌群呈现促炎革兰阴性菌增加,而产SCFAs的有益菌减少的特点^[16,47]。这种菌群失调通过破坏肠道黏膜屏障完整性,导致LPS易位入血,形成内毒素血症^[74]。进入血液的LPS通过血液循环到达全身免疫细胞,与巨噬细胞表面的TLR4结合,激活下游髓样分化因子88依赖信号通路,促使NF- κ B转录因子入核,上调促炎因子的表达^[75-76]。同时,围绝经期雌激素缺乏可上调免疫细胞中TLR4的表达,形成正反馈循环,进一步放大炎症反应^[77]。研究^[48,78]表明,围绝经期女性外周血中IL-6和TNF- α 水平较育龄期显著升高,且与肠道内促炎菌丰度呈正相关。

2.3.2 炎症与围绝经期代谢紊乱的协同放大

围绝经期女性因雌激素缺乏引发的代谢变化与肠道菌群介导的炎症形成协同放大效应^[79-80]。脂肪细胞分泌的瘦素可通过激活巨噬细胞表面的瘦素受体,增强巨噬细胞对LPS的反应性,从而放大IL-6、TNF- α 的释放^[81]。这些促炎因子可通过Janus激酶—信号转导与转录激活因子3信号通路促进肝细胞合成C反应蛋白,而C反应蛋白升高可进一步抑制胰岛素敏感性,加剧脂肪堆积,形成“炎症—代谢紊乱—炎症”的恶性循环,为肥胖相关妇科肿瘤,如子宫内膜癌的进展提供条件^[82-83]。

2.3.3 围绝经期特异性炎症特征与妇科肿瘤的关联

围绝经期肠道菌群介导的慢性炎症,与不同妇科肿瘤的发生发展存在靶向关联,其机制结合了肿瘤病理特征与围绝经期生理特点,在妇科常见的恶性肿瘤中均有体现。

2.3.3.1 宫颈癌:菌群介导的炎症促进 HPV 持续感染与恶性转化

HPV感染是宫颈癌的主要诱因,而围绝经期肠道菌群介导的炎症可通过多方面促进HPV感染进展为宫颈癌^[66]。肠道菌群紊乱导致的LPS入血,可通过激活宫颈上皮细胞中的NF- κ B信号,直接上调HPV癌基因E6、E7的表达^[66]。研究^[68]表明,围

绝经期HPV持续感染女性中,肠道促炎菌丰度较高者进展为高级别宫颈上皮内瘤变(CIN II/III)的风险显著增加。

2.3.3.2 卵巢癌:炎症促进肿瘤血管生成与侵袭

围绝经期女性肠道菌群紊乱导致的LPS入血后,可通过血液循环到达卵巢TME,激活TAMs向M1型极化^[84]。M1型巨噬细胞分泌的TNF- α 可通过激活卵巢癌细胞中的NF- κ B信号,上调血管内皮生长因子的表达,促进肿瘤新生血管形成^[85]。同时,LPS可直接与卵巢癌细胞表面的TLR4结合,激活细胞内丝裂原活化蛋白激酶/细胞外信号调节激酶信号通路,促进基质金属蛋白酶的分泌,增强肿瘤细胞的侵袭与转移能力^[86]。此外,阴道微生物失调也会通过局部炎症反应激活TLR4通路,进一步放大系统性炎症,形成“炎症—肿瘤”恶性循环。

2.3.3.3 子宫内膜癌:菌群—炎症—代谢紊乱协同促进肿瘤进展

子宫内膜癌的发生与雌激素过度刺激、肥胖密切相关,而围绝经期肠道菌群介导的炎症与上述因素协同,加速癌变进程^[87]。同时,围绝经期肥胖女性的脂肪细胞分泌的瘦素,可与肠道菌群介导的IL-6协同,激活子宫内膜细胞中的JAK-STAT3信号通路,促进子宫内膜细胞从“增生”向“癌变”转化^[88-89]。此外,生物信息学研究显示,子宫内膜癌患者肠道中微小微单胞菌等菌株丰度与Treg细胞浸润呈负相关关系,其代谢产物可通过抑制Treg细胞功能,加剧局部炎症紊乱^[33]。

综上所述,围绝经期女性肠道菌群变化导致的双向失衡形成活性雌激素过量与雌马酚保护不足的恶性微环境,以及通过调控免疫及炎症相关通路形成的免疫监视削弱、慢性炎症放大共同构成围绝经期女性恶性肿瘤发生的风险网络,通过调整围绝经期女性菌群来改善上述调控机制,在妇科恶性肿瘤的防治中具有潜能。

3 围绝经期肠道菌群调控在妇科恶性肿瘤防治中的潜能

针对上述“三重调控轴”失衡,通过靶向肠道菌群的干预策略,可有效降低围绝经期女性肿瘤风险,具体包括益生菌干预、饮食调整和生活方式优化。

3.1 益生菌干预

围绝经期菌群紊乱诱发的慢性炎症与免疫逃逸,可通过特定益生菌干预改善。如通过补充双歧杆菌竞争性抑制致病菌定植以降低LPS水平,增强

肠道屏障功能,同时阻断 TLR2/4-NF-κB 促炎通路,将肿瘤微环境从冷转热,提升免疫治疗响应率^[90-91];或补充乳酸杆菌来分泌 3-吡啶乙酸激活孕烷 X 受体/TLR4 (Pregnane X Receptor/TLR4, PXR/TLR4) 信号,诱导 IL-35⁺B 细胞迁移,下调 TNF-α/IL-6 等促炎因子,维持生殖道免疫稳态^[92]。益生菌在围绝经期女性的健康调控中发挥重要作用,在不同疾病中都有体现。

3.1.1 宫颈癌: 益生菌介导 HPV 清除与放化疗毒性缓解的双重效应

围绝经期 HPV 持续感染患者肠道及阴道菌群紊乱促进 HPV 免疫逃逸^[93]。益生菌可通过调节肠道—阴道轴平衡,降低高危型 HPV 感染风险,部分菌株如鼠李糖乳杆菌、嗜酸乳杆菌能促进 HPV 相关病变得以清除,降低宫颈上皮内瘤变进展风险^[93-94]。放疗期间补充益生菌可显著降低放射性腹泻发生率及严重程度,改善粪便性状,并减少洛哌丁胺等止泻药物的使用^[95]。

同时联用特定益生元(如菊粉、低聚果糖),降低肠道通透性并减轻放疗诱导的肠道炎症,且安全性良好^[93]。

3.1.2 卵巢癌: 靶向化疗耐药与肿瘤微环境重塑的菌群调控方案

卵巢癌具有隐匿性强、化疗耐药率高的特点,围绝经期肠道菌群紊乱可能将通过补充益生菌来实现逆转耐药+抑制转移的靶向治疗。采用经基因改造的罗伊氏柠檬酸杆菌 IL-22 (LR-IL-22),通过口服使其定植于肿瘤缺氧微环境,分泌 IL-22 调控肿瘤相关基因表达,下调促炎因子,同时上调程序性死亡配体 1 表达并招募 CD8⁺T 细胞,增强免疫检查点抑制剂疗效,显著延长卵巢癌模型小鼠生存期^[96]。而在化疗期间补充植物乳杆菌与两歧双歧杆菌复合制剂,可通过胆汁盐水解酶活性降低血浆胆

固醇水平,改善内皮功能障碍,同时减轻化疗诱导的肠道黏膜损伤^[97];对于铂类耐药患者,联合嗜酸乳杆菌与阿司匹林干预,可通过抑制磷脂酰肌醇 3-激酶/蛋白激酶 B 通路增强肿瘤细胞对化疗药物的敏感性^[98]。

通过饮食补充,经肠道菌群发酵产生的丁酸作为 HDAC 抑制剂,可诱导卵巢癌细胞周期阻滞于 G₀/G₁ 期并促进铁死亡,在卵巢肿瘤的抑制过程中也发挥重要作用^[99]。

3.1.3 子宫内膜癌: 围绕激素平衡与增生抑制的菌群调控方案

子宫内膜癌与围绝经期雌激素/孕激素失衡密切相关,肠道菌群失调通过减少雌激素再吸收、增强子宫内膜炎症促进癌变。补充相应益生菌可能会通过“调节激素代谢+抑制内膜增生”在预防和控制疾病进展中发挥重要作用。

通过口服生孢梭菌联合大豆异黄酮,可通过肠道菌群水解大豆异黄酮为活性苷元,增强其雌激素受体调节作用,既抑制子宫内膜过度增生,又改善围绝经期症状^[97];补充鼠李糖乳杆菌可分泌乳酸降低阴道 pH 值,抑制阿托波氏菌等致病菌增殖,减少子宫内膜感染风险^[99]。同时子宫内膜癌腹腔镜术后补充凝结芽孢杆菌 TBC169,也可缩短首次排气时间与肠鸣音恢复时间,减少术后并发症发生率,通过修复肠道屏障功能加速康复^[95]。

3.2 调整生活方式

通过针对性摄入功能性食物,可定向调节肠道菌群结构,促进有益代谢物生成,结合以体育锻炼+压力/睡眠管理为核心的生活方式调整,可通过非药物手段改善肠道菌群结构,打破炎症—代谢紊乱恶性循环为肿瘤防治提供肠道微生态基础,具体方案及临床效果如下(见表 2)。

表 2 不同干预方式临床效果对比
Table 2 Comparison of clinical outcomes among different intervention methods

干预方式	具体方式	目标菌群	临床效果
调整饮食方案	地中海饮食	双歧杆菌增加	改善雌激素代谢 ^[100]
	高纤维饮食	罗斯氏菌属增加	加固肠道屏障 ^[101]
	低糖饮食	肠道放线菌增加	抑制全身炎症 ^[102]
	乳制品饮食	拟杆菌门/厚壁菌门的比例增加	缓解糖代谢紊乱 ^[103]
		阿克曼菌门增加 瘤胃球菌科降低	
调整生活方式	有氧运动	增加乳杆菌属、双歧杆菌属	减少腹部脂肪堆积 ^[104]
	抗阻运动	增加产酪酸菌	增强肠道屏障,改善葡萄糖代谢 ^[104]
	压力管理	恢复乳杆菌属、双歧杆菌属丰度 ^[105]	促进 3-吡啶乙酸生成 ^[106]
	睡眠干预	提升菌群 α 多样性,增加阿克曼菌	减轻全身炎症 ^[91]

饮食、运动、压力管理与健康结果之间的机制是复杂的、多方面的、相互作用的^[107], 通过联合干预, 如补充相关益生元, 摄入高纤维素饮食, 进行压力及睡眠干预, 围绝经期女性可能通过有效调控肠道菌群结构, 打破炎症与代谢紊乱的恶性循环, 为实现围绝经期女性恶性肿瘤防治提供可行方案。

4 小结

尽管围绝经期肠道菌群调控在妇科恶性肿瘤防治中展现出潜力, 当前研究仍面临核心挑战, 需通过针对性研究突破。

4.1 个体菌群差异导致干预效果不均

绝经后女性的肠道微生物组多样性通常较低, 并呈现一致的变化趋势, 例如厚壁菌门/拟杆菌门改变, 以及特定菌属丰度的变化。个体差异可能导致对干预措施的响应不同^[108]。例如, 免疫功能低下患者需谨慎使用活菌制剂, 优先选择灭活益生菌或代谢产物制剂; 避免在抗生素治疗期间同步补充益生菌, 需间隔2 h以上^[97]; HPV阳性患者若肠道双歧杆菌丰度低, 可优先补充长双歧杆菌; 卵巢癌耐药患者重点增加产丁酸菌株^[99]等。

4.2 机制研究深度不足

现有研究对核心机制的解析仍存在不足。尽管观察到菌群结构变化与肿瘤风险的相关性, 但具体作用机制需进一步阐明。如SCFAs如何通过抑制HDAC促进Treg的分化; 肠道菌群相关的代谢物如何影响远端器官的功能, 其具体分子靶点和信号通路需深入研究。同时肠道菌群与激素轴、免疫轴、炎症轴之间的交叉互作缺乏动态、系统的研究数据。

4.3 临床转化局限

当前菌群干预研究在临床转化中面临挑战: 多数研究的样本量有限、随访时间较短, 缺乏大规模、长期的随访数据来支撑干预措施的长期安全性和有效性评估^[109]。

未来需探索基于菌群分型的精准干预方案, 针对特定菌群特征的人群, 制定个性化的饮食、益生菌或生活方式组合策略^[110]; 同时针对普雷沃氏菌属富集型或拟杆菌属主导型菌群的特定干预措施, 可能为围绝经期女性的健康管理提供更有效的解决方案^[15], 结合代谢组学筛选关键效应分子, 开发个性化益生菌、益生元或粪菌移植方案^[90]; 同时与其他治疗方法的联合应用, 通过同步“三重调控轴”功能, 使肠道菌群成为改善围绝经期女性健康的有效干预靶点, 为健康管理提供新的思路和策略。

参考文献

- [1] MAURO L J, SPARTZ A, AUSTIN J R, et al. Reevaluating the role of progesterone in ovarian cancer: Is progesterone always protective[J]. *Endocrine Reviews*, 2023, 44(6): 1029-1046.
- [2] YANG M N, WEN S, ZHANG J, et al. Systematic review and meta-analysis: Changes of gut microbiota before and after menopause[J]. *Disease Markers*, 2022, 2022: 3767373.
- [3] WENG H D, DENG L, WANG T Y, et al. Humid heat environment causes anxiety-like disorder via impairing gut microbiota and bile acid metabolism in mice[J]. *Nature Communications*, 2024, 15(1): 5697.
- [4] DETWEILER P, WU P, LI C J, et al. Comment on "Estrogen deficiency induces bone loss through the gut microbiota"[J]. *Pharmacological Research*, 2024, 202: 107132.
- [5] WANG G, FAN Y, ZHANG G, et al. Microbiota-derived indoles alleviate intestinal inflammation and modulate microbiome by microbial cross-feeding[J]. *Microbiome*, 2024, 12(1): 59.
- [6] HUANG F, CAO Y, LIANG J, et al. The influence of the gut microbiome on ovarian aging[J]. *Gut Microbes*, 2024, 16(1): 2295394.
- [7] LI N, TAN S, WANG Y, et al. Akkermansia muciniphila supplementation prevents cognitive impairment in sleep-deprived mice by modulating microglial engulfment of synapses[J]. *Gut Microbes*, 2023, 15(2): 2252764.
- [8] CHEN J, CHEN X, HO C L. Recent development of probiotic bifidobacteria for treating human diseases[J]. *Frontiers in Bioengineering and Biotechnology*, 2021, 9: 770248.
- [9] PINTO-SANCHEZ M I, HALL G B, GHAJAR K, et al. Probiotic bifidobacterium longum NCC3001 reduces depression scores and alters brain activity: A pilot study in patients with irritable bowel syndrome[J]. *Gastroenterology*, 2017, 153(2): 448-459.e8.
- [10] DESBONNET L, GARRETT L, CLARKE G, et al. Effects of the probiotic bifidobacterium infantis in the maternal separation model of depression[J]. *Neuroscience*, 2010, 170(4): 1179-1188.
- [11] RETTEDAL E A, ILESANMI-OYELERE B L, ROY N C, et al. The gut microbiome is altered in postmenopausal women with osteoporosis and osteopenia[J]. *JBM Plus*, 2021, 5(3): e10452.
- [12] WANG Z X, CHEN K, WU C C, et al. An emerging role of prevotella histicola on estrogen deficiency-induced bone loss through the gut microbiota-bone axis in postmenopausal women and in ovariectomized mice[J].

- The American Journal of Clinical Nutrition, 2021, 114(4): 1304-1313.
- [13] LIU X, MAO B, GU J, et al. Blautia-a new functional genus with potential probiotic properties?[J]. Gut Microbes, 2021, 13(1): 1-21.
- [14] RIVIÈRE A, SELAK M, LANTIN D, et al. Bifidobacteria and butyrate-producing colon bacteria: Importance and strategies for their stimulation in the human gut[J]. Frontiers in Microbiology, 2016, 7: 979.
- [15] CROSS T L, SIMPSON A M R, LIN C Y, et al. Gut microbiome responds to alteration in female sex hormone status and exacerbates metabolic dysfunction[J]. Gut Microbes, 2024, 16(1): 2295429.
- [16] KIM Y S, UNNO T, KIM B Y, et al. Sex differences in gut microbiota[J]. The World Journal of Men's Health, 2020, 38(1): 48-60.
- [17] SALLISS M E, FARLAND L V, MAHNERT N D, et al. The role of gut and genital microbiota and the estrobolome in endometriosis, infertility and chronic pelvic pain[J]. Human Reproduction Update, 2021, 28(1): 92-131.
- [18] HU S, DING Q, ZHANG W, et al. Gut microbial beta-glucuronidase: A vital regulator in female estrogen metabolism[J]. Gut Microbes, 2023, 15(1): 2236749.
- [19] LV J, JIN S K, ZHANG Y W, et al. Equol: A metabolite of gut microbiota with potential antitumor effects[J]. Gut Pathogens, 2024, 16(1): 35.
- [20] JACKMAN K, WOODMAN O, SOBEY C. Isoflavones, equol and cardiovascular disease: Pharmacological and therapeutic insights[J]. Current Medicinal Chemistry, 2007, 14(26): 2824-2830.
- [21] LU J, CHEN P P, ZHANG J X, et al. GPR43 deficiency protects against podocyte insulin resistance in diabetic nephropathy through the restoration of AMPKalpha activity[J]. Theranostics, 2021, 11(10): 4728-4742.
- [22] KUMARI N, KUMARI R, DUA A, et al. From gut to hormones: Unraveling the role of gut microbiota in (Phyto) estrogen modulation in health and disease[J]. Molecular Nutrition & Food Research, 2024, 68(6): e2300688.
- [23] KIM S, LEE J Y, SHIN S G, et al. ESRRA (estrogen related receptor alpha) is a critical regulator of intestinal homeostasis through activation of autophagic flux via gut microbiota[J]. Autophagy, 2021, 17(10): 2856-2875.
- [24] WU Y Y, GOU W, YAN Y, et al. Gut microbiota and acylcarnitine metabolites connect the beneficial association between equol and adiposity in adults: a prospective cohort study[J]. The American Journal of Clinical Nutrition, 2022, 116(6): 1831-1841.
- [25] ELKAFAS H, WALLS M, AL-HENDY A, et al. Gut and genital tract microbiomes: Dysbiosis and link to gynecological disorders[J]. Frontiers in Cellular and Infection Microbiology, 2022, 12: 1059825.
- [26] SUNG H, FERLAY J, SIEGEL R L, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA: A Cancer Journal for Clinicians, 2021, 71(3): 209-249.
- [27] RAGLAN O, KALLIALA I, MARKOZANNES G, et al. Risk factors for endometrial cancer: An umbrella review of the literature[J]. International Journal of Cancer, 2019, 145(7): 1719-1730.
- [28] CALLE E E, KAAKS R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms[J]. Nature Reviews Cancer, 2004, 4(8): 579-591.
- [29] ZHENG W Q, LIN X, CHEN H, et al. Gut microbiota and endometrial cancer: Research progress on the pathogenesis and application[J]. Annals of Medicine, 2025, 57(1): 2451766.
- [30] SOBSTYL M, BRECHT P, SOBSTYL A, et al. The role of microbiota in the immunopathogenesis of endometrial cancer[J]. International Journal of Molecular Sciences, 2022, 23(10): 5756.
- [31] WANG L, YANG J, SU H, et al. Endometrial microbiota from endometrial cancer and paired pericancer tissues in postmenopausal women: Differences and clinical relevance [J]. Menopause, 2022, 29(10): 1168-1175.
- [32] LI C, GU Y, HE Q, et al. Integrated analysis of microbiome and transcriptome data reveals the interplay between commensal bacteria and fibrin degradation in endometrial cancer[J]. Frontiers in Cellular and Infection Microbiology, 2021, 11: 748558.
- [33] ALKHALIL S S, ALMANAA T N, ALTAMIMI R A, et al. Interactions between microbiota and uterine corpus endometrial cancer: A bioinformatic investigation of potential immunotherapy[J]. PLoS One, 2024, 19(10): e0312590.
- [34] YAO X R, DONG S T, LI X, et al. Causal relationship between gut microbiota and endometrial cancer: A two-sample mendelian randomization study[J]. International Journal of Medical Sciences, 2025, 22(12): 3142-3153.
- [35] LIANG W O, ZHAO L C, ZHANG J F, et al. Colonization potential to reconstitute a microbe community in pseudo germ-free mice after fecal microbe transplant from equol producer[J]. Frontiers in Microbiology, 2020, 11: 1221.
- [36] CUNAT S, HOFFMANN P, PUJOL P. Estrogens and epithelial ovarian cancer[J]. Gynecologic Oncology, 2004, 94(1): 25-32.
- [37] MATSUMURA S, OHTA T, YAMANOUCHI K, et al.

- Activation of estrogen receptor α by estradiol and cisplatin induces platinum-resistance in ovarian cancer cells[J]. *Cancer Biology & Therapy*, 2017, 18(9): 730-739.
- [38] SMOLARZ B, BIERNACKA K, ŁUKASIEWICZ H, et al. Ovarian cancer-epidemiology, classification, pathogenesis, treatment, and estrogen receptors' molecular backgrounds[J]. *International Journal of Molecular Sciences*, 2025, 26(10): 4611.
- [39] LIN H, ZENG Z, ZHANG H, et al. Gut-vaginal microbiome crosstalk in ovarian cancer: Implications for early diagnosis[J]. *Pathogens*, 2025, 14(7): 635.
- [40] PETRICK J L, JOSLIN C E, JOHNSON C E, et al. Menopausal hormone therapy use and risk of ovarian cancer by race: The ovarian cancer in women of African ancestry consortium[J]. *British Journal of Cancer*, 2023, 129(12): 1956-1967.
- [41] LEE H J, LEE B, CHOI H, et al. Impact of hormone replacement therapy on risk of ovarian cancer in postmenopausal women with de novo endometriosis or a history of endometriosis[J]. *Cancers*, 2023, 15(6): 1708.
- [42] KUMAGAI K, TAKANASHI M, OHNO S I, et al. WAPL induces cervical intraepithelial neoplasia modulated with estrogen signaling without HPV E6/E7[J]. *Oncogene*, 2021, 40(21): 3695-3706.
- [43] LEE S A, BAIK S, CHUNG S H. Functional roles of female sex hormones and their nuclear receptors in cervical cancer[J]. *Essays in Biochemistry*, 2021, 65(6): 941-950.
- [44] NICOLÒ S, ANTONELLI A, TANTURLI M, et al. Bacterial Species from vaginal microbiota differently affect the production of the E6 and E7 oncoproteins and of p53 and p-Rb oncosuppressors in HPV16-infected cells[J]. *International Journal of Molecular Sciences*, 2023, 24(8): 7173.
- [45] GOPALAKRISHNAN V, SPENCER C N, NEZI L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients[J]. *Science*, 2018, 359(6371): 97-103.
- [46] ZITVOGEL L, DAILLÈRE R, ROBERTI M P, et al. Anticancer effects of the microbiome and its products[J]. *Nature Reviews Microbiology*, 2017, 15(8): 465-478.
- [47] FLORES R, SHI J, FUHRMAN B, et al. Fecal microbial determinants of fecal and systemic estrogens and estrogen metabolites: A cross-sectional study[J]. *Journal of Translational Medicine*, 2012, 10: 253.
- [48] BAKER J M, AL-NAKKASH L, HERBST-KRALOVETZ M M. Estrogen-gut microbiome axis: Physiological and clinical implications[J]. *Maturitas*, 2017, 103: 45-53.
- [49] RÍOS-COVIÁN D, RUAS-MADIEDO P, MARGOLLES A, et al. Intestinal short chain fatty acids and their link with diet and human health[J]. *Frontiers in Microbiology*, 2016, 7: 185.
- [50] MARTIN-GALLAUSIAUX C, MARINELLI L, BLOTTIÈRE H M, et al. SCFA: Mechanisms and functional importance in the gut[J]. *The Proceedings of the Nutrition Society*, 2021, 80(1): 37-49.
- [51] KRAUSE F F, MANGOLD K I, RUPPERT A-L, et al. Clostridium sporogenes-derived metabolites protect mice against colonic inflammation[J]. *Gut Microbes*, 2024, 16(1): 2412669.
- [52] NADJSOMBATI M S, MCGINTY J W, LYONS-COHEN M R, et al. Detection of succinate by intestinal tuft cells triggers a Type 2 innate immune circuit[J]. *Immunity*, 2018, 49(1): 33-41.e7.
- [53] YANG W J, YU T M, HUANG X S, et al. Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity[J]. *Nature Communication*, 2020, 11(1): 4457.
- [54] LUU M, PAUTZ S, KOHL V, et al. The short-chain fatty acid pentanoate suppresses autoimmunity by modulating the metabolic-epigenetic crosstalk in lymphocytes[J]. *Nature Communications*, 2019, 10(1): 760.
- [55] KELLY C J, ZHENG L, CAMPBELL E L, et al. Crosstalk between microbiota-derived short-chain fatty acids and intestinal epithelial HIF augments tissue barrier function[J]. *Cell Host & Microbe*, 2015, 17(5): 662-671.
- [56] SMITH P M, HOWITT M R, PANIKOV N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic treg cell homeostasis[J]. *Science*, 2013, 341(6145): 569-573.
- [57] CHANG P V, HAO L, OFFERMANN S, et al. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition [J]. *Proceedings of the National Academy of Sciences of the United States of America* 2014, 111(6): 2247-2252.
- [58] AGUS A, PLANCHAIS J, SOKOL H. Gut microbiota regulation of tryptophan metabolism in health and disease [J]. *Cell Host & Microbe*, 2018, 23(6): 716-724.
- [59] GAO J, XU K, LIU H, et al. Impact of the gut microbiota on intestinal immunity mediated by tryptophan metabolism [J]. *Frontiers in Cellular and Infection Microbiology*, 2018, 8: 13.
- [60] LAMAS B, RICHARD M L, LEDUCQ V, et al. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands[J]. *Nature Medicine*, 2016, 22(6): 598-605.
- [61] ZHENG D P, LIWINSKI T, ELINAV E. Interaction

- between microbiota and immunity in health and disease [J]. *Cell Research*, 2020, 30(6): 492-506.
- [62] MICHAUDEL C, SOKOL H. The gut microbiota at the service of immunometabolism[J]. *Cell Metabolism*, 2020, 32(4): 514-523.
- [63] ROAGER H M, LICHT T R. Microbial tryptophan catabolites in health and disease[J]. *Nature Communications*, 2018, 9(1): 3294.
- [64] PLATTEN M, NOLLEN E A A, RÖHRIG U F, et al. Tryptophan metabolism as a common therapeutic target in cancer, neurodegeneration and beyond[J]. *Nature Reviews Drug Discovery*, 2019, 18(5): 379-401.
- [65] KIM H J, LEE S H, HONG S J. Antibiotics-induced dysbiosis of intestinal microbiota aggravates atopic dermatitis in mice by altered short-chain fatty acids[J]. *Allergy, Asthma & Immunology Research*, 2020, 12(1): 137-148.
- [66] NORENHAG J, DU J, OLOVSSON M, et al. The vaginal microbiota, human papillomavirus and cervical dysplasia: A systematic review and network meta-analysis [J]. *BJOG: An International Journal of Obstetrics and Gynaecology*, 2020, 127(2): 171-180.
- [67] CHEN Y L, HONG Z B, WANG W J, et al. Association between the vaginal microbiome and high-risk human papillomavirus infection in pregnant Chinese women[J]. *BMC Infectious Diseases*, 2019, 19(1): 677.
- [68] AUDIRAC-CHALIFOUR A, TORRES-POVEDA K, BAHENA-ROMÁN M, et al. Cervical microbiome and cytokine profile at various stages of cervical cancer: A pilot study[J]. *PLoS One*, 2016, 11(4): e0153274.
- [69] WANG Y, LIU N, GUO X, et al. The immune microenvironment in endometrial carcinoma: Mechanisms and therapeutic targeting[J]. *Frontiers in Immunology*, 2025, 16: 1586315.
- [70] FUSAGAWA M, TOKITA S, MURATA K, et al. Identification and phenotypic characterization of neoantigen-specific cytotoxic CD4⁺ T cells in endometrial cancer[J]. *Cancer Immunology Research*, 2025, 13(2): 171-184.
- [71] KANDALAFT L E, DANGAJ LANITI D, COUKOS G. Immunobiology of high-grade serous ovarian cancer: Lessons for clinical translation[J]. *Nature Reviews. Cancer*, 2022, 22(11): 640-656.
- [72] ZHANG J H, HUANG D, SAW P E, et al. Turning cold tumors hot: From molecular mechanisms to clinical applications[J]. *Trends in Immunology*, 2022, 43(7): 523-545.
- [73] KOZIEŁ M J, PIASTOWSKA-CIESIELSKA A W. Estrogens, Estrogen receptors and tumor microenvironment in ovarian cancer[J]. *International Journal of Molecular Sciences*, 2023, 24(19): 14673.
- [74] CANI P D, AMAR J, IGLESIAS M A, et al. Metabolic endotoxemia initiates obesity and insulin resistance[J]. *Diabetes*, 2007, 56(7): 1761-1772.
- [75] KAWAI T, AKIRA S. TLR signaling[J]. *Cell Death and Differentiation*, 2006, 13(5): 816-825.
- [76] LU Y C, YEH W C, OHASHI P S. LPS/TLR4 signal transduction pathway[J]. *Cytokine*, 2008, 42(2): 145-151.
- [77] BENEDEK G, ZHANG J, NGUYEN H, et al. Estrogen protection against EAE modulates the microbiota and mucosal-associated regulatory cells[J]. *Journal of Neuro-immunology*, 2017, 310: 51-59.
- [78] ERVIN S M, LI H, LIM L, et al. Gut microbial β -glucuronidases reactivate estrogens as components of the estrobolome that reactivate estrogens[J]. *The Journal of Biological Chemistry*, 2019, 294(49): 18586-18599.
- [79] TILG H, MOSCHEN A R. Microbiota and diabetes: An evolving relationship[J]. *Gut*, 2014, 63(9): 1513-1521.
- [80] CANI P D, OSTO M, GEURTS L, et al. Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity [J]. *Gut Microbes*, 2012, 3(4): 279-288.
- [81] PROCACCINI C, LA ROCCA C, CARBONE F, et al. Leptin as immune mediator: Interaction between neuroendocrine and immune system[J]. *Developmental & Comparative Immunology*, 2017, 66: 120-129.
- [82] LUMENG C N, SALTIEL A R. Inflammatory links between obesity and metabolic disease[J]. *The Journal of Clinical Investigation*, 2011, 121(6): 2111-2117.
- [83] HOTAMISLIGIL G S. Inflammation and metabolic disorders[J]. *Nature*, 2006, 444(7121): 860-867.
- [84] MANTOVANI A, ALLAVENA P, SICA A, et al. Cancer-related inflammation[J]. *Nature*, 2008, 454(7203): 436-444.
- [85] SAINZ R M, LOMBO F, MAYO J C. Radical decisions in cancer: Redox control of cell growth and death[J]. *Cancers*, 2012, 4(2): 442-474.
- [86] RIDNOUR L A, WINDHAUSEN A N, ISENBERG J S, et al. Nitric oxide regulates matrix metalloproteinase-9 activity by guanylyl-cyclase-dependent and -independent pathways[J]. *Proceedings of the National Academy of Sciences of the United States of America*, 2007, 104(43): 16898-16903.
- [87] LU W T, HE F, LIN Z, et al. Dysbiosis of the endometrial microbiota and its association with inflammatory cytokines in endometrial cancer[J]. *International Journal of Cancer*, 2021, 148(7): 1708-1716.
- [88] WUNDERLICH C M, HÖVELMEYER N, WUNDERLICH

- F T. Mechanisms of chronic JAK-STAT3-SOCS3 signaling in obesity[J]. *JAKSTAT*, 2013, 2(2): e23878.
- [89] CHEN H, QI J, LIU T, et al. Leptin accelerates B cell dysfunctions via activating JAK/STAT3/5 and ERK1/2 pathways in patients with systemic lupus erythematosus [J]. *Clinical and Experimental Rheumatology*, 2022, 40 (11): 2125-2132.
- [90] GUNJUR A, SHAO Y, ROZDAY T, et al. A gut microbial signature for combination immune checkpoint blockade across cancer types[J]. *Nature Medicine*, 2024, 30(3): 797-809.
- [91] SO D, WHELAN K, ROSSI M, et al. Dietary fiber intervention on gut microbiota composition in healthy adults: A systematic review and meta-analysis[J]. *The American Journal of Clinical Nutrition*, 2018, 107(6): 965-983.
- [92] KONG Y, YAN T, TONG Y, et al. Gut microbiota modulation by polyphenols from aronia melanocarpa of lps-induced liver diseases in rats[J]. *Journal of Agricultural and Food Chemistry*, 2021, 69(11): 3312-3325.
- [93] GUTIÉRREZ SALMEÁN G, DELGADILLO GONZÁLEZ M, RUEDA ESCALONA A A, et al. Effects of prebiotics, probiotics, and synbiotics on the prevention and treatment of cervical cancer: Mexican consensus and recommendations [J]. *Frontiers in Oncology*, 2024, 14: 1383258.
- [94] XU P, MAGESWARAN U M, NISAA A A, et al. Roles of probiotics against HPV through the gut-vaginal axis[J]. *International Journal of Gynecology and Obstetrics*, 2025, 169(1): 1-8.
- [95] CHALIF J, MORTON M, HAIGHT P, et al. Assessment of probiotic and prebiotic use in gynecologic cancer patients: A systematic review[J]. *American Journal of Obstetrics and Gynecology*, 2025(25): S0002-9378.
- [96] HAMADE D F, EPPERLY M W, FISHER R, et al. Genetically engineered probiotic *limosilactobacillus reuteri* releasing IL-22 (LR-IL-22) modifies the tumor microenvironment, enabling irradiation in ovarian cancer [J]. *Cancers*, 2024, 16(3): 474.
- [97] BARREA L, VERDE L, AURIEMMA R S, et al. Probiotics and prebiotics: Any role in menopause-related diseases[J]. *Current Nutrition Reports*, 2023, 12(1): 83-97.
- [98] GIORGI C, LOMBARDI F, AUGELLO F R, et al. Probiotics as anti-tumor agents: Insights from female tumor cell culture studies[J]. *Biomolecules*, 2025, 15(5): 657.
- [99] KIM N, YANG C. Butyrate as a potential modulator in gynecological disease progression[J]. *Nutrients*, 2024, 16 (23): 4196.
- [100] AHMAD S, MOORTHY M V, LEE I M, et al. Mediterranean diet adherence and risk of all-cause mortality in women[J]. *JAMA Network Open*, 2024, 7(5): e2414322.
- [101] SINHA A K, LAURSEN M F, BRINCK J E, et al. Dietary fibre directs microbial tryptophan metabolism via metabolic interactions in the gut microbiota[J]. *Nature Microbiology*, 2024, 9(8): 1964-1978.
- [102] RAD Z A, MOUSAVI S N, CHITI H. A low-carb diet increases fecal short-chain fatty acids in feces of obese women following a weight-loss program: Randomized feeding trial[J]. *Scientific Reports*, 2023, 13(1): 18146.
- [103] LI T G, YUAN Q C, GONG H, et al. Gut microbiota mediates the alleviative effect of polar lipids-enriched milk fat globule membrane on obesity-induced glucose metabolism disorders in peripheral tissues in rat dams[J]. *International Journal of Obesity*, 2022, 46(4): 793-801.
- [104] WANG Y, CHEN J R, NI Y Q, et al. Exercise-changed gut mycobiome as a potential contributor to metabolic benefits in diabetes prevention: An integrative multi-omics study[J]. *Gut Microbes*, 2024, 16(1): 2416928.
- [105] KARL J P, HATCH A M, ARCIDIACONO S M, et al. Effects of psychological, environmental and physical stressors on the gut microbiota[J]. *Frontiers in Microbiology*, 2018, 9: 2013.
- [106] KATO-KATAOKA A, NISHIDA K, TAKADA M, et al. Fermented milk containing *lactobacillus casei* strain shirota prevents the onset of physical symptoms in medical students under academic examination stress[J]. *Beneficial Microbes*, 2016, 7(2): 153-160.
- [107] MARX W, LANE M, HOCKEY M, et al. Diet and depression: Exploring the biological mechanisms of action[J]. *Molecular Psychiatry*, 2021, 26(1): 134-150.
- [108] ZMORA N, ZEEVI D, KOREM T, et al. Taking it personally: Personalized utilization of the human microbiome in health and disease[J]. *Cell Host & Microbe*, 2016, 19(1): 12-20.
- [109] SUEZ J, ZMORA N, SEGAL E, et al. The pros, cons, and many unknowns of probiotics[J]. *Nature Medicine*, 2019, 25(5): 716-729.
- [110] KOŁODZIEJCZYK A A, ZHENG D, ELINAV E. Diet-microbiota interactions and personalized nutrition[J]. *Nature Reviews. Microbiology*, 2019, 17(12): 742-753.