基于肠道微生物与G蛋白偶联受体互作关系探讨中药有效成分筛选新模式

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摘要: 肠道微生物及其代谢物与人类疾病密切相关, 其通过与受体互作而影响疾病的发生发展。G蛋白偶联受体 (G protein-coupled receptor, GPCR) 是一类存在于细胞膜表面的受体超家族, 该受体家族广泛参与人体生理活动, 被认为是重要的药物靶点。中药具有多成分、多靶点、多通路的特点。越来越多的研究表明中药可通过调节肠道微生物及其代谢物而影响GPCR调控模式, 最终干预疾病。本文综述了肠道微生物与人类疾病的现状、肠道微生物及其代谢物与GPCR互作关系、GPCR药物开发现状。基于上述研究, 本文提出“中药−肠道功能菌群单元−GPCR−疾病”研究新模式。运用多组学技术阐释中药有效成分、肠道功能菌群单元及GPCR三者之间互作关系及其对疾病的影响。本文将为解析中药药效物质基础, 寻找中药作用新靶标提供新思路。

关键词: 肠道微生物; G蛋白偶联受体; 疾病; 中药; 药物筛选

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A new model for screening active ingredients in traditional Chinese medicine based on the interactions between gut microorganisms and G protein-coupled receptor

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Abstract: Gut microbiome and their metabolites are closely related to human diseases, which influence the development of diseases by interacting with receptors. G protein-coupled receptor (GPCR) is a receptor superfamily that exists on the surface of cell membrane, which is involved in a wide range of human physiological activities. GPCR is currently considered as important drug targets. Traditional Chinese medicines (TCM) are characterized by multi-components, multi-targets, and multi-pathways. More and more studies have demonstrated that TCM can ultimately intervene in diseases by modulating gut microbiome and their metabolites, affecting their interactions with GPCR. This review discusses the status of gut microbiome and human diseases, the interactions of gut microbiome and their metabolites with GPCR, and the status of GPCR drug development. Based on the above contents, a new model of "TCM-gut microbiome panel-GPCR-disease" is proposed. The interactions between active ingredients of TCM, gut microbiome panel, and GPCR and their effects on disease are elucidated through multi-omics techniques. This review will provide new ideas for analyzing the pharmacological mechanism of TCM efficacy and searching for new targets of TCM.

Key words: gut microbiome; G protein-coupled receptor; disease; traditional Chinese medicine; drug screening

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微生物广泛存在于人类口腔、胃肠道黏膜、皮肤及阴道等部位, 其种类繁多, 包括细菌、真菌、病毒、支原体等。它们能够在人体内形成动态平衡的微生态环境, 协助人体维持正常的生理功能, 同时又能够影响人体病理进程。有研究表明微生物与代谢性疾病、消化系统疾病、心血管系统疾病、神经系统疾病、肿瘤等密切相关[1-3]。肠道微生态是指肠道微生物及其所生存的环境[4]。肠道微生态稳态的维持在许多生理过程中起着至关重要的作用, 包括保障免疫系统的正常功能、维持肠道黏膜屏障的完整性等[5]。肠道黏膜结构的完整性及正常的肠道微环境的组成对维持肠道微生态的稳定有重要作用。例如糖尿病小鼠中肠道微生物代谢物短链脂肪酸 (short-chain fatty acids, SCFAs) 的含量降低, 其肠道微生态系统可能发生紊乱[6]。肠道微生态失衡及其代谢产物的异常与炎症性肠病发生也有关[7], 这些证据进一步强调微生物在人类疾病中扮演重要角色。

微生物及其代谢产物能通过与各类受体相结合, 发挥特异性作用。如*Mycelia sterilia*产生的多球壳菌素作用于细胞表面的1-磷酸−鞘氨醇受体 (sphingosine 1-phosphate receptor, S1PR) 来发挥免疫抑制和免疫调控作用[8]; *Psilocybe mexicana*产生的psilocybin作用于血清素2A受体 (serotonin 2A receptor, 5-HT_{2A}R) 治疗抑郁症[9]。肺炎链球菌 (*Streptococcus pneumoniae*) 产生的肽酶可通过激活蛋白酶活化受体2 (protease activated receptor 2, PAR2) 促进炎症发生[10]; 胆汁酸类代谢物可作用于法尼醇X受体 (farnesoid X receptor, FXR)、孕烷X受体 (pregnane X receptor, PXR)、维生素D受体 (vitamin D receptor, VDR) 和G蛋白偶联受体5 (takeda G protein-coupled receptor 5, TGR5) 等[11,12], 起到调节机体代谢、免疫和炎症等多种生理病理过程的作用。G蛋白偶联受体 (G protein-coupled receptor, GPCR) 是近年来新药研发的热门靶点, 其激活机制是理解其生理功能及相关疾病成因的必由之路, 并一直是该领域研究的核心内容和前沿热点。

1 肠道微生物与人类疾病

1.1 肠道微生物研究现状

人类肠道中存在着数量庞大、种类繁多的微生物。相比于其他器官组织, 肠道中生存的微生物在数量上最具优势[13]。肠道微生物包括1 500余种, 多数为细菌, 其中以拟杆菌门 (Bacteroidetes) 和厚壁菌门 (Firmicutes) 最为常见, 其他包括变形菌门 (Proteobacteria)、梭菌门 (Fusobacteria)、软壁菌门 (Tenericutes)、放线菌门 (Actinobacteria) 和疣微菌门 (Verrucomicrobia) 等[14]。肠道微生物是人类生长发育和生理活动过程中不可缺少的部分, 其功能广泛, 包括调节免疫和能量稳态、产生生物活性代谢物、抵御病原体等。然而, 不良饮食、不规律作息、药物滥用以及生活环境变化均可能导致肠道微生物的稳态失衡, 引发胃肠道功能紊乱, 甚至多器官功能失调, 诱导疾病的发生[15]。此外, 肠道微生物与其他器官间调控作用也在近年来得到广泛报道。有学者提出了“肠−X轴”理念, 所谓“肠−X轴”理念即肠道微生物与肠外器官如脑、肝、肾、骨骼等器官之间相互调控, 以维持人体的稳态, 包括肠−脑轴、肠−肝轴、肠−肌肉轴、肠−骨髓/免疫轴等分支[16-18]。肠道微生物不仅与肠道健康存在直接关系, 通过“肠−X轴”也间接影响着其他器官系统的生理病理状态, 这为疾病治疗提供了新的方向和可能性。

1.2 肠道微生物与人类疾病研究现状

肠道微生物与人类健康密切相关, 各种因素所致肠道稳态失衡可导致多种疾病的发生。常见与之相关的疾病包括肿瘤、胃肠道疾病、代谢性疾病和脑部疾病等[19]。

肠道微生物可参与肿瘤的发生发展。据估计, 约15%的恶性肿瘤与肠道微生物有关[20]。肠道微生物代谢产生的胆汁酸可通过多种途径促进肿瘤的发生进展, 并影响预后。疏水性胆汁酸如脱氧胆酸 (deoxycholic acid, DCA)、牛磺胆酸 (taurocholic acid, TCA)、牛磺胆酸酯 (taurochenodeoxycholic acid, TCDCA) 等代谢物含量在链脲佐菌素和高脂饮食诱导的非酒精性脂肪性肝炎−肝细胞癌小鼠模型中显著增加, 该模型HepG2细胞中抑癌基因CEBPα表达下调, 促进肝癌的发生[21]。研究发现, 空肠弯曲杆菌 (*Campylobacter jejuni*) 通过细胞致死性膨胀毒素改变无菌肿瘤小鼠 ($Apc^{Min/+}$) 肠道菌群结构, 并促进结直肠肿瘤的发生[22]; 幽门螺杆菌 (*Helicobacter pylori*) 上调癌症相关基因转化生长因子β (TGF-β) 的表达, 降低微生物的多样性, 导致肠道微生物失调及易位定植, 促进胃癌的发生[23]。近年来, 肠道微生物已成为治疗恶性肿瘤的重要靶点, 而中药能够有效调控肠道微生物防治恶性肿瘤。黄芪多糖[24]通过抑制肠道微生物中的革兰阴性菌, 减少脂多糖的释放, 抑制Toll样受体-4/核因子-κB (TLR4/NF-κB) 信号通路, 有效抑制人结肠癌细胞的上皮间充质转化过程, 控制肿瘤的增殖和迁移, 调控结肠炎癌转化进程。人参皂苷Rk3[25]可以调节肠道微生物群的组成和多样性, 上调有益细菌嗜黏蛋白阿克曼菌 (*Akkermansia muciniphila*) 和肠道巴氏杆菌 (*Barnesiella intestinihominis*) 的相对丰度, 调节先天淋巴细胞免疫应答, 抑制促肿瘤Janus激酶信号转导和转录激活因子3 (JAK-STAT3) 信号通路, 进而抑制结肠肿瘤发生。此外, 研

究表明黄连、茯苓、车前子和大枣等[26-29]中药干预恶性肿瘤的机制与肠道微生物也存在密切联系。

胃肠道疾病包括炎症性肠病、乳糜泻及肠易激综合征等。炎症性肠病 (inflammatory bowel disease, IBD) 是一种非特异性的慢性复发性肠道炎症性疾病, 包括溃疡性结肠炎 (ulcerative colitis, UC) 与克罗恩病 (Crohn's disease, CD)。有研究表明[30], 在IBD活动期, 肠道微生物组功能失调, 胆汁酸、短链脂肪酸、酰基肉碱等代谢途径发生紊乱。中药通过调控肠道微生物稳态改善胃肠道疾病也有广泛研究。慢性IBD小鼠的肠道菌群的多样性和物种丰富度呈现下降趋势, 其中拟杆菌门相对丰度显著下调, 疣微菌门相对丰度显著上调。江香薷[31]可显著降低葡聚糖硫酸钠 (dextran sulfate sodium, DSS) 诱导的结肠炎小鼠模型活性氧的产生, 降低拟杆菌科 (Bacteroidaceae) 的相对丰度, 增加双歧杆菌目 (Bifidobacteriales) 和黑素菌门 (Melainabacteria) 的相对丰度, 抑制丝裂原活化蛋白激酶 (MAPKs) 信号通路的激活, 改善IBD。苦参碱[32]可显著提高2,4,6-三硝基苯磺酸诱导的小鼠结肠炎肠道微生物消化链球菌科 (Peptostreptococcaceae)、甲基杆菌科 (Methylobacteriaceae)、鞘氨醇单胞菌科 (Sphingomonadaceae) 和毛螺菌科 (Lachnospiraceae) 的相对丰度, 抑制NF-κB的上游信号Toll样受体4 (TLR4)/髓样分化因子88 (myeloid differentiation factor 88, My D88) 的表达, 进而治疗IBD。此外, 黄蜀葵花、火麻仁、黄芩、芍药、党参、茯苓及黄柏等[33-38]中药也广泛应用于胃肠道相关疾病的临床治疗。

肠道微生物与肝脏的双向作用关系催生了“肠−肝轴”这一概念[39], 而“肠−肝轴”是维持机体内环境稳态的关键[40], 肠道中小肠细菌过度生长会增加脂肪肝变性的风险, 促进非酒精性脂肪肝的进展[41]。在代谢性疾病中, 普雷沃菌 (*Prevotella copri*) 的增加可诱导胰岛素抵抗和糖代谢紊乱, 促进2型糖尿病的发生[42,43]。姜长涛团队[44]近日提出肠道菌源宿主同工酶的新概念, 并且发现菌源DPP4是一种重要的同工酶, 可以在肠屏障损伤条件下进入肠组织, 降解宿主活性胰高血糖素样肽-1 (glucagon-like peptide-1, GLP-1), 诱导糖耐量异常, 促进2型糖尿病的进展。在代谢性疾病的治疗中, 中药对调控肠道微生物的紊乱具有显著效果。普洱茶作为一种特产于中国云南地区的发酵茶, 可缓解高脂血症、肥胖症、脂肪肝等疾病。普洱茶提取物[45]可降低携带胆盐水解酶的肠道微生物的相对丰度, 如芽孢杆菌属 (*Bacillus*)、乳酸菌属 (*Lactobacillus*) 等, 从而降低胆盐水解酶活性, 增加回肠结合型胆汁酸, 抑制肠道FXR相关信号通路传导, 减轻高胆固醇血症。五味子酯甲和五味子乙素可降低厚壁菌门相对丰度、增加疣微菌门相对丰度, 增强肠道黏膜屏障功能, 降低血清中脂多糖含量, 减少脂多糖进入肝脏和体循环, 从而有效改善高脂饮食诱导模型动物的肝脏脂肪变性和炎症[46,47]。桑叶、丹参、地黄、麦冬、黄芪、灵芝、黄连等[48-54]中药对治疗代谢性疾病也具有显著疗效。

肠道微生物与大脑之间进行双向调节被称为“肠−脑轴”[55], 肠道微生物在其中承担关键角色。通过调节γ-氨基丁酸、多巴胺、5-羟色胺 (5-hydroxytryptamine, 5-HT) 等代谢物[56,57], 维持“肠−脑轴”的正常运作。多项研究结果显示, 在多种神经退行性疾病与精神疾病患者肠道中都发现携带脂多糖的革兰阴性杆菌如脆弱拟杆菌 (*Bacteroides fragilis*) 数量增加, 分泌脆弱拟杆菌−脂多糖 (BF-LPS) 神经毒素, 促进阿尔茨海默症的进展[58-60]。来源于传统中药的有效成分也是重要的肠道微生物调节剂, 包括生物碱类、黄酮类、多糖类、多酚类和皂苷类等[61], 与肠道微生物相互作用, 影响微生物结构和代谢, 最终发挥脑部疾病治疗作用。

肠道微生态的失衡能够诱发疾病、促进疾病发展。反之, 机体的病理状态也会进一步诱导肠道微生态的紊乱。因此, 肠道微生物与人类疾病双向调节的复杂调控机制已成为当今医学研究的热点。

1.3 中药调控肠道微生物干预人类疾病的现状

中药能够通过调控肠道微生物来改善多种疾病, 包括糖尿病、非酒精性脂肪肝、溃疡性结肠炎、阿尔茨海默症和抑郁症等。例如白藜芦醇能够纠正高脂饮食诱导的大鼠肠道微生物比例的失调, 有效预防肥胖和胰岛素抵抗的进展[62]。绞股蓝皂苷能促进动物双歧杆菌 (*Bifidobacterium animalis*) 的增长, 从而抑制结直肠癌的发展[63]。Gou等[64]研究发现片仔癀通过控制肠道微生物群和代谢物向更有利的方向发展, 改善肠道屏障功能, 抑制致癌和促炎途径, 从而抑制结直肠癌的发生。近年来, GPCR家族成为中药药效机制研究的热门靶点。小檗碱通过激活肾小球系膜细胞中的G蛋白偶联受体TGR5并抑制其下游鞘氨醇1-磷酸受体2 (S1P2)/丝裂原活化蛋白激酶 (MAPK) 信号通路来减轻高葡萄糖诱导的纤维化[65]。龙胆苦苷激活TGR5促进β-抑制蛋白2 (β-arrestin 2) 与人核因子κB抑制蛋白α (inhibitor kappa B alpha, IκBα) 的相互作用, 增强IκBα的稳定性, 抑制NF-κB信号通路, 改善糖尿病肾纤维化的病理进展[66]。Gintonin是从人参中新发现的化合物, 是新型溶血磷脂酸−蛋白质复合物, 可激活G蛋白偶联受体溶血磷脂酸受体, 引起 $[Ca^{2+}]_i$ 的瞬时增加[67]。中药在疾病治疗中有着广泛应用, 可以调控肠道微生物群和代谢物, 保护胃肠道黏膜屏障功能, 促进

益生菌的繁殖、抑制有害菌的生长, 改善肠道微生态平衡, 肠道微生物也可以代谢中药成分, 产生多种代谢产物, 影响药物疗效 (图1)。

2 GPCR与肠道微生物

2.1 GPCR研究现状

GPCR是具有七次跨膜结构的膜蛋白家族。据相关统计, 目前人体中包含超过800个带注释的GPCR基因, 约占整个人类蛋白质编码基因的4%。GPCR通过与相关配体结合以调节多种细胞功能, 进而参与人体的生理病理过程, 尤其在糖尿病、肥胖、抑郁、癌症、阿尔茨海默症等重大疾病中扮演着极其重要的角色。因此GPCR近年来也成为治疗相关疾病的明星靶点之一。根据GRAFS分类法[68], GPCR家族可分为A类视紫红质受体家族、B1类分泌素受体家族、B2类黏附素受体家族、C类谷氨酸受体家族及F类卷曲/味觉受体2家族。这些受体结构和功能的异常可能介导多种疾病的形成。如腺苷A2A受体 (adenosine 2A receptor, A2AR) 具有抑制炎症和保护组织免受损伤的功能[69]。低剂量壬基酚可以促进G蛋白偶联雌激素受体GPR30的表达, 对人前列腺癌细胞株DU-145细胞具有促增殖作用[70]。GLP-1受体属于B类家族, GLP-1受体的激活可抑制胰高血糖素的释放, 增加β细胞增殖和减少β细胞凋亡, 有助于调节血糖水平[71]。G蛋白偶联受体124 (GPR124) 在人血白蛋白的脑保护机制中发挥重要作用, 人血白蛋白能减轻大鼠全脑缺血/再灌注损伤和血脑屏障的破坏, 促进GPR124在脑组织中的表达[72]。C家族中的蛋白酶活化受体 (protease activated receptors, PARs) 具有促进炎症、抑制肿瘤细胞的生长、促进肿瘤血管生长等作用[73,74], 使各种参与肿瘤生长及血管生成的相关因子的表达增强, 通过抑制PARs的表达来抑制肝癌细胞的生长和转移[75]。

2.2 肠道微生物代谢物与GPCR互作关系

GPCR广泛分布于肠道的肠黏膜上皮细胞、免疫细胞、内分泌细胞等多种细胞中, 参与机体发育以及多种生理功能的调控。表1[76-104]列出了肠道微生物代谢物如短链脂肪酸、色氨酸和胆汁酸等作为GPCR的天然内源性配体[105,106], 通过作用于GPCR或其他通路, 能够有效地调节人体生理病理过程。

2.2.1 短链脂肪酸与GPCR互作 短链脂肪酸主要是由肠道微生物包括梭菌属 (*Clostridium*)、双歧杆菌属 (*Bifidobacterium*) 及拟杆菌属 (*Bacteroides*) 等发酵膳食纤维而产生的, 包括乙酸、丙酸和丁酸等。

SCFAs通过作用于肠内分泌L细胞表面表达的特异性GPCR (如GPR41、GPR43和GPR109A) 刺激肠肽的分泌, 进而参与血糖调节[19]。乙酸通过刺激GPR43来调节肠道炎症状态, 有助于维持肠道上皮屏障功能[107]。丙酸盐激活GPR43后能显著刺激肠内分泌L细胞释放厌食肠道激素肽YY和GLP-1, 抑制肠道运输, 增加葡萄糖耐量, 从而降低食欲[108]; 激活GPR109A降低血浆三酰甘油水平和游离脂肪酸水平[109]。同时也能激活GPR41使游离脂肪酸水平降低及脂肪分解减少, 从而影响肥胖的发生发展[110]。丁酸盐[80,111]能够与小鼠结肠上皮细胞、巨噬细胞和树突状细胞上的GPR109A结合, 引起白细胞介素-10 (interleukin, IL-10) 的分泌, 从而诱导调节性T细胞的分化, 抑制肠道炎症。除内源性SCFAs外, Shimizu等[112]发现补充外源性SCFAs同样可激活GPR41的表达改善肝脏代谢功能, 从而抑制肝脏质量增加和脂质合成, 延缓由小鼠高脂肪饮食诱导的肥胖发生。菊粉可以增加小鼠肠道SCFAs代谢物丙酸盐、丁酸盐和戊酸盐的含量, 抑制

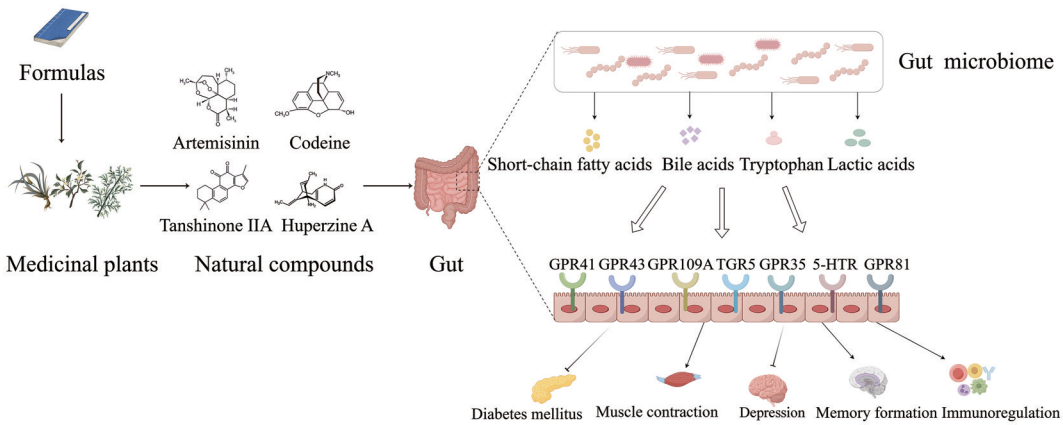

Figure 1 Traditional Chinese medicines active ingredients modulate gut microbiome and their metabolites to interplay with G protein-coupled receptor (GPCR) to intervene in human diseases. GPR41: G-protein-coupled receptor 41; GPR43: G-protein-coupled receptor 43; GPR109A: G-protein-coupled receptor 109A; TGR5: Takeda G protein-coupled receptor 5; GPR35: G-protein-coupled receptor 35; 5-HTR: 5-Hydroxyptamine receptor; GPR81: G-protein-coupled receptor 81

Table 1 Gut microbial metabolites and disease. MAPK: Mitogen-activated protein kinase; OPG: Osteoprotegerin; RANKL: Receptor activator of nuclear factor kappa-B ligand; MMP-2: Matrix metalloproteinase-2; OPN: Osteocalcin and osteopontin; PI3K: Phosphatidylinositide 3 kinase; NF-κB: Nuclear factor kappa-B; MCP-1: Monocyte chemotactic protein-1; VCAM-1: Vascular cell adhesion molecule 1; Akt/PKB: Akt/protein kinase B; MMP-9: Matrix metalloproteinase-9; DCA: Deoxycholic acid; JNK: C-jun N-terminal kinase; Wnt: Wingless/integrated; DNA: Deoxyribonucleic acid; cAMP: Cyclic adenosine monophosphate; PKA: Protein kinase A; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; ERK: Extracellular regulated protein kinases; 5-HT: 5-Hydroxytryptamine; HTR3A: 5-Hydroxytryptamine receptor 3A; FoxO6: Forkhead Box O6; 5-HT1D: 5-Hydroxytryptamine receptor 1D; PIK3R1: Phosphoinositide-3-kinase regulatory subunit 1; SCFAs: Short-chain fatty acids

Gut microbial metabolite		Target/pathway	Disease	Mechanism	Ref.
SCFAs	Acetic acid	Histone deacetylase	Allergic asthma	Promote T-cell differentiation into both effector and regulatory T cells to promote either immunity or immune tolerance	[76]
	Propanoic acid	Regulatory T cell	Multiple sclerosis	Increased the expression of Treg-cell-inducing genes in the gut while normalizing Treg cell mitochondrial function and morphology	[77]
		p38-MAPK and interleukin-10 signaling	Obesity	Restoration of Treg-Th17 homeostasis and inhibition of obesity and related comorbidities	[78]
	Butyric acid	OPG/RANKL	Osteoporosis	Alteration of OPG/RANKL expression/secretion, 8-isoprostane, MMP-2 and OPN secretion induces bone destruction and impairs bone repair and affects cell viability	[79]
		GPR109A	Colonic inflammation	Inhibits colonic inflammation by activating the GPR109A receptor	[80]
	Propanoic acid Butyric acid	−	Cardiovascular diseases	−	[81]
		GPR109A, GPR41	Hyperlipidemia	Activates GPR109A receptor and GPR41 receptor to reduce cholesterol production and improve lipid metabolism	[82, 83]
	Acetic acid Propanoic acid Butyric acid	−	Lung diseases	Regulation of metabolic processes in lipopolysaccharide-exposed alveolar macrophages and maintains lung immune metabolism	[84]
		GPR41, GPR43, GPR109A	Cancer	Regulation of GPR41, GPR43 and GPR109A expression reduces inflammation and cancer effects	[85]
		GPR43, GPR109A	Gut inflammation	Reduces inflammation by activating G protein-coupled receptors such as GPR43, GPR109A	[80, 86]
Bile acids	Tauroursodeoxycholic acid	Amyloid-beta peptide	Alzheimer's disease	Inhibits cell death by interfering with the mitochondrial pathway of apoptosis in a PI3K-dependent manner, thereby inhibiting the translocation of the pro-apoptotic protein Bax	[87]
		NF-κB pathway	Acute neuroinflammation	Reduced glial cell activation and expression of MCP-1 and VCAM-1	[88]
		−	Huntington's disease	Reduces apoptosis in striatal cells; reduced intracellular levels of inclusions; improved motor and sensorimotor function	[89]
	Ursodeoxycholic acid	PI3K-Akt/PKB pathways	Parkinson's disease	Dose-dependent inhibition of apoptosis by the PI3K-Akt/PKB pathway reduces reactive oxygen species (ROS) and reactive nitrogen and maintains intracellular glutathione levels	[90]
	Glycoursodeoxycholic acid	Caspase-9 and MMP-9	Amyotrophic lateral sclerosis	Reduced cell death by blocking caspase-9 activation	[91]
	Glycodeoxycholic acid Tauroursodeoxycholic acid	TGR5-GATA binding protein 3 signaling pathway	Polycystic ovary syndrome	Promoting intestinal intestinal group 3 secretion of interleukin-22 *via* the TGR5-GATA binding protein 3 signaling pathway ameliorates polycystic ovary syndrome	[92]
	DCA Lithocholic acid	NF-κB and Wnt signaling pathway	Colonic carcinogenesis	Activation of Wnt and NF-κB signaling pathways triggers oxidative DNA damage and impaired mitogenic activity, which subsequently leads to excessive proliferation of colon cells	[93]

Continued

Gut microbial metabolite		Target/pathway	Disease	Mechanism	Ref.
		TGR5-cAMP-PKA axis	Gut inflammation	Inhibition of NLRP3 inflammasome activation *via* the TGR5-cAMP-PKA axis	[94]
	DCA	JNK	Atherosclerosis	Up-regulation of c-jun N-terminal kinase (JNK) and platelet-derived growth factor beta receptor	[95]
	Lithocholic acid	TGR5	Rheumatoid arthritis	Activated TGR5 receptor and exhibits anti-inflammatory effects	[96]
Tryptophan	Kynurenine	–	Diabetic nephropathy	–	[97]
		PI3K/Akt and MAPK signaling pathways	Colorectal cancer	Inhibition of PI3K/AKT and ERK pathways suppresses proliferation of colorectal cancer cells	[98]
	5-HT	–	Metabolic disease	Affects hepatocyte and adipocyte function to regulate blood glucose and obesity	[99]
		–	Neurosis	–	[100]
		HTR3A receptor	Colorectal cancer	Activation of HTR3A receptor enhances NLRP3 inflammatory vesicle activation and causes intestinal inflammation	[101]
		PI3K/Akt/FoxO6	Hepatocellular carcinoma	5-HT1D interacts with PIK3R1 to activate the PI3K/Akt/FoxO6 pathway and exacerbates hepatocellular carcinoma progression	[102]
		–	Depression	–	[103]
		–	Chronic inflammation	Toll-like receptor 2 inhibits 5-HT transporter function and reduces 5-HT release, thereby improving chronic inflammation	[104]

M1巨噬细胞, 促进小鼠M2巨噬细胞的炎症来缓解酒精性肝病的炎症[113]; 吴茱萸碱粪便菌群移植实验缓解DSS诱导的结肠炎, 增加嗜酸乳杆菌 (*Lactobacillus acidophilus*) 的丰度和乙酸盐的水平, 降低促炎细胞因子, 促进杯状细胞的增加和抗菌肽的分泌, 调节厚壁菌门/拟杆菌门的比例, 提高乙酸盐的水平, 治疗UC[114]。

2.2.2 色氨酸与GPCR互作 色氨酸作为必需氨基酸在机体内参与广泛代谢。大多数肠道微生物可以通过不同的途径代谢色氨酸, 产生多种生物活性分子, 如犬尿氨酸、色胺、吲哚衍生物等[115]。色氨酸的微生物代谢产物是“肠–脑轴”双向交流系统的重要信号因子, 所以色氨酸代谢的平衡对于“肠–脑轴”的稳态十分重要。有研究表明, 在慢性约束应激小鼠模型中, 长期压力会破坏沿肠脑轴的犬尿氨酸代谢和内分泌功能, 并引起微生物群稳态的紊乱, 从而导致抑郁症的发展[116]。色氨酸代谢产物比例与机体健康相关联, 色氨酸代谢产物主要有犬尿氨酸、喹啉酸、烟酸和犬尿烯酸等, 其中犬尿烯酸通过激活GPR35受体, 发挥保护肠道黏膜和免疫调节作用[117,118]。厚朴酚有效提高血清色氨酸代谢物水平, 包括犬尿烯酸、5-羟基吲哚乙酸、吲哚乙酸、吲哚乳酸和吲哚硫酸等芳烃受体配体, 降低结肠中炎症细胞因子白细胞介素-6 (IL-6)、白细胞介素-1β (IL-1β) 水平, 从而改善DSS诱导的UC小鼠结肠病变状态[119]。人参多糖和αPD-1单克隆抗体联合使用[120]增加狄氏副拟杆菌 (*Parabacteroides distasonis*) 和普通拟杆菌 (*Bacteroides vulgatus*) 的相对丰度, 降低*L*-犬尿氨酸以及*L*-犬尿氨酸/色氨酸比率来增加对αPD-1单克隆抗体的抗肿瘤反应。

2.2.3 胆汁酸与GPCR互作 胆汁酸的组成受肠道细菌代谢的调节, 与宿主生理有内在联系。初级胆汁酸包括胆酸 (cholic acid, CA)、鹅去氧胆酸 (chenodeoxycholic acid, CDCA) 等在毛梭状芽孢杆菌 (*Clostridium hiranonis*)、梭状芽孢杆菌 (*Clostridium scindens*)、索氏梭菌 (*Clostridium sordelli*) 等肠道微生物的作用下转化为次级胆汁酸如DCA和石胆酸 (lithocholic acid, LCA)[121,122], 胆汁酸受体主要包括FXR、VDR、PXR、TGR5和1-磷酸–鞘氨醇受体2 (sphingosine 1-phosphate receptor 2, S1PR2) 等, 其中TGR5及S1PR2为GPCR[123]。胆汁酸代谢物CDCA、LCA等能够激活TGR5, 通过修饰胆汁酸衍生物, 如在胆汁酸支架的7位掺入硫酸盐基团、甲基、甲氧基等, 来预防艰难梭菌感染和治疗IBD[124,125]。结合胆汁酸TCA、甘氨胆酸 (glycocholic acid, GCA)、甘氨鹅脱氧胆酸 (glycochenodeoxycholic acid, GCDCA) 和牛磺熊去氧胆酸 (tauroursodeoxycholic acid, TUDCA) 能上调S1PR2的基因表达, 促进脂肪肝的发展[126]。金丝桃苷可以通过调节胆固醇代谢以及胆汁酸代谢和排泄, 增加FXR和肝X受体α (LXRα) 在内的核受体的表达, 肝脏新生脂肪生成催化酶的蛋白表达量减少, 胆汁酸合成途径酶的蛋白水平增加, 进而改善非酒精性脂肪肝的状况[127]。黄芪红花

合剂[128]是通过降低瘤胃菌科 (Ruminococcaceae)、脱硫弧菌科 (Desulfovibrionaceae)、拟杆菌门和考拉杆菌属 (*Phascolarctobacterium*) 的相对丰度, 提高毛螺菌科、布劳菌属 (*Blautia*)、颤螺菌属 (*Oscillospira*) 和双歧杆菌属的相对丰度, 激活胆汁酸受体 FXR, 维持胆汁酸内稳态, 保护血脑屏障的完整性, 改善脑缺血再灌注损伤。

2.3 中药调控肠道微生物及其代谢物与 GPCR 互作关系

探究肠道微生物与 GPCR 互作关系, 是当前中药药效机制研究的关键切入点。巴戟天寡糖通过调节肠道微生物群中的色氨酸羟化酶水平, 从而加速色氨酸的 5-羟色氨酸生产, 同时, 巴戟天寡糖抑制 5-羟色氨酸脱羧酶活性, 从而减少 5-HT 的产生, 并积累 5-羟色氨酸。从肠道微生物群中升高的 5-羟色氨酸被吸收到血液中, 然后穿过血脑屏障以提高大脑中的 5-HT 水平, 从而发挥抗抑郁作用[129]; 甜茶提取物可显著预防 DSS 诱导的 UC 症状, 抑制促炎介质水平, 还通过增加拟杆菌门、乳酸菌属和阿克曼菌属 (*Akkermansia*) 等有益菌, 抑制有害菌厚壁菌门、变形菌门和螺杆菌门 (Helicobacter), 并显著增加丁酸含量, 此外, 甜茶提取物增加了结肠中 GPR43 和 GPR109A 的表达, 抑制其下游 HDAC3/NF-κB 炎症信号传导, 起到预防 UC 的作用[130]; 红参提取物显著缓解了高脂肪饮食诱导的小鼠肥胖和胰岛素抵抗, 提高血清、回肠和白色脂肪组织中的胆汁酸水平, 通过激活肠道中的 TGR5 来改善葡萄糖代谢, 促进脂肪分解和能量代谢, 并且促进了顶端钠依赖性胆汁酸转运蛋白 (ABST) 在质膜上的定位, 最终促进了胆汁酸的转运以调节代谢表型[131]。小檗碱联合谷维素和维生素 B_6 用药能够增加糖尿病小鼠模型中拟杆菌科和梭状芽孢杆菌科 (Clostridiaceae) 相对丰度, 可促进 CA 向 DCA 的转化, 并激活了 TGR5-GLP 通路, 改善了糖尿病小鼠的葡萄糖、脂质和能量代谢[132]。人参皂苷 Rg3 给药正常小鼠后, 肠道中 *Blautia* spp. 大量富集。其代谢产物乙酸、丙酸作用于巨噬细胞表面受体 GPR43, 提高细胞内 Ca^{2+} 水平。当病毒入侵宿主时, 线粒体上的线粒体抗病毒信号蛋白 (MAVS) 被激活。在乙酸、丙酸以及病毒的双重信号作用下, 线粒体通透性转换孔道的开放程度增加, 线粒体 DNA (mtDNA) 外溢增强, 从而激活下游环磷酸鸟苷−腺苷酸合成酶 (cGAS)−膜蛋白干扰素刺激因子 (STING)-I 型干扰素 (IFN-I) 信号通路, 促进干扰素刺激基因的表达, 进而产生抗病毒蛋白, 拮抗肠道病毒感染[133]。近年来, 肠道微生物及其代谢物与 GPCR 互作机制得到广泛研究, 该机制可能成为解析中药药效机制的关键媒介。

3 GPCR 药物开发

3.1 开发现状

GPCR 在人体的生理病理过程中起着重要作用, 一直以来都是药物开发的主要靶点之一。目前经 GPCR 数据库统计结果显示, 已有 475 个美国食品药品监督管理局 (FDA) 批准上市的 GPCR 药物 (https://gpcrdb.org/drugs/drugbrowser) 和 483 个正在进行临床试验的 GPCR 药物。西尼莫德 (siponimod, 选择性 S1PR1 和 S1PR5 激动剂) 在 2019 年经 FDA 批准上市, 治疗多发性硬化症[134]; 同年, 司美格鲁肽 (semaglutide, GLP-1 受体激动剂) 经 FDA 批准上市, 用于治疗 2 型糖尿病[135]; 此外, 2019 年 Ubrelvy (ubrogepant, 降钙素基因相关肽受体拮抗剂)、Reyvow (lasmiditan, 一种选择性 5-HT_{1F}R 拮抗剂)、Wakix (pitolisant, 选择性组胺 H3 受体拮抗剂)、Nourianz (istradefylline, 选择性 A2AR 拮抗剂) 等[136-139]药物进入市场。2023 年, 美国 FDA 共批准了 55 种新药, 其中 GPCR 靶向药或 GPCR 通路相关药物 10 个, 包括 Filspari[140] (sparsentan, 双重内皮素−血管紧张素受体拮抗剂); Zavzpret[141](zavegepant, 降钙素基因相关肽受体拮抗剂); Veozah[142](fezolinetant, 神经激肽-3-受体拮抗剂) 等。目前 GPCR 靶点开发研究仍在继续, 受体药理学、结构生物学等学科的快速发展将为 GPCR 靶点开发及药物发现将开拓新途径。

3.2 GPCR 药物/配体筛选相关技术

药物筛选方法常见的主要有两种[143], 一种是基于表型筛选的药物发现 (phenotypic drug discovery, PDD), 这种药物发现方式是选择和疾病高度相关的临床前模型或实验模型来筛选化合库或抗体库中的药物; 另一种是以靶点为基础的药物研发 (target-based drug discovery, TDD), 这种方法是基于对疾病和靶点机制的理解, 针对某一个和疾病机制高度相关的特定的靶点, 从而有针对性地设计大分子或小分子药物的研发方式。随着 20 世纪 80 年代分子生物学革命的出现、2001 年人类基因组测序的兴起以及 2001 年靶向抗肿瘤药物伊马替尼的成功获批, 使 TDD 成为非常火热的创新药研发形式之一, 至今仍占据主体地位[144]。

目前, 人工智能已经成为靶点发现和药物开发中的有力工具, 并且正在彻底改变如何识别新型药物靶点和重新利用现有药物。PRESTO-Tango 是 GPCR 领域的一种高通量筛选工具, 通过 GPCR 活化来寻找可以调控宿主生理功能的肠道微生物代谢物, 逐渐成为另外一种重要的药物筛选方法 (图 2)。

3.2.1 虚拟筛选技术 天然产物是 GPCR 配体的重要来源, 对研究 GPCR 配体和药物发现具有重要价值。

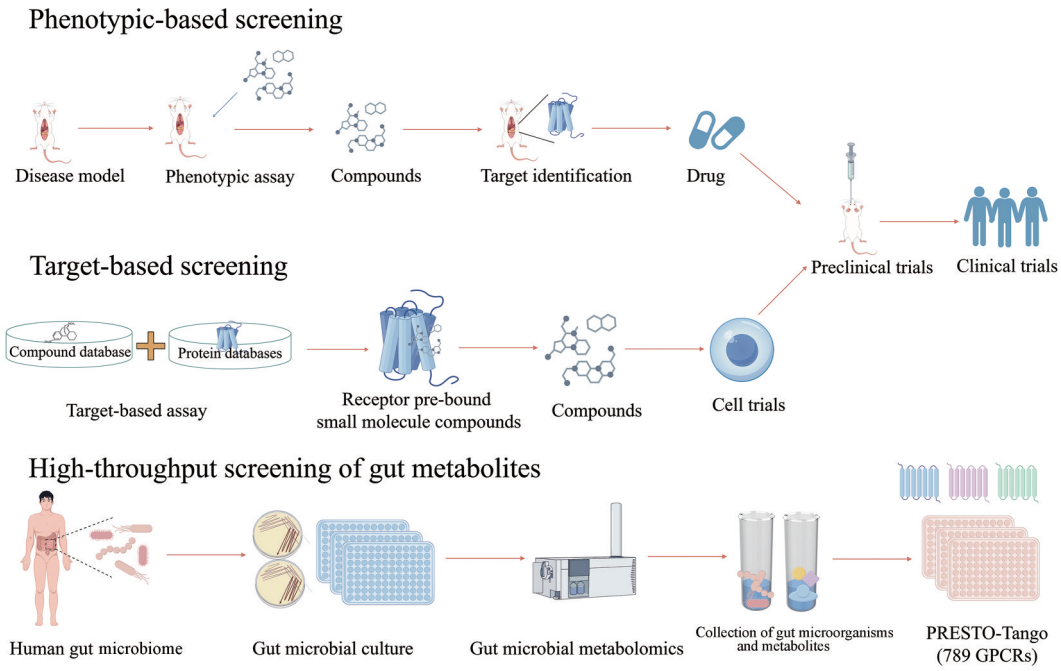

Figure 2 Screening methods for GPCR drugs

目前, 公共数据库中至少存储了数百万种天然产物, 这些天然产物与人体中已鉴定出的800多个GPCR的潜在组合数量极为庞大。虚拟筛选是一种基于作用机制的药物筛选方法, 具有低成本、高效率的优点, 已成为GPCR药物筛选及开发的有力工具。Chen等[145]提出了基于人工智能的GPCR配体筛选体系, 并分别从数据资源、数据描述、模型设计等方面介绍了如何利用人工智能方法构建GPCR配体筛选模型。

3.2.2 高通量细胞筛选技术 肠道内的GPCR可以感受细菌代谢物, 如SCFAs可以被GPR41/GPR43感受[146], 丙酮酸和乳酸可以被G蛋白偶联受体31 (GPR31) 感受[147], 以及最近的一系列研究持续发现肠道微生物来源的GPCR配体可以调节宿主生理活动。因此, 肠道微生物代谢物是一个潜在的丰富的GPCR配体库。由于缺乏对所有肠道微生物代谢物的系统性筛选体系, 使得大部分肠道微生物代谢物的功能尚未解析。PRESTO-Tango是2015年被开发出来的基于*β*-arrestin招募来筛选全新激活GPCR的配体的平台。Chen等[148]通过利用PRESTO-Tango技术来筛选可以产生激活人类GPCR的配体的肠道微生物, 通过GPCR活化来寻找可以调控宿主生理功能的肠道微生物代谢物, 结合条形码技术和高通量基因测序技术, 将PRESTO-Tango技术升级为PRESTO-Salsa筛选平台[149], 在单孔 (96孔板) 中集成314个GPCR报告细胞系, 用于“一对多”功能筛选, 可以系统性寻找与多种疾病相关的活性分子或生物标志物 (如小分子代谢物、多肽类荷尔蒙、蛋白类趋化因子、自身抗体等), 为多种疾病的分子诊断和病理学机制研究提供技术支撑。成簇规律间隔短回文重复序列 (CRISPR)-CRISPR相关蛋白 (Cas) 系统检测技术具有高灵敏度、高特异度、快速等特点, 广泛用于功能基因筛选、基因互作筛选、病毒靶点筛选和药物靶点筛选等[150,151], 通过CRISPR激活 (CRISPRa) 和CRISPR干扰 (CRISPRi) 技术增强或抑制特定基因的表达, 在基因功能研究和疾病治疗中拥有巨大潜力, 本团队基于CRISPR相关技术建立GPCR文库并搭建GPCR高通量药物筛选平台, 在GPCR文库细胞中加入混合化合物, 系统快速地进行高通量GPCR药物筛选, 助力新药发现。

3.3 多组学技术

多组学技术作为一种高通量的研究手段, 能够全面测定生物样品中同类型的分子, 分析复杂表型背后潜在的分子特性[152], 通过运用基因组学、转录组学、代谢组学、蛋白质组学、宏基因组学、表观遗传学等技术对生物样本进行系统研究, 同时将各组学的数据加以整合分析[153]。陈士林团队于2009年提出本草基因组计划, 即利用现代多组学技术解决中药研究中问题。团队经过多年的努力, 已将多组学技术成功应用于中药相关研究。Sun等[154]利用单细胞转录组技术获得首个药用植物单细胞转录组图谱–长春花叶片的单细胞转录组图谱; Leng等[155]基于基因组等技术揭示了千金藤素及其代谢产物的广谱抗冠状病毒能力。Chen等[145]提出了一种融合基因组、转录组、蛋白质组和代

谢组等多组学数据的GPCR配体筛选方法, 为靶向GPCR的药物发现和开展GPCR泛组学研究提供了理论指导。经过多年的发展, 本草基因组学相关技术未来将为探究人类疾病发生过程中肠道微生物与GPCR互作机制、解析中药体内代谢和药效的影响研究提供技术支持。

多组学技术有利于对疾病的发病机制、生理变化进行深层次、多维度分析, 有利于阐明肠道微生物与GPCR互作机制, 能够更系统、全面地认知疾病的发生和发展状况及药物作用机制, 同时为获得疾病治疗相关的分子标志物、药物潜在治疗靶点等提供新思路。

4 筛选中药有效成分的新模式

随着现代科学技术的不断发展, 可多方面对中药有效成分进行筛选, 使用先进的技术筛选中药中的有效成分。多组学技术的出现不仅为筛选中药有效成分提供新的技术, 也为肠道微生物群落研究打开新视角。肠道微生物群落十分复杂, 由功能各异的微生物组成。基于此, 本团队认为在人体微生物菌群功能研究中有必要将功能相似的菌株富集构建功能菌群单元, 以此作为基本单元开展研究。近年来, 越来越多的研究证明菌群代谢物与宿主靶点或通路间存在广泛互作关系, 直接或间接影响疾病的发生发展。机体内物质在肠道的代谢往往由多种执行相似功能的肠道微生物共同参与, 但这些微生物在分类水平可能存在显著差异。因此, 相比于探究相近种属微生物在肠道中代谢作用, 将执行相似功能微生物富集成基本单元开展研究具有重要意义。功能菌群单元的研究依托于宏基因组、宏转录组、宏代谢组、培养组等的技术支持。利用宏基因组学数据将功能相似肠道微生物进行聚类并对聚类单元进行功能预测分析, 初步确定功能菌群单元的组成和功能。同时, 利用培养组学技术尽量分离功能菌群单元中的微生物并在体外模拟构建体内环境, 利用宏转录组、宏代谢组深入探究功能菌群单元在过程中响应机制。中药进入体内被不同功能的功能菌群单元代谢成有效成分或刺激功能菌群单元产生代谢物, 进而与GPCR结合, 影响疾病发生发展。通过多组学技术获得功能菌群单元中的微生物组成、中药被功能菌群单元代谢的有效成分、功能菌群单元产生的代谢物以及调控疾病发生发展的基因。因此, 多组学数据联合分析可更全面地解析肠道微生物与GPCR互作是如何影响疾病发生发展进程及药物干预机制。在诊断标志物的筛选、药效学评价等研究中多组学技术均发挥重要作用。依托本团队建立的泛GPCR细胞株系资源库、靶向GPCR受体的药物筛选平台、全基因组泛GPCR现代中药发现与评价体系及高通量微生物分离筛选平台结合多组学技术筛选调控肠道微生物与GPCR间互作的复杂中药中的有效成分及新药筛选[156]。该模式将为传统中药药效机制解析及新药筛选提供新的研究范式 (图3)。

5 展望

人体中定殖着大量微生物, 这些微生物及其代谢物与人体中不同受体互作对于疾病的发生发展具有显著影响。近年来, 越来越多的研究聚焦于不同部位微生物与疾病的关系, 其中以肠道微生物研究最为广泛, 尤其关注肠道微生物与其他组织器官之间联系, 因此所提出“肠−X轴”的理论被多数学者所认可。随着人类微生物组计划的持续推进, 关于微生物组的研究也逐渐深入。培养组、微流控等技术的不断完善, 越来越多的体内微生物可实现体外培养, 为菌株水平的研究提供技术支持。此外, 组学技术的发展也使人体微生物组研究内容已逐渐从基于宏基因组测序揭示微生物群落结构组成、多样性等内容拓展到利用宏转录组、宏蛋白质组等技术分析菌群基因及蛋白表达差异等深层次内容, 对于从机制水平解析疾病与微生物关系以及药物通过微生物干预疾病具有重要意义。但值得注意的是, 微生物在体内不是单独存在的, 而是与其他微生物共同构建微生物群落发挥作用。该群落组成十分复杂, 不同微生物间存在多种关系, 包括拮抗、协作、竞争等, 因此在研究微生物菌群的研究中过于关注单菌性状而忽略其与其他微生物间的互作往往不能真实反映该菌在体内实际状态。相比于传统单菌株研究, “功能菌群单元”具有以下优势。首先, “功能菌群单元”更全面反映人体内执行相似功能微生物在体内真实状态。此外, 目前有研究表明微生物可通过合成某些代谢产物与受体结合影响下游通路。这类代谢物多由“功能菌群单元”产生, 因此探究“功能菌群单元”的代谢物差异及代谢能力具有更重要意义。然而, “功能菌群单元”的构建依赖于体内微生物的体外分离培养, 因此有必要进一步开发高效的分离体系为后续研究提供保障。“功能菌群单元”会为人体微生物与疾病之间关联研究提供新思路。

GPCR作为人体中最大的一类膜蛋白受体家族, 其与微生物之间的互作, 尤其是与肠道微生物之间的互作已被报道与多种疾病有关。值得注意的是, 人体微生物与GPCR间互作也为中药药理机制研究提供了新思路。中药在临床使用中具有多靶点、多通路、口服利用度低等特点, 其在口服后在体内如何发挥药效成为学界讨论的热点。越来越多的研究证明中药可通过调节肠道微生物及其代谢物, 进而影响代谢物与GPCR靶点结合, 最终起到治疗疾病的效果。近年来,

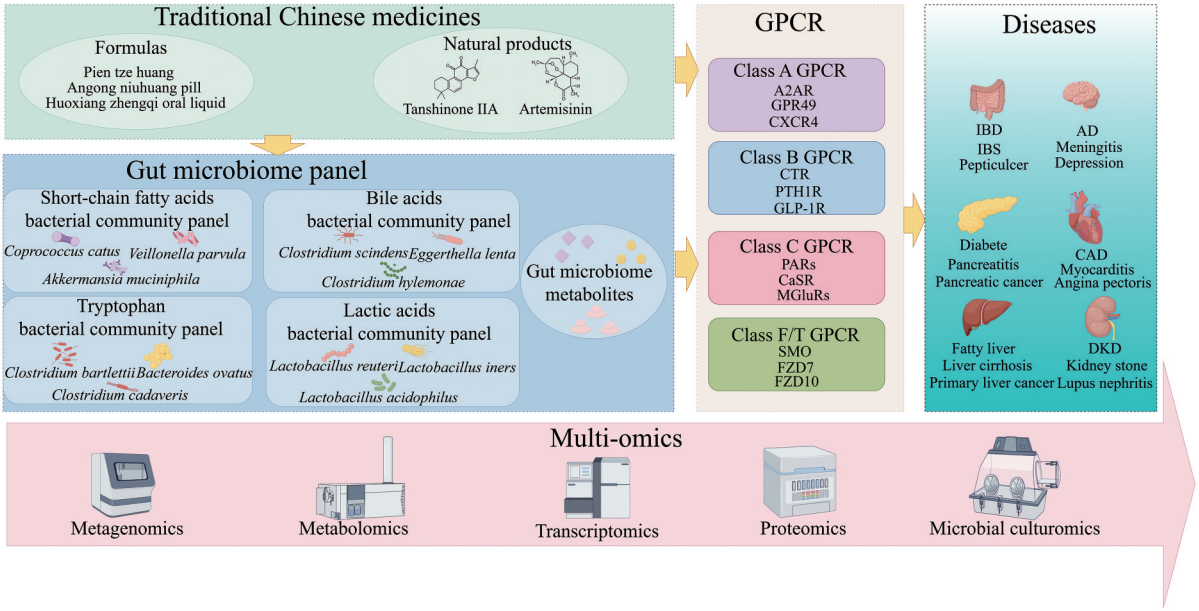

Figure 3 Multi-omics analysis of "gut microbiome panel"-GPCR-disease interactions. A2AR: Adenosine 2A receptor; GPR49: G-protein-coupled receptor 49; CXCR4: C-X-C motif chemokine receptor 4; CTR: Calcitonin receptor; GLP-1R: Glucagon-like peptide 1 receptor; PTH1R: Parathyroid hormone receptor 1; CaSR: Calcium-sensing receptor; PARs: Protease activated receptor; MgluRs: Metabotropic glutamate receptors; FZD7: Frizzled receptor 7; FZD10: Frizzled receptor 10; SMO: Smoothened receptor; IBD: Inflammation bowel disease; IBS: Irritable bowel syndrome; AD: Alzheimer's disease; CAD: Coronary artery disease; DKD: Diabetic kidney disease

基因组、转录组、蛋白质组、代谢组等多组学技术发展取得了长足进步。利用多组学技术探讨菌群与GPCR互作已成为科研工作者的首选方法。目前菌群与GPCR互作报道越来越多, 其中产生海量数据。为了全面地将前人研究数据进行汇总整理, 本团队认为有必要构建人体微生物-GPCR多组学数据库, 其中数据涉及宏基因组、转录组、蛋白质组、代谢组等组学数据。该数据库的构建将整合现有所有关于人体微生物-GPCR多组学数据, 实现数据信息共享。同时, 多组学数据库构建将有助于临床诊断标志物开发及新药研发等工作。

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利益冲突: 本文中所有作者声明无任何利益冲突。

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