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肠道菌群对卵巢衰老的影响及其潜在的机制

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摘要　卵巢衰老是影响女性生殖健康的关键因素，与生育能力下降、更年期提前等问题密切相关。最新研究显示，肠道菌群的变化可能通过肠道–卵巢轴影响卵巢的功能和衰老进展。这些研究进展不仅提供了从肠道菌群角度探讨女性生殖健康的新视角，也为卵巢衰老的预防和干预提出了新的策略。该文回顾了近年来肠道菌群对卵巢衰老影响及其机制方面的研究进展，强调了研究肠道菌群与卵巢衰老相互作用的重要性。加强肠道菌群与卵巢衰老的关联机制研究不仅有助于深化对卵巢衰老机制的理解，也为研发新的治疗策略提供了理论和实验基础。

关键词　肠道菌群；卵巢衰老；微生物–肠道–卵巢轴

The Effect of Gut Microbiota on Ovarian Aging and Its Potential Mechanism

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Abstract　Ovarian aging is a key factor affecting women's reproductive health, closely related to decreased fertility and early menopause. Recent studies indicated that alteration of gut microbiota influenced ovarian function and aging processes through microbiota-gut-ovary axis. These findings not only offer a new perspective for exploring women's reproductive health through gut microbiota, but also propose novel strategies for the prevention and intervention of ovarian aging. This review summarized the recent research progress regarding connection between gut microbiota and ovarian aging, discussed the potential impact of gut microbiota on ovarian function, and the pos-

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sible association between gut microbiota imbalance and ovarian aging-related diseases. Exploring the relationship between gut microbiota and ovarian aging is essential to enhance comprehension of the mechanisms involved in ovarian aging, laying the groundwork for the development of novel therapeutic approaches for preventing ovarian aging.

Keywords gut microbiota; ovarian aging; microbiota-gut-ovary axis

肠道微生物组作为人体的“第二套基因组”, 对多个远端器官(如大脑、肝脏、肺和生殖器官)的功能产生显著影响。在女性健康的研究领域中, 卵巢衰老作为影响生育能力和整体健康的关键因素, 一直是科研工作者关注的焦点。卵巢衰老不仅关系到女性生育问题, 还与多种疾病的发生发展密切相关。本篇综述回顾了肠道菌群通过多种机制影响卵巢功能衰退过程的研究, 提出了未来研究的可能方向, 旨在为深入探索肠道菌群与女性生殖健康之间的关系提供理论基础和实践指导。

1 卵巢衰老

1.1 卵巢衰老的定义

卵巢是女性生殖和内分泌系统的关键器官, 经历五个主要的生理阶段: 发生、生长、成熟、衰退和衰竭。卵巢衰老指的是随着年龄的增长, 卵巢的储备能力和功能逐渐下降直至完全丧失的过程。这种衰老是女性生殖系统最常见的与年龄相关的疾病, 通常发生在40至50岁之间[1]。从临床角度, 卵巢衰老可以分为几种类型, 包括卵巢储备功能减退(diminished/decreased ovarian reserve, DOR)[2]、早发性卵巢功能不全(premature ovarian insufficiency, POI)[3]、早绝经(early menopause)和绝经(menopause)[4], 这些类型根据它们的发展程度、发病年龄以及对内分泌系统和生育能力的影响而有所区别。DOR指的是由于卵巢中成熟卵子的数量和/或质量的降低导致卵巢功能下降的病理状态。DOR可能与年龄有关, 但也可以由多种因素如药物使用、放疗、手术、自身免疫疾病, 以及卵巢感染、卵巢过度刺激综合征和药物不当使用等引起。这些因素可能直接损害卵巢或干扰其正常生理功能, 从而导致卵巢储备能力下降[5]。POI指的是在40岁以下的女性中出现的卵巢功能不足。它表现为持续高水平的促卵泡生成激素(follicle-stimulating hormone, FSH)和低水平的雌二醇(estradiol, E2), 通常伴随着闭经(连续12个月无月经)。这种情况可能导致女性不孕或提前进入停经期, 并可能引起其他健康问题, 例如骨质疏松症和心血管疾病[6]。

1.2 卵巢衰老的影响因素

如图1所示, 卵巢衰老是一种受多种因素影响的复杂生物学过程, 其中遗传、环境和生活方式起着关键作用。遗传方面, 诸如*FMR1*、*BMP15*和*FOXL2*等基因的变异对卵巢衰老有直接影响, 它们通过影响卵子的质量和数量, 以及调控DNA损伤反应, 影响卵巢衰老进程[7-11]。近年来研究还发现。表观遗传学的作用方式如DNA甲基化和组蛋白修饰等方式调控基因表达, 也会间接影响卵巢功能[12-18]。然而, 除了遗传因素外, 卵巢衰老的过程还受到环境和生活方式等非遗传因素的显著影响。自身免疫性卵巢衰竭、早期的手术或放疗等医疗干预措施对卵巢功能有显著影响[19-22]。不良生活习惯(如吸烟和频繁饮酒)和环境污染因素(如双酚A和重金属暴露)也会构成对卵巢健康的潜在威胁[23-28]。这些因素的共同作用加速了卵巢衰老过程。尽管如此, 卵巢衰老的具体机制和各因素间的相互作用尚未被完全阐明, 因此加强对卵巢衰老因素的探究对开发有效的预防和治疗策略至关重要。

2 肠道菌群

2.1 肠道菌群的功能

肠道微生态由约1×10^6亿微生物构成, 对人体健康起着至关重要的作用[29]。如图2所示, 这些微生物群体不仅助力于分解通常难以降解的食物成分, 如复杂碳水化合物、蛋白质和脂肪, 还能将这些物质转化为有益的短链脂肪酸(short-chain fatty acids, SCFAs)。SCFAs不仅促进免疫细胞的成熟和活化, 还通过调节促炎Th17细胞和抑炎Treg细胞的平衡等方式抑制病原体的增长, 增强宿主的整体防御能力[30-35]。此外, 肠道菌群能合成多种对宿主有益的维生素、酶和氨基酸, 它们通过调节肠道蠕动和黏膜屏障的稳定性, 防止有害物质的侵入, 维护肠道健康[36]。

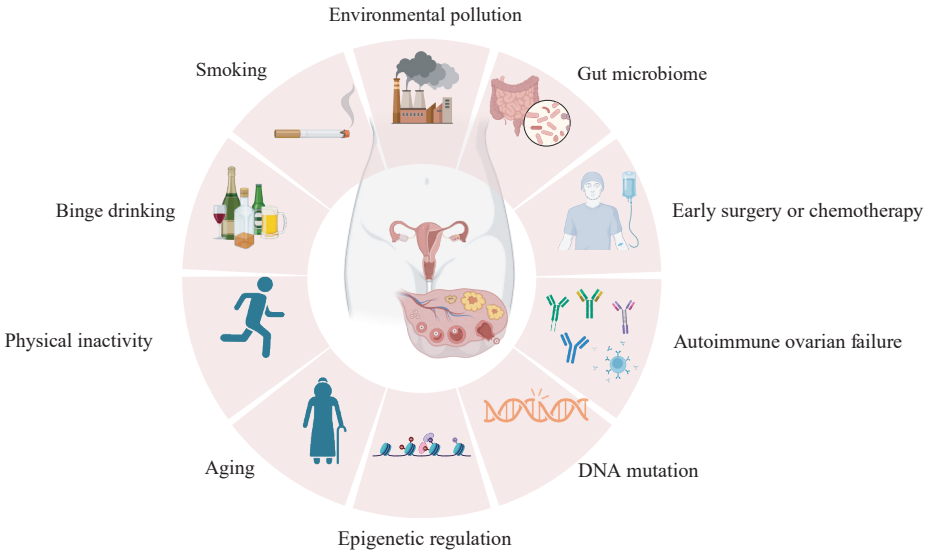

图1 卵巢衰老的影响因素

Fig.1 Influencing factors of ovarian aging

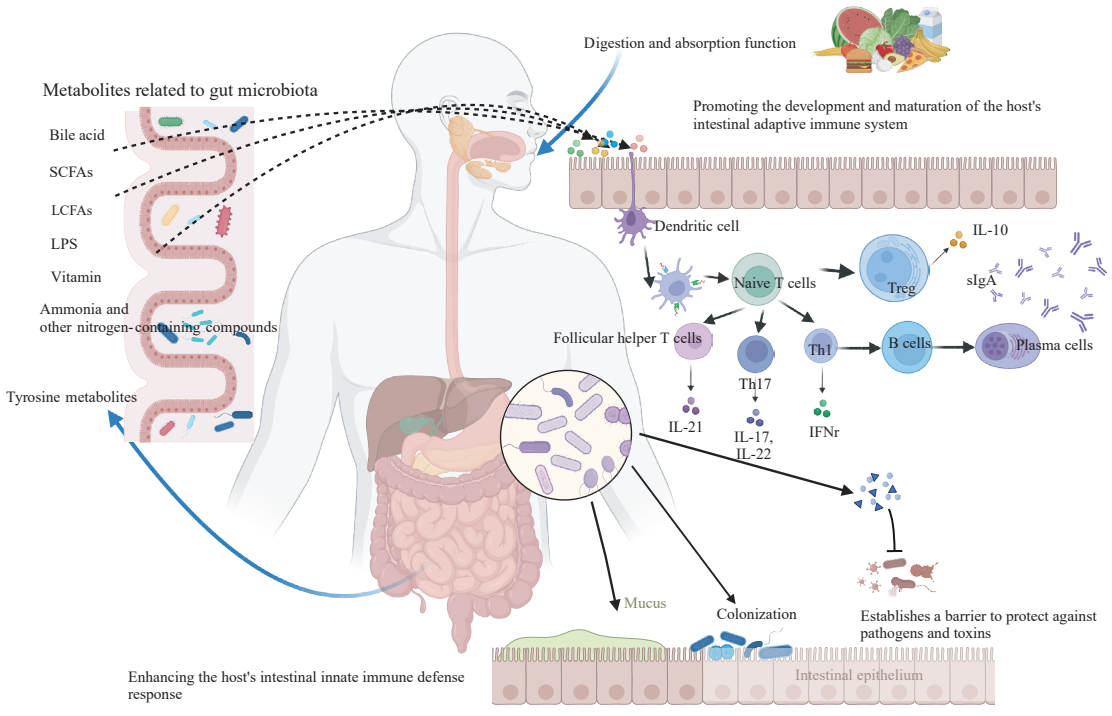

图2 肠道菌群的功能

Fig.2 Function of gut microbiota

2.2 肠道菌群对卵巢功能的影响

肠道菌群在女性卵巢功能和整体生殖健康中扮演着至关重要的角色。肠道中的特定细菌群能通过微生物−肠道−卵巢轴参与雌激素的代谢，从而影响卵巢的激素产生和功能。例如，YAN等[37]研究发现母体接触玉米赤霉烯酮显著改变子代的肠道菌群结构，包括拟杆菌门、变形菌门和厚壁菌门的变化，这些改变引起卵巢中谷胱甘肽代谢和抗氧化酶活性的调整，进而对子代的卵母细胞发育产生影响。WANG等[38]的研究证明了白藜芦醇通过调节肠道菌群改善氧化应激导致的卵巢功能下降。LÜLL等[39]在2021年的研究发现，与健康对照组相比，PCOS患者的肠道菌群存在显著差异，这些差异与患者的代谢指标，如胰岛素抵抗和体重紧密相关。类似地，PCOS小鼠的

肠道菌群结构与正常小鼠不同, 不同的饮食干预对其肠道菌群结构和代谢产生影响[40]。

更年期, 作为女性生命中的一个重要转折点, 伴随着卵巢功能的衰退和激素水平的变化。这些内分泌变化可能会进一步影响肠道菌群的组成和代谢活动, 从而影响整体健康。ZHAO等[41]研究发现绝经后女性体内罗氏菌属(*Roseburia*)的含量降低与代谢性及内分泌疾病有关联, 同时还发现了与骨密度相关的有害细菌甲苯单胞菌属(*Tolumonas*)的增多。FUHRMAN等[42]发现, 更年期妇女的肠道菌群多样性和结构与尿液中的雌激素和雌激素代谢物水平存在相关性, 尿中的总雌激素与瘤胃球菌呈正相关, 而这种菌参与复杂碳水化合物的发酵并生成SCFAs。这些发现暗示肠道菌群可能在更年期妇女内分泌代谢调节中发挥重要作用。

2.3 肠道菌群与卵巢衰老的关系

众多研究逐渐揭开了肠道微生物多样性与女性卵巢衰老复杂而深刻的联系。如表1所示, SANTOS等[43]的研究揭示了绝经前后妇女肠道菌群的显著变化。具体来说, 绝经前妇女的肠道中厚壁菌门(*Firmicutes*)与拟杆菌门(*Bacteroidetes*)的比例升高以及毛螺菌属(*Lachnospira*)和罗斯氏菌属(*Roseburia*)的丰度均高于绝经后妇女及同龄男性。WANG等[44]发现优杆菌属(*Eubacterium hallii*)和凸腹真杆菌(*Eubacterium ventriosum*)与POI有显著的保护性关联。相对地, 肠杆菌属(*Enterobacter*)和土孢杆菌属(*Terrisporobacter*)与POI的不良影响相关联。WU等[45]的研究进一步揭示, 健康女性与POI女性在肠道菌群落结构上存在显著差异, 这可能与激素水平的变化有关。在多囊卵巢综合征(polycystic ovary syndrome, PCOS)方面的研究中, LI等[46]指出了特定肠道菌群与PCOS之间的潜在因果关系。例如, 双歧杆菌属(*Bifidobacterium*)、布劳特氏菌属(*Blautia*)和霍尔德曼菌属(*Holdemania*)与降低PCOS风险相关, 而毛螺菌科(*Lachnospiraceae*)丰度的增加似乎与PCOS的不良后果相关。ZOU等[47]和LI等[48]的研究进一步证实, PCOS女性的肠道菌群α多样性降低, 菌群丰度发生显著变化, 这种菌群失调可能在PCOS的病理进展中发挥重要作用。

3 肠道菌群通过微生物–肠道–卵巢轴对卵巢衰老影响机制探索

对于肠道菌群如何调节卵巢衰老的机制, 当前的研究揭示了多个潜在调控途径。

3.1 肠道菌群通过调节机体整体的免疫系统和卵巢的微环境影响卵巢衰老

肠道菌群通过多种机制, 如调节免疫系统的平衡、影响免疫细胞活性以及产生代谢产物对宿主整体免疫系统产生影响, 进而调控卵巢免疫微环境, 从而影响卵巢功能。

WANG等[51]发现阿克曼氏菌(*Akkermansia*)可以通过激活T细胞的信号途径并增加干扰素γ(interferon γ, IFNγ)的产生来增强对肿瘤细胞的杀伤效果, 进而抑制卵巢癌细胞的生长和扩散。在PCOS患者中, 肠道菌群的变化与特定胆汁酸水平的变化相关, 例如, PCOS患者中甘氨脱氧胆酸(glycodeoxycholic acid, GDCA)和牛磺熊脱氧胆酸(tauroursodesoxycholic acid, TUDCA)的水平降低, 并与普通拟杆菌(*Bacteroides vulgatus*)呈负相关。通过向健康小鼠移植*Bacteroides vulgatus*, 重塑其肠道菌群, 可诱导出PCOS样表型, 并伴随肠道免疫因子IL-22水平下降, 而补充IL-22则可改善激素异常和生育力下降等症状[52]。此外, HUANG等[53]的研究发现, 在脱氢表雄酮诱导的PCOS小鼠模型中, *Akkermansia*丰度降低, 而革兰氏阴性菌如脱硫弧菌(*Desulfovibrio*)和伯克霍尔德菌(*Burkholderia*)的丰度增加, 导致血清中脂多糖(lipopolysaccharide, LPS)水平上升, 与此同时, 血清中的LPS水平上升, 进一步导致小鼠卵巢中的巨噬细胞死亡, 影响雌激素的产生, 并促使颗粒细胞死亡。在这些小鼠的PCOS和卵巢中, 升高的IFN-γ促进巨噬细胞的死亡, 并进一步影响颗粒细胞对雌激素受体的响应。肥胖个体中肠道菌群组的失衡与增加的LPS、IL-6和IL-1β等促炎物质相关, 这些物质可能直接影响卵母细胞的质量, 进一步加剧PCOS等疾病的症状[54]。值得注意的是, ω-3多不饱和脂肪酸(omega-3 fatty acids, PUFAs)的补充已显示出改善PCOS表型的潜力, 这可能通过增加肠道中有益细菌的丰度, 从而抑制炎症细胞因子如IL-1β、TNF-α和IL-18的释放[55]。

在PCOS患者的卵巢组织中, 通常会观察到大量巨噬细胞的浸润。这可能是由于不良饮食习惯导致的肠道菌群失衡, 增加了内毒素的生成, 从而引发了M1型巨噬细胞在卵巢中的积聚[53]。这些巨噬细胞会释放促炎性细胞因子如IL-6、IL-8和TNFα, 激活STAT3信号通路, 导致原始卵泡的死亡, 粪便微生

表1 肠道菌群与卵巢衰老队列研究

Table 1 Cohort study of gut microbiota and ovarian aging

类型 Type	作者 Authors	样本量 Sizes	关键发现 Key findings	菌群变化 Microbiota Changes
Menopause	SANTOS-MARCOS, et al[43]	17 premenopausal women, 19 age-matched men, 20 postmenopausal women, 20 age-matched men	Gut microbiota composition differences may be related to the gender differences in metabolic diseases	Higher *Firmicutes* to *Bacteroidetes* ratio in the gut microbiota of premenopausal women. Increased relative abundance of *Lachnospira* and *Roseburia*
	ZHU, et al[49]	18 premenopausal breast cancer patients, 25 premenopausal healthy controls, 44 postmenopausal breast cancer patients, 46 postmenopausal healthy controls	There are significant differences in the microbiota structure between postmenopausal breast cancer patients and premenopausal healthy women and postmenopausal women	In postmenopausal breast cancer patients, there is an increased relative abundance of 38 microbial species, including *Escherichia coli*, *Enterococcus gallinarum*, *Klebsiella*, etc. At the same time, there is a decreased relative abundance of 7 microbial species in breast cancer patients, including *Eubacterium eligens* and *Lactobacillus vaginalis*
	ZHAO, et al[41]	24 premenopausal women and 24 postmenopausal women	There are significant differences in gut microbiota composition and metabolism between premenopausal and postmenopausal women	Significant changes in gut microbiota composition in postmenopausal women compared to premenopausal women: decrease in *Firmicutes* and *Roseburia*, increase in *Bacteroidetes* and *Tolumonas genus*
POI	WANG, et al[44]	A total of 13,266 participants (from the MiBioGen consortium); 424 cases of POI, 181,796 controls (from the FinnGen consortium R8)	A causal relationship between specific gut microbiota and POI exists	*Eubacterium hallii* group and *Eubacterium ventriosum* group have a significant protective association with POI. The genera *Intestinibacter* and *Terrisporobacter* were found to have adverse effects on POI
	WU, et al[45]	18 healthy women, 35 women with POI	Gut microbial communities in POI patients are altered and correlate with serum hormone levels	In POI patients, increased relative abundance of *Butyricimonas*, *Dorea*, *Lachnobacterium*, and Sutterella, while in healthy women, *Bulleidia* and *Faecalibacterium* are more abundant
PCOS	LI, et al[46]	18 340 individuals from 24 cohorts, mainly from Europe	A causal relationship exists between specific gut microbiota genera and PCOS	*Bilophila* has a protective association with PCOS; *Blautia* and *Holdemania* have a protective association with PCOS; *Lachnospiraceae* has adverse effects on PCOS
	ZOU, et al[47]	Nine human observational studies, 617 women with PCOS, 439 healthy individuals	Women with PCOS have significant changes in gut microbiota α-diversity	Women with PCOS have lower Chao index, Shannon index, and OTU counts; higher abundance of *Bacteroidaceae*
	LI, et al[48]	28 studies, 1 022 patients with PCOS, 928 controls	Gut microbiota dysbiosis in PCOS patients is associated with decreased diversity and changes in microbiota composition	Decreased microbial evenness and phylogenetic diversity in PCOS; decrease in *Lachnospira* and *Prevotella*, increase in *Bacteroides*, *Parabacteroides*, *Lactobacillus*, *Fusobacter*
	SOLA-LEYVA, et al[50]	34 studies included in a systematic review, of which 14 were used for meta-analysis of the gut microbiota composition	Most studies found an association between PCOS and alterations in the microbiome composition	The meta-analysis of 14 studies showed that women with PCOS have significantly lower gut microbiota α-diversity compared to control groups

物移植(fecal microbiota transplant, FMT)可以改善这些炎症反应, 防止原始卵泡的死亡[56-57]。此外, 最近XU等[58]报道, 将年轻供体FMT到老年卵巢小鼠中可以改善其卵巢免疫微环境, 减少巨噬细胞和巨核细胞的数量, 并延缓卵巢的衰老过程。总之, 以上研究结果进一步提示通过调控肠道菌群, 能改善卵巢的免疫微环境, 促进其恢复健康和功能。

3.2 肠道菌群通过调节内分泌系统影响卵巢的功能

肠道菌群被广泛认为是一个复杂的内分泌器官, 如通过产生激素代谢酶和影响体内激素水平的平衡, 进而调节卵巢激素的合成和代谢。肠道菌群在雌激素代谢中起到关键作用。研究表明, 肠道菌群能产生许多与激素相似的化合物[59]。FUHRMAN等[42]的研究显示, 肠道菌群的不同组成与尿液中雌激素代谢产物和雌二醇的浓度密切相关。而FLORES等[60]的研究进一步发现, 特定的菌群与粪便和血液中的雌激素水平和代谢产物水平显著相关。其中梭状芽孢杆菌和瘤胃球菌与升高的雌二醇和16α-羟基雌酮水平相关, 而拟杆菌和葡萄球菌等菌群与雌酮和2-羟基雌酮水平显著相关。此外, 肝脏会结合雌激素, 生成共轭雌激素和共轭雌激素代谢物, 并将它们排入胃肠道, 胃肠道中特定的细菌酶将它们转化为游离形式, 一旦肠道中的细菌具备高解偶联和羟基化酶活性, 就会导致宿主体内的雌激素浓度相对增高, 从而影响其生理功能[61]。值得注意的是, YADAV等[62]和KHAN等[63]指出肠道菌群代谢产物丁酸可以激活“肠−脑”轴中的胰高血糖素样肽-1(glucagon-like peptide-1, GLP-1)信号通路, 进而影响卵巢和子宫的生长。吲哚-3-醋酸被认为能够提升宿主脂肪组织中瘦素的分泌水平。研究表明, 瘦素浓度与卵母细胞的成熟度存在直接关联, 这一点在体外受精(*in vitro* fertilization, IVF)的过程中尤为明显。瘦素浓度已被证实是一种有效的生物标志物, 可用于预测卵母细胞的成熟度[64-65]。总之, 上述研究为我们进一步揭示肠道菌群通过调控激素水平影响卵巢的功能提供了重要的研究线索。

在PCOS的研究中, 肠道菌群与激素水平的变化也显示出密切的相关性。具体地, PCOS患者体内β-葡萄糖醛酸苷酶和β-葡萄糖苷酶的活性显著高于健康对照组, 提示肠道菌群通过这些酶影响激素代谢, 尤其是睾酮和雌二醇水平[66]。通过调整肠道菌群, PCOS模型小鼠中激素水平和卵巢功能发生变化, 进一步证实了肠道菌群在调节PCOS相关激素水平中的作用[53]。生酮饮食和中医补肾化痰方在改善PCOS症状方面可能通过调节肠道菌群的结构来实现, 从而影响激素代谢和肠道屏障功能[67-68]。此外, 肠道菌群的代谢产物, 如SCFAs, 也可能通过多种途径影响卵巢功能。例如, LI等[70]的研究发现, 中国中部地区PCOS患者的粪便中乙酸和丙酸的含量显著高于健康人群, 这提示肠道菌群的代谢产物SCFAs可能在PCOS的发病机制中起到关键作用[69]。胆汁酸, 作为胆汁的重要成分, 不仅与胆固醇代谢密切相关, 而且其合成、代谢和生物转化过程与肠道菌群有着紧密的联系。LI等[71]的研究表明, 抗氧化剂Tempol能够改善PCOS大鼠的症状, 主要是通过调节胆汁酸水平和改善肠道菌群失衡来实现的。此外, 有研究发现, 在持续光照条件下的小鼠模型中, 胆石酸水平的降低与*Turicibacter*属微生物的丰度增加有关。通过增加胆石酸浓度, 可以改善昼夜节律紊乱引起的卵子质量下降问题, 这一过程部分通过调节肠道内的氧化应激水平来实现[72]。QIAO等[52]最近的研究表明, 在PCOS患者中, 普通拟杆菌(*Bacteroides vulgatus*)的丰度明显增加, 这与胆汁酸代谢相关。他们的研究指出肠道菌群及其代谢产物对PCOS相关的卵巢功能障碍和胰岛素抵抗具有显著调节作用。特别是胆汁酸通过激活GATA结合蛋白3(GATA binding protein 3, GATA3)通路刺激IL-22分泌, 从而改善PCOS表型, 这表明胆汁酸在肠道菌群与卵巢功能之间的调节作用中担任着关键角色。在卵巢癌的研究中, 菌群能够通过β-葡萄糖醛酸苷酶活性介导的雌激素解偶联, 影响循环中活性雌激素的数量。而增加的雌激素与雌激素受体阳性细胞系的黏附和迁移能力增强相关, 从而促进了卵巢癌的转移和定植[73]。

综上所述, 这些发现揭示了肠道菌群代谢物通过内分泌系统影响卵巢功能, 这些研究为未来深入揭示肠道菌群来源的代谢物调控卵巢衰老的功能的分子机制提供了重要的研究线索。

3.3 肠道菌群通过“肠–脑”轴和“垂体–卵巢” (“pituitary-ovarian axis”, HPO)轴影响卵巢的功能

如图3所示, 肠道菌群和大脑之间的通讯构建了被称为“肠−脑”轴的生理网络, 涉及通过中枢神经系统(central nervous system, CNS)、肠神经系统(enteric nervous system, ENS)以及内分泌和免疫途

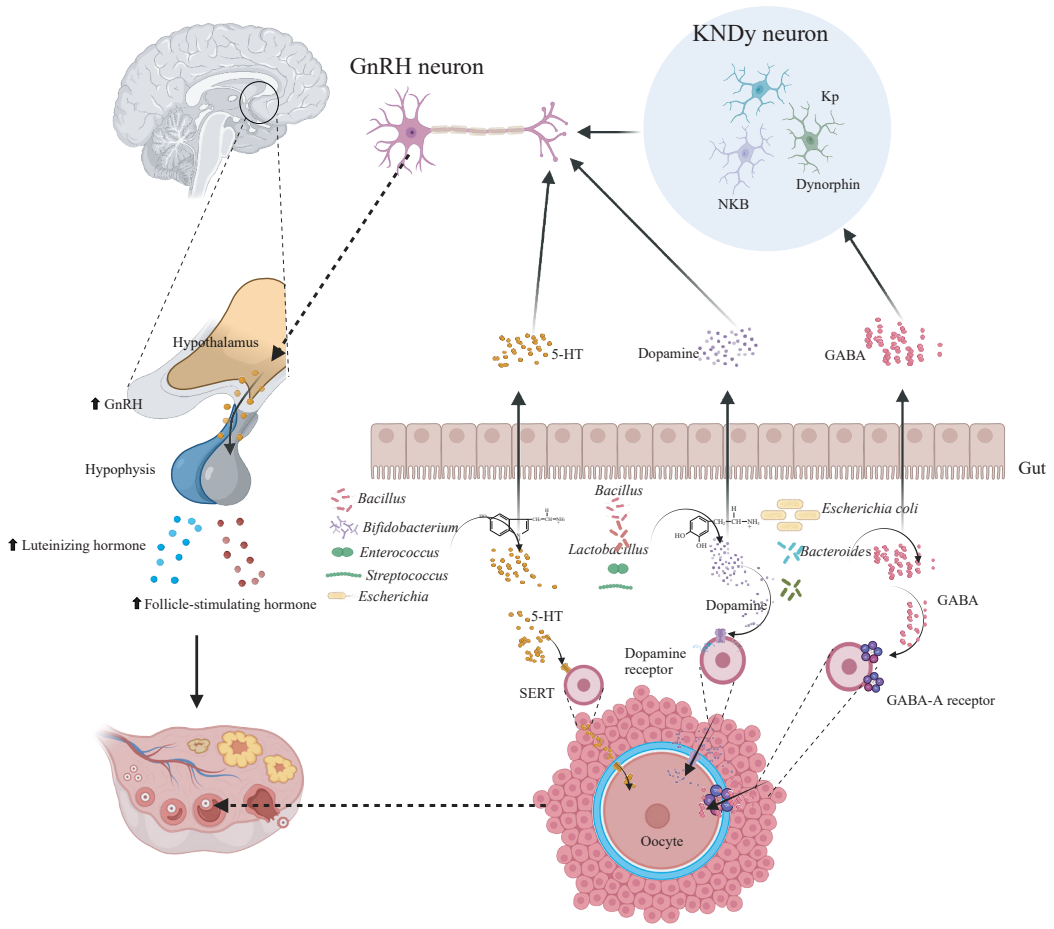

图3 “肠道−微生物−脑”轴与“下丘脑−垂体−性腺”轴

Fig.3 “Gut-microbiota-brain” axis and “HPO” axis

径的连接[74]。此外，这一轴与卵巢功能的神经内分泌调节密切相关，又被称为HPO轴。它是下丘脑−垂体−性腺(hypothalamus-pituitary-gonadal, HPG)轴的一部分。垂体腺位于大脑的底部，接收下丘脑的生殖激素释放激素(gonadotropin-releasing hormone GnRH)信号，然后分泌促黄体生成素(luteinizing hormone, LH)和FSH。卵巢中的卵泡在FSH的作用下成熟，成熟的卵泡产生雌激素，雌激素水平的升高反过来抑制垂体腺分泌FSH，促使垂体腺分泌LH，高水平的LH最终触发卵泡的排卵，释放出成熟的卵子[75]。越来越多的证据表明，肠道菌群能够通过“肠−脑”轴与中枢神经系统进行交流。这种交流可能影响神经递质的合成与释放，从而间接影响到HPO轴。γ-氨基丁酸(γ-aminobutyric acid, GABA)、5-羟色胺(5-hydroxytryptamine, 5-HT)和多巴胺(dopamine, DA)是其中的三个核心神经递质，它们通过神经信号途径对卵巢功能产生影响。

3.3.1 5-HT 5-HT在中枢神经系统中占据重要地位，其合成和代谢途径已被证实会受到肠道菌群的影响。例如，链球菌属、肠球菌属、埃希菌属、双歧杆菌属和芽孢杆菌属等肠内细菌被证实可以合成5-HT[76]。5-HT通过影响GnRH神经元的活动，从而调控促性腺激素(gonadotropins, Gn)的分泌[77-78]。一项研究发现，给予5-HT及其不同的受体拮抗剂会影响雄性大鼠的*GnRH* mRNA水平[79]。同时，5-HT能激活不同的受体亚型，从而影响信号转导途径和GnRH的释放[77]。例如，激活Gi偶联的5-HT1A受体显著降低了下丘脑GnRH神经元的自发动作电位(action potentials, APs)的发放频率和环磷酸腺苷(cyclic AMP, cAMP)的产生，进而影响脉冲式GnRH的释放。反之，激活Gq偶联的5-HT2C受体和Gs偶联的5-HT4受体会增加APs的发放频率，刺激不同的信号转导途径，可能会导致GnRH释放初期的延迟，但随后可能引发释放量的持续增加[80]。由于GnRH是控制LH和FSH释放的主要激素，5-HT可能通过影响GnRH的释放来间接影响LH的释放[81-82]。SHENG等[83]和

DUBE等[84]则进一步展示了5-HT如何通过作用于卵巢的特定受体来直接影响卵巢功能。SHENG等研究着重于5-HT受体在调节卵巢激素产生、卵泡成熟和排卵过程中的关键角色, 突显了将这些受体视为治疗卵巢功能障碍的潜在治疗靶点的意义。DUBE等则展示了5-HT如何调整卵巢对FSH和LH反应的机制, 强调了5-HT在调控卵巢细胞激素感受性、进而影响生殖内分泌过程中的作用。此外, 5-HT能诱导生殖细胞的产生并启动卵子成熟过程, 促使生殖囊泡的破裂、染色体的凝缩、第一和第二极体的排出以及原核的形成[85]。虽然这些研究共同展现了5-HT在生殖生理调控中的多层次、多方面的作用, 但具体的分子机制还有待进一步阐明。

3.3.2 DA DA是在大脑的愉悦和奖励系统中起作用的一种神经递质, 同时, 它也是抑制GnRH释放通路的主要因素。研究显示, 在大鼠的脑中给予DA激动剂可以显著增加*GnRH* mRNA的表达水平, 这表明DA对GnRH的合成和释放具有调控作用[86]。进一步的研究发现, DA能够显著抑制大约50%的GnRH神经元的放电, 这种抑制作用是通过D1样和D2样受体实现的[87]。DA的这种抑制作用对于GnRH神经元的活动和随后的GnRH分泌具有重要意义。另外, 一些研究也探讨了DA对卵巢类固醇生成酶以及某些激素的合成和释放的影响。例如, DA能促进孕马血清促性腺激素(pregnant mare serum gonadotropin, PMSG)处理的未成熟大鼠的卵巢中的孕酮合成[88]。在幼年欧洲鳗鱼中, DA抑制LH的合成和释放, 作为阻止进入青春期的神经内分泌锁[89]。在甲壳类动物中, 包括DA在内的神经激素的合成和释放被认为控制了生殖过程, 特别是卵巢成熟[90]。HAMED等[91]深入探讨了DA对卵巢的直接影响, 尤其关注了它如何调节生殖激素的合成与释放过程。在PCOS患者中, DA水平降低, 低水平DA表现为增加的疲劳、压力和抑郁情绪[92-93]。DA与肠道菌群的关系也引起研究者的关注[94-95]。研究发现, 芽孢杆菌属、乳酸杆菌属以及链球菌属在体外表现出合成DA的能力[76]。特别是, 来自肠球菌属的粪肠球菌被发现能够稳定表达DA合成路径上的关键转化酶, 如酪氨酸羟化酶和芳香族L-氨基酸脱羧酶, 体外培养粪肠球菌并添加酪氨酸, 发现粪肠球菌能自主转化合成多巴(dopa, DOPA)及DA。将粪肠球菌定植于抗生素处理的无菌小鼠的肠道内后, 发现定植小鼠的粪便、血浆以及脑组织中DOPA及DA水平较对照组有所增加[96]。这些研究共同揭示了肠道菌群、DA以及生殖激素之间的复杂交互关系, 并为进一步理解DA在生殖生理和生殖疾病中的作用提供了新的视角。

3.3.3 GABA 某些细菌属如*Bacteroidetes*和*Escherichia*属已被证实可产生GABA, 而GABA是中枢神经系统的主要抑制性神经递质, 对GnRH神经元具有兴奋作用[97-103]。KNDy神经元(表达Kiss1和Tac2神经肽), 通过控制GnRH的脉冲释放成为调节生殖功能的关键调节器。GnRH的脉冲释放进一步影响LH的分泌, 这对生殖功能至关重要。通过这种方式, KNDy神经元对生殖神经内分泌系统起着核心的调控作用[104]。肠道菌群过度产生的GABA可能会干扰KNDy神经元的活动, 从而影响GnRH的分泌, 进而影响LH和FSH的水平, 从而对生育能力、性激素水平、月经周期等方面产生影响[97,104]。

总之神经递质通过多种途径包括激素的合成、分泌和作用, 卵泡发育、排卵以及黄体形成等调节卵巢功能。深入了解这些神经递质及其在卵巢功能调控中的作用机制, 有助于为诊断和治疗生殖系统疾病提供理论依据。

3.4 肠道菌群通过影响线粒体功能调控卵巢的功能和潜在的机制

如图4所示, 肠道菌群和线粒体存在双向通讯机制, 肠道菌群能够对一系列关键的转录共激活子、转录因子和酶进行调节, 这些分子涉及线粒体生物合成过程, 其中包括*PGC-1α*、*SIRT1*和腺苷酸激活蛋白激酶(AMP-activated protein kinase, *AMPK*)基因[105]。如肠道菌群产生SCFAs, 通过激活AMPK途径, 促进线粒体的生物合成以及线粒体融合, 从而提升线粒体的效能。以丁酸为例, 它能够通过激活AMPK途径来积极促进结肠细胞中的线粒体功能[106-108]。

此外, 肠道菌群可通过调控线粒体DNA的甲基化程度来影响线粒体功能, 这种调控机制主要是通过影响宿主的营养摄取和代谢来实现的, 可间接影响DNA甲基化和其他表观遗传调节过程。如肠道菌群通过调节一碳代谢途径中的关键分子, 如叶酸和维生素B_{12}的可用性, 来影响DNA甲基化。而这些分子对于线粒体DNA甲基化和线粒体的正常功能至关重要[109]。而肠道菌群通过细菌衍生的线粒体辅酶促进卵母细胞生成和生育能力。消除肠

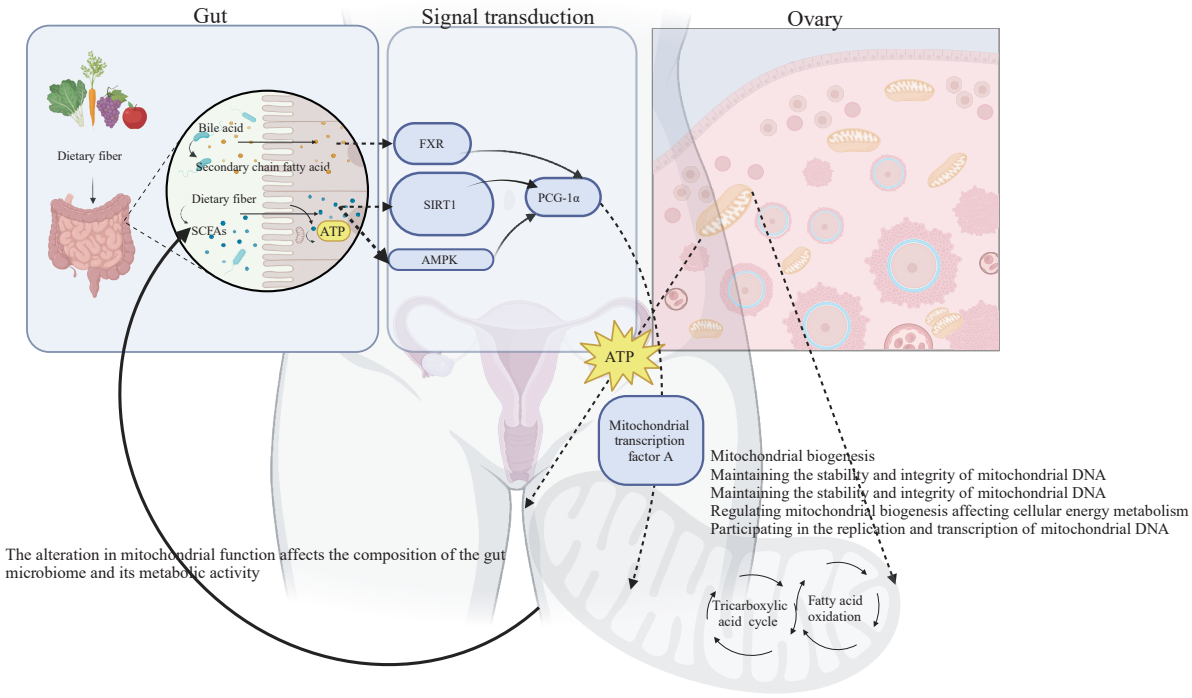

图4　肠道菌群与线粒体功能

Fig.4　Gut microbiota and mitochondrial function

道菌群会导致线粒体功能下降，可能对卵巢功能造成不利影响[110]。另外，有研究报道烟酰胺单核苷酸(nicotinamide mononucleotide, NMN)和烟酰胺核苷酸(nicotinamide riboside, NR)作为NAD^+的前体对线粒体功能和肠道菌群结构产生积极影响[111-114]，但是菌群来源的能量物质是否对宿主的线粒体功能有明确的改善作用，这需要更深入的探究。

4　通过调整肠道菌群改善卵巢功能的途径和应用研究进展

近年来，研究者们正在探索调整肠道菌群结构作为改善卵巢衰老的一种可能方法。在卵巢衰老的病理过程中，肠道菌群的结构和功能的变化可能导致诸如黄体生成障碍和雌激素代谢异常等问题。因此，摄入益生菌补充剂调整肠道菌群的结构和功能，可能有助于改善卵巢衰老症状。一项针对60名PCOS患者进行的随机双盲研究发现，连续补充嗜酸乳杆菌菌株T16等益生菌可以显著降低身体质量指数、血清胰岛素水平及血脂水平，进一步突显了利用益生菌治疗多囊卵巢综合症的潜在价值，尤其是在提高胰岛素敏感性方面[114]。此外，市场上也出现了许多针对女性生殖健康的益生菌产品，如Femdophilus和RepHreshPro-B，它们在维护女性的阴道等生殖健康方面发挥重要作用。

益生元作为一类碳水化合物，也在肠道健康和卵巢功能改善中发挥重要作用。它们不会被肠道消化酶水解，但可以被益生菌发酵利用，促进肠道菌群平衡和维护肠道健康[115-116]。例如，抗性糊精摄入能有效降低PCOS女性的甘油三酯、总胆固醇、空腹血糖、高敏C反应蛋白、脱氢表雄酮硫酸盐和游离睾酮的血清水平，同时改善月经周期不规律和多毛症状[117]。

运动对肠道菌群和卵巢功能也有积极影响。它能提高肠道动力，促进排便，清除肠道垃圾，维持肠道环境的健康和稳定[118]。此外，运动还能调节肠道菌群的群落结构和代谢功能，增加有益菌的数量，抑制有害菌的生长，促进肠道菌群的平衡和多样性[119-120]。研究表明，运动可以通过促进肠道菌群有益代谢物的产生，并进一步通过调节神经内分泌系统和免疫系统等途径，直接或间接地影响卵巢功能[121-123]。

综上所述，肠道菌群在治疗卵巢衰老中扮演着重要角色，益生菌、益生元、二者的联合应用，以及运动等生活方式的改变，为女性的生殖健康提供新的干预治疗措施。

5 肠道菌群与卵巢衰老的研究展望

目前, 肠道菌群与卵巢衰老之间的联系仍未明确, 但这一领域的研究被认为具有重要的临床转化潜力。未来的研究将致力于解析肠道菌群通过肠−脑轴如何调控卵巢功能, 以及肠道微生物产生的代谢物(如短链脂肪酸和NAD^+)如何影响卵巢健康的分子机制, 包括理解这些代谢物对线粒体功能的影响, 以及它们在卵巢的生物合成、自噬和氧化还原平衡中的作用。通过这些研究, 有望开发出更为精确的治疗卵巢衰老的方法, 包括使用新型微生态调节手段, 如粪便微生物移植和微生物代谢物治疗, 从而为恢复卵巢功能及整体健康提供新的治疗策略。

参考文献 (References)

[1] BROEKMANS F J, SOULES M R, FAUSER B C. Ovarian aging: mechanisms and clinical consequences [J]. Endocr Rev, 2009, 30(5): 465-93.

[2] COHEN J, CHABBERT-BUFFET N, DARAI E. Diminished ovarian reserve, premature ovarian failure, poor ovarian responder: a plea for universal definitions [J]. J Assist Reprod Genet, 2015, 32(12): 1709-12.

[3] CHON S J, UMAIR Z, YOON M S. Premature ovarian insufficiency: past, present, and future [J]. Front Cell Dev Biol, 2021, 9: 672890.

[4] DIVARIS E, ANAGNOSTIS P, GKEKAS N K, et al. Early menopause and premature ovarian insufficiency may increase the risk of sarcopenia: a systematic review and meta-analysis [J]. Maturitas, 2023, 175: 107782.

[5] TARÍN J J, GARCÍA-PÉREZ M A, HAMATANI T, et al. Infertility etiologies are genetically and clinically linked with other diseases in single meta-diseases [J]. Reprod Biol Endocrinol, 2015, 13: 31.

[6] NELSON L M. Clinical practice. Primary ovarian insufficiency [J]. N Engl J Med, 2009, 360(6): 606-14.

[7] HUANG J, ZHANG W, LIU Y, et al. Association between the FMR1 CGG repeat lengths and the severity of idiopathic primary ovarian insufficiency: a meta analysis [J]. Artif Cells Nanomed Biotechnol, 2019, 47(1): 3116-22.

[8] SCHMIDT D, OVITT C E, ANLAG K, et al. The murine winged-helix transcription factor Foxl2 is required for granulosa cell differentiation and ovary maintenance [J]. Development, 2004, 131(4): 933-42.

[9] CRISPONI L, DEIANA M, LOI A, et al. The putative forkhead transcription factor FOXL2 is mutated in blepharophimosis/ptosis/epicanthus inversus syndrome [J]. Nat Genet, 2001, 27(2): 159-66.

[10] LEUNG D T H, FULLER P J, CHU S. Impact of FOXL2 mutations on signaling in ovarian granulosa cell tumors [J]. Int J Biochem Cell Biol, 2016, 72: 51-4.

[11] SANTOS M, CORDTS E B, PELUSO C, et al. Association of BMP15 and GDF9 variants to premature ovarian insufficiency [J]. J Assist Reprod Genet, 2019, 36(10): 2163-9.

[12] WATTS G S, FUTSCHER B W, HOLTAN N, et al. DNA methylation changes in ovarian cancer are cumulative with disease progression and identify tumor stage [J]. BMC Med Genomics, 2008, 1: 47.

[13] GE Z J, LUO S M, LIN F, et al. DNA methylation in oocytes and liver of female mice and their offspring: effects of high-fat-diet-induced obesity [J]. Environ Health Perspect, 2014, 122(2): 159-64.

[14] ROY S, SINHA N, HUANG B, et al. Jumonji domain-containing protein-3 (JMJD3/Kdm6b) is critical for normal ovarian function and female fertility [J]. Endocrinology, 2022, doi: 10.1210/endocr/bqac047.

[15] SWAIN J E, DING J, BRAUTIGAN D L, et al. Proper chromatin condensation and maintenance of histone H3 phosphorylation during mouse oocyte meiosis requires protein phosphatase activity [J]. Biol Reprod, 2007, 76(4): 628-38.

[16] ESLAMI H, ESLAMI A, FAVAEDI R, et al. Epigenetic aberration of FMR1 gene in infertile women with diminished ovarian reserve [J]. Cell J, 2018, 20(1): 78-83.

[17] ZHANG L, HOU X, MA R, et al. Sirt2 functions in spindle organization and chromosome alignment in mouse oocyte meiosis [J]. FASEB J, 2014, 28(3): 1435-45.

[18] SHAO G B, WANG J, ZHANG L P, et al. Aging alters histone H3 lysine 4 methylation in mouse germinal vesicle stage oocytes [J]. Reprod Fertil Dev, 2015, 27(2): 419-26.

[19] SILVA C A, YAMAKAMI L Y, AIKAWA N E, et al. Autoimmune primary ovarian insufficiency [J]. Autoimmun Rev, 2014, 13(4/5): 427-30.

[20] LARSEN E C, MÜLLER J, SCHMIEGELOW K, et al. Reduced ovarian function in long-term survivors of radiation- and chemotherapy-treated childhood cancer [J]. J Clin Endocrinol Metab, 2003, 88(11): 5307-14.

[21] VAN DEN BERG M H, OVERBEEK A, LAMBALK C B, et al. Long-term effects of childhood cancer treatment on hormonal and ultrasound markers of ovarian reserve [J]. Hum Reprod, 2018, 33(8): 1474-88.

[22] BATH L E, CRITCHLEY H O, CHAMBERS S E, et al. Ovarian and uterine characteristics after total body irradiation in childhood and adolescence: response to sex steroid replacement [J]. Br J Obstet Gynaecol, 1999, 106(12): 1265-72.

[23] PLANTE B J, COOPER G S, BAIRD D D, et al. The impact of smoking on antimüllerian hormone levels in women aged 38 to 50 years [J]. Menopause, 2010, 17(3): 571-6.

[24] HAWKINS BRESSLER L, BERNARDI L A, DE CHAVEZ P J, et al. Alcohol, cigarette smoking, and ovarian reserve in reproductive-age African-American women [J]. Am J Obstet Gynecol, 2016, 215(6): 758,e1-e9.

[25] KIRANMAYEE D, PRAVEENA T, HIMABINDU Y, et al. The effect of moderate physical activity on ovarian reserve markers in reproductive age women below and above 30 years [J]. J Hum Reprod Sci, 2017, 10(1): 44-8.

[26] PATEL S, ZHOU C, RATTAN S, et al. Effects of endocrine-disrupting chemicals on the ovary [J]. Biol Reprod, 2015, 93(1): 20.

[27] RZYMSKI P, TOMCZYK K, RZYMSKI P, et al. Impact of heavy metals on the female reproductive system [J]. Ann Agric Environ Med, 2015, 22(2): 259-64.

[28] KIM H, CHOE S A, KIM O J, et al. Outdoor air pollution and diminished ovarian reserve among infertile Korean women [J]. Environ Health Prev Med, 2021, 26(1): 20.

[29] NEISH A S. Microbes in gastrointestinal health and disease [J]. Gastroenterology, 2009, 136(1): 65-80.

[30] KARCZEWSKI J, TROOST F J, KONINGS I, et al. Regulation of human epithelial tight junction proteins by *Lactobacillus plantarum in vivo* and protective effects on the epithelial barrier [J]. Am J Physiol Gastrointest Liver Physiol, 2010, 298(6): G851-9.

[31] IVANOV II, FRUTOS RDE L, MANEL N, et al. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine [J]. Cell Host Microbe, 2008, 4(4): 337-49.

[32] OMENETTI S, PIZARRO T T. The Treg/Th17 axis: a dynamic balance regulated by the gut microbiome [J]. Front Immunol, 2015, 6: 639.

[33] PARK J, KIM M, KANG S G, et al. Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway [J]. Mucosal Immunol, 2015, 8(1): 80-93.

[34] ROUND J L, LEE S M, LI J, et al. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota [J]. Science, 2011, 332(6032): 974-7.

[35] BELKAID Y, HAND T W. Role of the microbiota in immunity and inflammation [J]. Cell, 2014, 157(1): 121-41.

[36] VICENTINI F A, FAHLMAN T, RAPTIS S G, et al. New concepts of the interplay between the gut microbiota and the enteric nervous system in the control of motility [J]. Adv Exp Med Biol, 2022, 1383: 55-69.

[37] YAN J, KONG L, ZHANG X, et al. Maternal zearalenone exposure affects gut microbiota and follicular development in suckled offspring [J]. J Agric Food Chem, 2022, 70(49): 15570-82.

[38] WANG J, JIA R, CELI P, et al. Resveratrol alleviating the ovarian function under oxidative stress by alternating microbiota related tryptophan-kynurenine pathway [J]. Front Immunol, 2022, 13: 911381.

[39] LÜLL K, ARFFMAN R K, SOLA-LEYVA A, et al. The gut microbiome in polycystic ovary syndrome and its association with metabolic traits [J]. J Clin Endocrinol Metab, 2021, 106(3): 858-71.

[40] RODRIGUEZ PARIS V, WONG X Y D, SOLON-BIET S M, et al. The interplay between PCOS pathology and diet on gut microbiota in a mouse model [J]. Gut Microbes, 2022, 14(1): 2085961.

[41] ZHAO H, CHEN J, LI X, et al. Compositional and functional features of the female premenopausal and postmenopausal gut microbiota [J]. FEBS Lett, 2019, 593(18): 2655-64.

[42] FUHRMAN B J, FEIGELSON H S, FLORES R, et al. Associations of the fecal microbiome with urinary estrogens and estrogen metabolites in postmenopausal women [J]. J Clin Endocrinol Metab, 2014, 99(12): 4632-40.

[43] SANTOS-MARCOS J A, RANGEL-ZUÑIGA O A, JIMENEZ-LUCENA R, et al. Influence of gender and menopausal status on gut microbiota [J]. Maturitas, 2018, 116: 43-53.

[44] WANG J, LUO R, ZHAO X, et al. Association between gut microbiota and primary ovarian insufficiency: a bidirectional two-sample Mendelian randomization study [J]. Front Endocrinol, 2023, 14: 1183219.

[45] WU J, ZHUO Y, LIU Y, et al. Association between premature ovarian insufficiency and gut microbiota [J]. BMC Pregnancy Childbirth, 2021, 21(1): 418.

[46] LI J W, CHEN Y Z, ZHANG Y, et al. Gut microbiota and risk of polycystic ovary syndrome: insights from Mendelian randomization [J]. Heliyon, 2023, 9(12): e22155.

[47] ZOU Y, LIAO R, CHENG R, et al. Alterations of gut microbiota biodiversity and relative abundance in women with PCOS: a systematic review and meta-analysis [J]. Microb Pathog, 2023, 184: 106370.

[48] LI P, SHUAI P, SHEN S, et al. Perturbations in gut microbiota composition in patients with polycystic ovary syndrome: a systematic review and meta-analysis [J]. BMC Med, 2023, 21(1): 302.

[49] ZHU J, LIAO M, YAO Z, et al. Breast cancer in postmenopausal women is associated with an altered gut metagenome [J]. Microbiome, 2018, 6(1): 136.

[50] SOLA-LEYVA A, PÉREZ-PRIETO I, MOLINA N M, et al. Microbial composition across body sites in polycystic ovary syndrome: a systematic review and meta-analysis [J]. Reprod Biomed Online, 2023, 47(1): 129-50.

[51] WANG Z, QIN X, HU D, et al. Akkermansia supplementation reverses the tumor-promoting effect of the fecal microbiota transplantation in ovarian cancer [J]. Cell Rep, 2022, 41(13): 111890.

[52] QI X, YUN C, SUN L, et al. Gut microbiota-bile acid-interleukin-22 axis orchestrates polycystic ovary syndrome [J]. Nat Med, 2019, 25(8): 1225-33.

[53] HUANG J, CHEN P, XIANG Y, et al. Gut microbiota dysbiosis-derived macrophage pyroptosis causes polycystic ovary syndrome via steroidogenesis disturbance and apoptosis of granulosa cells [J]. Int Immunopharmacol, 2022, 107: 108717.

[54] BAHAR-TOKMAN H, DEMIRCI M, KESKIN F E, et al. Firmicutes/bacteroidetes ratio in the gut microbiota and IL-1β, IL-6, IL-8, TLR2, TLR4, TLR5 gene expressions in type 2 diabetes [J]. Clin Lab, 2022, doi: 10.7754/Clin.Lab.2022.211244.

[55] ZHANG H, ZHENG L, LI C, et al. Effects of gut microbiota on omega-3-mediated ovary and metabolic benefits in polycystic ovary syndrome mice [J]. J Ovarian Res, 2023, 16(1): 138.

[56] TEDESCO S, ADORNI M P, RONDA N, et al. Activation profiles of monocyte-macrophages and HDL function in healthy women in relation to menstrual cycle and in polycystic ovary syndrome patients [J]. Endocrine, 2019, 66(2): 360-9.

[57] FAN Z, ZHANG X, SHANG Y, et al. Intestinal flora changes induced by a high-fat diet promote activation of primordial follicles through macrophage infiltration and inflammatory factor secretion in mouse ovaries [J]. Int J Mol Sci, 2022, 23(9): 4797.

[58] XU L, ZHANG Q, DOU X, et al. Fecal microbiota transplantation from young donor mice improves ovarian function in aged mice [J]. J Genet Genomics, 2022, 49(11): 1042-52.

[59] CLARKE G, STILLING R M, KENNEDY P J, et al. Minireview: gut microbiota: the neglected endocrine organ [J]. Mol Endocrinol, 2014, 28(8): 1221-38.

[60] FLORES R, SHI J, FUHRMAN B, et al. Fecal microbial determinants of fecal and systemic estrogens and estrogen metabolites: a cross-sectional study [J]. J Transl Med, 2012, 10: 253.

[61] KWA M, PLOTTEL C S, BLASER M J, et al. The intestinal microbiome and estrogen receptor-positive female breast cancer [J].

J Natl Cancer Inst, 2016, 108(8): djw029.

[62] YADAV H, LEE J H, LLOYD J, et al. Beneficial metabolic effects of a probiotic via butyrate-induced GLP-1 hormone secretion [J]. J Biol Chem, 2013, 288(35): 25088-97.

[63] KHAN D, OJO O O, WOODWARD O R, et al. Evidence for involvement of GIP and GLP-1 receptors and the gut-gonadal axis in regulating female reproductive function in mice [J]. Biomolecules, 2022, 12(12): 1736.

[64] HONG K J, LIN J J, LIN L H, et al. The intrafollicular concentration of leptin as a potential biomarker to predict oocyte maturity in *in-vitro* fertilization [J]. Sci Rep, 2022, 12(1): 19573.

[65] WOŁODKO K, CASTILLO-FERNANDEZ J, KELSEY G, et al. Revisiting the impact of local leptin signaling in folliculogenesis and oocyte maturation in obese mothers [J]. Int J Mol Sci, 2021, 22(8): 4270.

[66] PATEL J, CHAUDHARY H, RAJPUT K, et al. Assessment of gut microbial β-glucuronidase and β-glucosidase activity in women with polycystic ovary syndrome [J]. Sci Rep, 2023, 13(1): 11967.

[67] WANG R, ZHAO Y, FANG X, et al. Effect of the ketogenic diet on gut microbiome composition and metabolomics in polycystic ovarian syndrome rats induced by letrozole and a high-fat diet [J]. Nutrition, 2023, 114: 112127.

[68] 崔媚婷, 洪艳丽, 黄菁宇, 等. 补肾化痰方通过调控肠道菌及PPARγ通路治疗多囊卵巢综合征的机制[J]. 浙江大学学报: 医学版(CUI M, HONG Y, HUANG J, et al. Efficiency of Chinese medicine Bushen Huatan formula for treatment of polycystic ovary syndrome in mice via regulating gut microbiota and PPARγ pathway [J]. Zhejiang Da Xue Xue Bao Yi Xue Ban), 2023, 52(1): 33-45.

[69] LI G, LIU Z, REN F, et al. Alterations of gut microbiome and fecal fatty acids in patients with polycystic ovary syndrome in central china [J]. Front Microbiol, 2022, 13: 911992.

[70] MCGLONE E R, BLOOM S R. Bile acids and the metabolic syndrome [J]. Ann Clin Biochem, 2019, 56(3): 326-37.

[71] LI T, ZHANG T, GAO H, et al. Tempol modulates lncRNA-miRNA-mRNA ceRNA networks in ovaries of DHEA induced PCOS rats [J]. J Steroid Biochem Mol Biol, 2023, 226: 106175.

[72] LI A, LI F, SONG W, et al. Gut microbiota-bile acid-vitamin D axis plays an important role in determining oocyte quality and embryonic development [J]. Clin Transl Med, 2023, 13(10): e1236.

[73] HE S, LI H, YU Z, et al. The gut microbiome and sex hormone-related diseases [J]. Front Microbiol, 2021, 12: 711137.

[74] HONG D, ZHANG C, WU W, et al. Modulation of the gut-brain axis via the gut microbiota: a new era in treatment of amyotrophic lateral sclerosis [J]. Front Neurol, 2023, 14: 1133546.

[75] DESROZIERS E. Unusual suspects: glial cells in fertility regulation and their suspected role in polycystic ovary syndrome [J]. J Neuroendocrinol, 2022, 34(6): e13136.

[76] TSAVKELOVA E A, BOTVINKO I V, KUDRIN V S, et al. Detection of neurotransmitter amines in microorganisms with the use of high-performance liquid chromatography [J]. Dokl Biochem, 2000, 372(1/6): 115-7.

[77] BHATTARAI J P, ROA J, HERBISON A E, et al. Serotonin acts through 5-HT1 and 5-HT2 receptors to exert biphasic actions on GnRH neuron excitability in the mouse [J]. Endocrinology, 2014, 155(2): 513-24.

[78] PRASAD P, OGAWA S, PARHAR I S. Serotonin reuptake inhibitor citalopram inhibits GnRH synthesis and spermatogenesis in the male zebrafish [J]. Biol Reprod, 2015, 93(4): 102.

[79] LI S, PELLETIER G. Involvement of serotonin in the regulation of GnRH gene expression in the male rat brain [J]. Neuropeptides, 1995, 29(1): 21-5.

[80] WADA K, HU L, MORES N, et al. Serotonin (5-HT) receptor subtypes mediate specific modes of 5-HT-induced signaling and regulation of neurosecretion in gonadotropin-releasing hormone neurons [J]. Mol Endocrinol, 2006, 20(1): 125-35.

[81] 董婷, 尹小琴, 李妍, 等. 青春发育期5-羟色胺合成下降对雌鼠青春期启动的影响[J]. 上海交通大学学报(医学版)(DONG T, LI Y, LI P, et al. Effect of decreased 5-hydroxytryptamine synthesis during puberty development on the onset of puberty in female rats [J]. Journal of Shanghai Jiao Tong University, Medical Science), 2022, 42(3): 307-11.

[82] ALYOSHINA N M, TKACHENKO M D, MALCHENKO L A, et al. Uptake and metabolization of serotonin by granulosa cells form a functional barrier in the mouse ovary [J]. Int J Mol Sci, 2022, 23(23): 14828.

[83] SHENG Y, WANG L, LIU X S, et al. A serotonin receptor antagonist induces oocyte maturation in both frogs and mice: evidence that the same G protein-coupled receptor is responsible for maintaining meiosis arrest in both species [J]. J Cell Physiol, 2005, 202(3): 777-86.

[84] DUBÉ F, AMIREAULT P. Local serotonergic signaling in mammalian follicles, oocytes and early embryos [J]. Life Sci, 2007, 81(25/26): 1627-37.

[85] HIRAI S, KISHIMOTO T, KADAM A L, et al. Induction of spawning and oocyte maturation by 5-hydroxytryptamine in the surf clam [J]. JEZ, 1988, 245(3): 318-21.

[86] LI S, PELLETIER G. Role of dopamine in the regulation of gonadotropin-releasing hormone in the male rat brain as studied by in situ hybridization [J]. Endocrinology, 1992, 131(1): 395-9.

[87] LIU X, HERBISON A E. Dopamine regulation of gonadotropin-releasing hormone neuron excitability in male and female mice [J]. Endocrinology, 2013, 154(1): 340-50.

[88] ARAKAWA S, YAGO N, ISOBE S, et al. [Dopamine increases the ovarian progesterone synthesis of PMSG-treated rats by regulating 3 beta-HSD activity] [J]. Nihon Naibunpi Gakkai Zasshi, 1994, 70(4): 447-56.

[89] VIDAL B, PASQUALINI C, LE BELLE N, et al. Dopamine inhibits luteinizing hormone synthesis and release in the juvenile European eel: a neuroendocrine lock for the onset of puberty [J]. Biol Reprod, 2004, 71(5): 1491-500.

[90] TINIKUL Y, POLJAROEN J, TINIKUL R, et al. Effects of gonadotropin-releasing hormones and dopamine on ovarian maturation in the pacific white shrimp, litopenaeus vannamei, and their presence in the ovary during ovarian development [J]. Aquaculture, 2014, 420-421: 79-88.

[91] HAMED E A, SAYYED H G, ABBAS A M, et al. Nesfatin-1, dopamine, and NADPH levels in infertile women with polycystic ovary syndrome: is there a relationship between their levels and metabolic and hormonal variables [J]. J Reprod Infertil, 2022, 23(3): 160-8.

[92] CHAUDHARI N, DAWALBHAKTA M, NAMPOOTHIRI L.

GnRH dysregulation in polycystic ovarian syndrome (PCOS) is a manifestation of an altered neurotransmitter profile [J]. Reprod Biol Endocrinol, 2018, 16(1): 37.

[93] AMIN M, HORST N, GRAGNOLI C. Linkage and association of variants in the dopamine receptor 2 gene (DRD2) with polycystic ovary syndrome [J]. J Ovarian Res, 2023, 16(1): 158.

[94] SIMPSON C A, DIAZ-ARTECHE C, ELIBY D, et al. The gut microbiota in anxiety and depression-a systematic review [J]. Clin Psychol Rev, 2021, 83: 101943.

[95] CHEN Y, XU J, CHEN Y. Regulation of neurotransmitters by the gut microbiota and effects on cognition in neurological disorders [J]. Nutrients, 2021, 13(6): 2099.

[96] WANG Y, TONG Q, MA S R, et al. Oral berberine improves brain dopa/dopamine levels to ameliorate Parkinson's disease by regulating gut microbiota [J]. Signal Transduct Target Ther, 2021, 6(1): 77.

[97] STRANDWITZ P, KIM K H, TEREKHOVA D, et al. GABA-modulating bacteria of the human gut microbiota [J]. Nat Microbiol, 2019, 4(3): 396-403.

[98] SON J, BARITUGO K A, SOHN Y J, et al. Production of γ-Aminobutyrate (GABA) in recombinant corynebacterium glutamicum by expression of glutamate decarboxylase active at neutral pH [J]. ACS Omega, 2022, 7(33): 29106-15.

[99] YAO L L, CAO J R, LYU C J, et al. Food-grade γ-aminobutyric acid production by immobilized glutamate decarboxylase from Lactobacillus plantarum in rice vinegar and monosodium glutamate system [J]. Biotechnol Lett, 2021, 43(10): 2027-34.

[100] HORVATH T D, IHEKWEAZU F D, HAIDACHER S J, et al. Bacteroides ovatus colonization influences the abundance of intestinal short chain fatty acids and neurotransmitters [J]. iScience, 2022, 25(5): 104158.

[101] WATANABE M, FUKUDA A, NABEKURA J. The role of GABA in the regulation of GnRH neurons [J]. Front Neurosci, 2014, 8: 387.

[102] HAN S-K, ABRAHAM I M, HERBISON A E. Effect of GABA on GnRH neurons switches from depolarization to hyperpolarization at puberty in the female mouse [J]. Endocrinology, 2002, 143(4): 1459-66.

[103] ACEVEDO-RODRIGUEZ A, KAUFFMAN A S, CHERRINGTON B D, et al. Emerging insights into hypothalamic-pituitary-gonadal axis regulation and interaction with stress signalling [J]. J Neuroendocrinol, 2018, 30(10): e12590.

[104] MOORE A M, COOLEN L M, LEHMAN M N. Kisspeptin/Neurokinin B/Dynorphin (KNDy) cells as integrators of diverse internal and external cues: evidence from viral-based monosynaptic tract-tracing in mice [J]. Sci Rep, 2019, 9(1): 14768.

[105] DUAN L, AN X, ZHANG Y, et al. Gut microbiota as the critical correlation of polycystic ovary syndrome and type 2 diabetes mellitus [J]. Biomed Pharmacother, 2021, 142: 112094.

[106] CLARK A, MACH N. The crosstalk between the gut microbiota and mitochondria during exercise [J]. Front Physiol, 2017, 8: 319.

[107] NICESE M N, BIJKERK R, VAN ZONNEVELD A J, et al. Sodium butyrate as key regulator of mitochondrial function and barrier integrity of human glomerular endothelial cells [J]. Int J Mol Sci, 2023, 24(17): 13090.

[108] LI Y, YANG S, JIN X, et al. Mitochondria as novel mediators linking gut microbiota to atherosclerosis that is ameliorated by herbal medicine: a review [J]. Front Pharmacol, 2023, 14: 1082817.

[109] D'AQUILA P, CARELLI L L, DE RANGO F, et al. Gut microbiota as important mediator between diet and DNA methylation and histone modifications in the host [J]. Nutrients, 2020, 12(3): 597.

[110] GNAINSKY Y, ZFANYA N,ELGART M, et al. Systemic regulation of host energy and oogenesis by microbiome-derived mitochondrial coenzymes [J]. Cell Rep, 2021, 34(1): 108583.

[111] BERTOLDO M J, LISTIJONO D R, HO W J, et al. NAD^+ repletion rescues female fertility during reproductive aging [J]. Cell Rep, 2020, 30(6): 1670-81,e7.

[112] YOSHINO J, BAUR J A, IMAI S I. NAD^+ intermediates: the biology and therapeutic potential of NMN and NR [J]. Cell Metab, 2018, 27(3): 513-28.

[113] LI H, WANG H, XU J, et al. Nicotinamide riboside supplementation ameliorated post-ovulatory oocyte quality decline [J]. Reproduction, 2023, 165(1): 103-11.

[114] SAMIMI M, DADKHAH A, HADDAD KASHANI H, et al. The effects of synbiotic supplementation on metabolic status in women with polycystic ovary syndrome: a randomized double-blind clinical trial [J]. Probiotics Antimicrob Proteins, 2019, 11(4): 1355-61.

[115] SANDERS M E, MERENSTEIN D J, REID G, et al. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic [J]. Nat Rev Gastroenterol Hepatol, 2019, 16(10): 605-16.

[116] BEDU-FERRARI C, BISCARRAT P, LANGELLA P, et al. Prebiotics and the human gut microbiota: from breakdown mechanisms to the impact on metabolic health [J]. Nutrients, 2022, 14(10): 2096.

[117] GHOLIZADEH SHAMASBI S, DEHGAN P, MOHAMMAD-ALIZADEH CHARANDABI S, et al. The effect of resistant dextrin as a prebiotic on metabolic parameters and androgen level in women with polycystic ovarian syndrome: a randomized, triple-blind, controlled, clinical trial [J]. Eur J Nutr, 2019, 58(2): 629-40.

[118] CLAUSS M, GÉRARD P, MOSCA A, et al. Interplay between exercise and gut microbiome in the context of human health and performance [J]. Front Nutr, 2021, 8: 637010.

[119] MOHR A E, JÄGER R, CARPENTER K C, et al. The athletic gut microbiota [J]. J Int Soc Sports Nutr, 2020, 17(1): 24.

[120] ARAGÓN-VELA J, SOLIS-URRA P, RUIZ-OJEDA F J, et al. Impact of exercise on gut microbiota in obesity [J]. Nutrients, 2021, 13(11): 3999.

[121] SIVASANKARI R, USHA B. Reshaping the gut microbiota through lifestyle interventions in women with PCOS: a review [J]. Indian J Microbiol, 2022, 62(3): 351-63.

[122] CLARK A, MACH N. Exercise-induced stress behavior, gut-microbiota-brain axis and diet: a systematic review for athletes [J]. J Int Soc Sports Nutr, 2016, 13: 43.

[123] DALTON A, MERMIER C, ZUHL M. Exercise influence on the microbiome-gut-brain axis [J]. Gut Microbes, 2019, 10(5): 555-68.