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专论与综述

益生菌在血糖调控中的作用

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摘　要：随着经济及生活水平的提高，营养过剩导致营养代谢疾病中 2 型糖尿病(type 2 diabetes mellitus, T2DM)发生率骤增。患者血糖升高及并发症严重降低生活质量，增加经济负担。现行降糖药存在局限性和副作用，而益生菌具有安全、经济和有效等特点，并且能够降血糖和减轻并发症等。益生菌在糖尿病预防、治疗和重塑肠道微生态健康方面具有良好的应用前景，逐渐成为糖尿病防治的研究热点。虽然益生菌有望攻克糖尿病，但是调控血糖的机制需要更加深入的研究。本文综述了益生菌调控血糖的应用及机制研究、发展趋势与前景及挑战，为调控血糖微生态制剂的开发提供理论基础。

关键词：益生菌；糖尿病；2 型糖尿病；血糖调控

The role of probiotics in blood glucose regulation

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Abstract: As the economic level and living standards are rising, the incidence of type 2 diabetes mellitus (T2DM), a nutritional metabolic disease caused by overnutrition, has increased sharply. The elevated blood glucose level and complications seriously affect the quality of life of the patients and bring economic burden to the family. The drug treatment of T2DM has limitations and side effects. Although T2DM is difficult to be cured, some new therapies for regulating blood glucose have emerged with the deepening of research. Probiotics are safe, economical, and effective, and recent studies have shown that probiotics used alone or in combination with

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other therapies can lower blood glucose level and alleviate complications. Demonstrating a promising application prospect in the prevention and treatment of T2DM and the remodeling of intestinal microbiota, probiotics have become a hot research spot. While probiotics have the potential to overcome T2DM, the mechanism of probiotics in regulating blood glucose remain to be deciphered. This article reviews the role, application, prospect, and challenges of probiotics in blood glucose regulation, aiming to provide a theoretical basis for the development of microecological agents for blood glucose regulation in humans and companion animals.

Keywords: probiotics; diabetes mellitus; type 2 diabetes mellitus; blood glucose regulation

据估计，全世界大约十分之一的成年人患有糖尿病，肥胖症和糖尿病的患病率在世界范围内持续上升[1-2]。全球糖尿病患者到 2030 年预计将有 6.43 亿，到 2045 年将有 7.83 亿[3]。2 型糖尿病(type 2 diabetes mellitus, T2DM)约占糖尿病患者的 90%，T2DM 患者血糖血脂异常及其他并发症与各种遗传和后天的危险因素有关[4-6]。现阶段的治疗措施不能治愈糖尿病，但是可以延缓发病及减轻并发症[7]。胰岛素治疗有效但是成本高，应该限制需要胰岛素的 2 型糖尿病患者的数量。例如，益生菌、胰岛素类似物等也是不错的选择[8]。降糖药物众多，各自有不同副作用。例如，磺脲类药物会诱导产生低血糖；吡格列酮导致体重增加；阿卡波糖与胃肠道副作用有关[9-11]。因此迫切需要一种安全无副作用的方法用于治疗 T2DM。

肠道菌群和稳态在 T2DM 治疗中发挥重要作用，未来益生菌及其产物在改善 T2DM 患者健康上将发挥重要作用[12-13]。益生菌是有益于宿主的多功能生物活性成分[14]。益生菌被认为是治疗慢性疾病经济、安全的替代品[15]。益生菌及其产物具有抗感染[16-18]、降低炎症水平[19]和增强免疫调节等作用[20]，已用于治疗炎症性肠病、高血压和神经功能障碍等多种疾病[21-23]。

益生菌可能是 T2DM 患者的一种有希望的辅助治疗方法，近些年来实验室和临床研究都取得了一定的进展[24-25]。临床研究结果表明益生菌能够对 T2DM 患者血糖进行调控，益生菌通过改善 T2DM 患者肠道菌群、肠漏和内毒素血症，进而降低血糖和炎症反应[26]；可以降低 T2DM 患者血糖并增加抗氧化酶[27]；可改善 T2DM 患者的代谢因子和炎症[28]；可以预防 T2DM 患者代表性临床参数的恶化[29]。实验室研究中益生菌通过介导小鼠肠道微生物-短链脂肪酸(short-chain fatty acids, SCFA)-激素/炎症通路改善 T2DM[30]。副干酪乳杆菌通过调节肠道菌群和减少肠漏来缓解糖尿病症状，通过磷脂酰肌醇 3 激酶/蛋白激酶 B 和腺苷酸激活蛋白激酶介导的胰岛素信号改善内毒素血症和炎症[31]。

本文综述益生菌调控 T2DM 的应用及机制研究、发展趋势与前景及挑战，以期为调控血糖微生态制剂的开发提供理论基础。

1 T2DM 的流行病学及发病机制

近些年来糖尿病患者骤增，治疗糖尿病刻不容缓。2016 年数据显示，全球成人患病率从 1980 年的 4.7%上升到 2014 年的 8.5%，高达 4.22 亿人[32]。国际糖尿病联合会 2021 年数据表明，到 2030 年全球约 6.43 亿糖尿病患者，到 2045 年约 7.83 亿患者(图 1A)[2-3]。2022 年，世界卫生组织制定了第 1 个针对糖尿病的全球目标，到 2030 年，使 80%的糖尿病患者得到诊断，

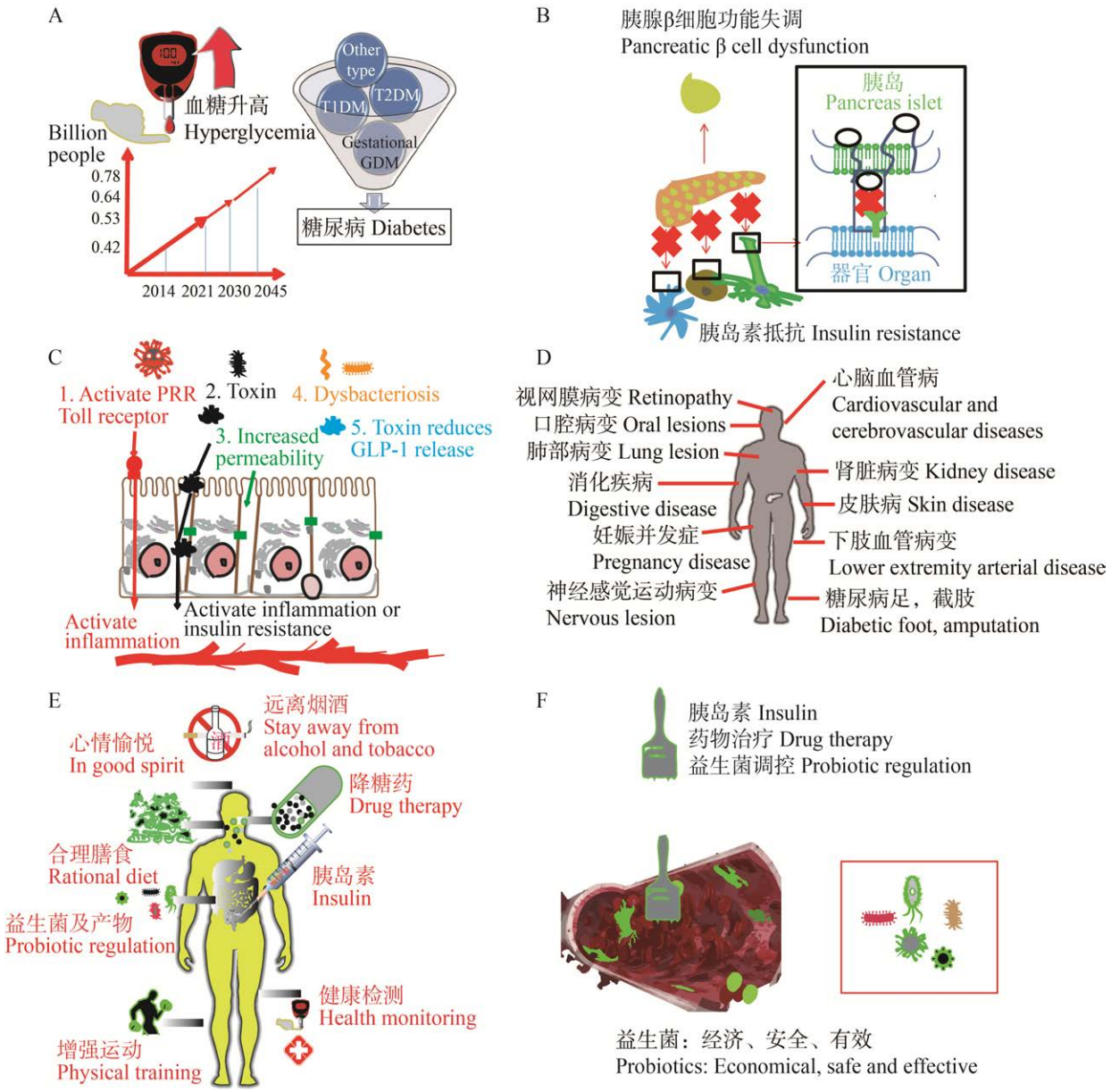

图 1　益生菌有望改善 T2DM 症状及并发症　A：近年来糖尿病患者增加，预计 2024 年将接近 8 亿，且 T2DM 居多. B：胰岛素抵抗和胰腺细胞功能失调导致 T2DM 的发生. C：肠道菌群失调，有害菌群产生的内毒素等引发炎症反应、氧化应激、破坏胰岛 β 细胞和胰岛素抵抗等导致 T2DM 及并发症. D：T2DM 并发症众多，涉及心脑血管疾病、肾病、糖尿病足和神经性疾病等. E：可以通过合理膳食、益生菌调控等方式调控 T2DM. F：相比于胰岛素和药物治疗，益生菌具有经济、安全、有效的优势

Figure 1　Probiotics are expected to improve T2DM symptoms and complications. A: The number of diabetic patients has increased in recent years and is expected to reach nearly 800 million in 2024, with T2DM predominating. B: Insulin resistance and pancreatic cell dysfunction lead to T2DM. C: Imbalance of intestinal flora, and endotoxins produced by harmful flora lead to inflammation, oxidative stress, destruction of pancreatic β cells and insulin resistance, leading to T2DM and complications. D: There are many complications of T2DM, including cardiovascular and cerebrovascular diseases, nephropathy, diabetic foot, neurological diseases, etc. E: T2DM can be controlled through rational diet and probiotic regulation. F: Compared with insulin and drug therapy, probiotics are economical, safe and effective.

80%的糖尿病患者血糖得到良好控制[33]。我国糖尿病患者以及未确诊患者均居全球首位，迫切需要有效的方法来改变现状[2,34]。

糖尿病分为胰岛素依赖的 T1DM、非胰岛素依赖的 T2DM、妊娠糖尿病、疾病或药物导致的其他类型糖尿病，其中 T2DM 居多(图 1A)[35]。T2DM 约占所有糖尿病病例的 90%，T2DM 与各种后天的危险因素有关[4-6]。例如，肥胖引起的糖尿病患病率上升[36]。T2DM 被认为是一种肠道疾病，病理生理基础包括胰岛素抵抗、胰岛素分泌不足和 β 细胞功能障碍等，但该疾病的病因和机制尚未完全明确(图 1B)[37-39]。在糖尿病的形成以及发展过程中，肠道菌群失调、有害菌群产生的内毒素进一步引发炎症反应、氧化应激、破坏胰岛 β 细胞和胰岛素抵抗等导致 T2DM 及并发症(图 1C)[40-44]。

T2DM 除典型症状外也会导致许多并发症，如心脏病、中风、肾衰竭、截肢、视力丧失、神经损伤和增加过早死亡的风险等，其中心血管疾病是糖尿病患者发病和死亡的主要原因(图 1D)[45-49]。2011 年至 2030 年期间，全球因糖尿病的直接医疗和间接费用造成的国内生产总值损失估计为 1.7 万亿美元，仅中低收入国家就损失 8 000 亿美元[1]。T2DM 患者死亡风险增加，并发症严重影响生活质量，经济和家庭压力大，因此糖尿病的治疗和预防刻不容缓。

现阶段的治疗措施中最有效的是胰岛素，但是胰岛素治疗成本高，只有大约 50%的 2 型糖尿病患者获得所需的胰岛素治疗[8]。降糖药物，如噻唑烷二酮[50]、胰高血糖素样肽-1 受体激动剂[51]、二肽基肽酶 IV 抑制剂[52]、钠葡萄糖共转运体 2 抑制剂[11]与高血糖、高血脂和高血压之间存在关系。不同降糖药物在血糖控制方面具有相当的疗效，但这些药物的耐受性不同，有副作用。除了增加运动、注意饮食和保持心情舒畅外，益生菌调控 T2DM 的研究众多且取得了一定进展，不失为一种安全无副作用的方法(图 1E、1F)。

2 益生菌调控血糖的应用及机制

益生菌通过调节肠道菌群平衡、肠道免疫、微生物-肠-脑轴、微生物-肠-肝轴等调控血糖(图 2A)[43-44,53]。益生菌调控糖尿病的作用机制可能包括以下途径(图 2B)。(1) 益生菌消耗葡萄糖；(2) 可能通过降低慢性低度炎症，减少氧化应激；(3) 调节肠道菌群，增加短链脂肪酸含量；(4) 增强免疫；(5) 改善胰岛素抵抗等达到调控血糖的作用[54-59]；(6) 益生菌能够产生细菌素等物质，保护胰岛、促进胰岛功能发挥和抑制 α-葡萄糖苷酶等发挥调控血糖的作用[60-61]；(7) 高脂饮食扰乱肠道内平衡，肠道中缺乏核苷酸结合寡聚化结构域蛋白 2 (nucleotide-binding oligomerization-2, NOD2)受体导致高脂肪饮食小鼠更严重的肥胖，肠道中的革兰氏阴性菌激活 NOD2 受体可通过减少细胞的生长来预防肥胖诱导的 T2DM[58-59]；(8) 益生菌增殖过程中产生的多肽可通过脑-肠轴作用于下丘脑 γ-氨基丁酸(γ-aminobutyric acid, GABA)能神经元中的 NOD2 受体，抑制突触后神经元的活性，起到抑制食欲和改善代谢的作用[62]。

2.1 益生菌可以通过升高脂联素水平调节血糖

益生菌辅助降糖药物在 T2DM 中应用效果良好，升高血浆脂联素水平，改善血糖且不良反应轻微，是未来 T2DM 治疗的新靶点[63-64]。脂联素可以增加胰岛素敏感性，改善胰岛素抵抗，保护 β 细胞[65]。脂联素通过降低肝脂肪酶和载脂蛋白水平降低甘油三脂水平[66]。脂联素临床上表现出降糖和抗炎的潜力、减轻胰岛素抵抗和增强糖代谢是糖尿病的治疗靶点[66-70]。

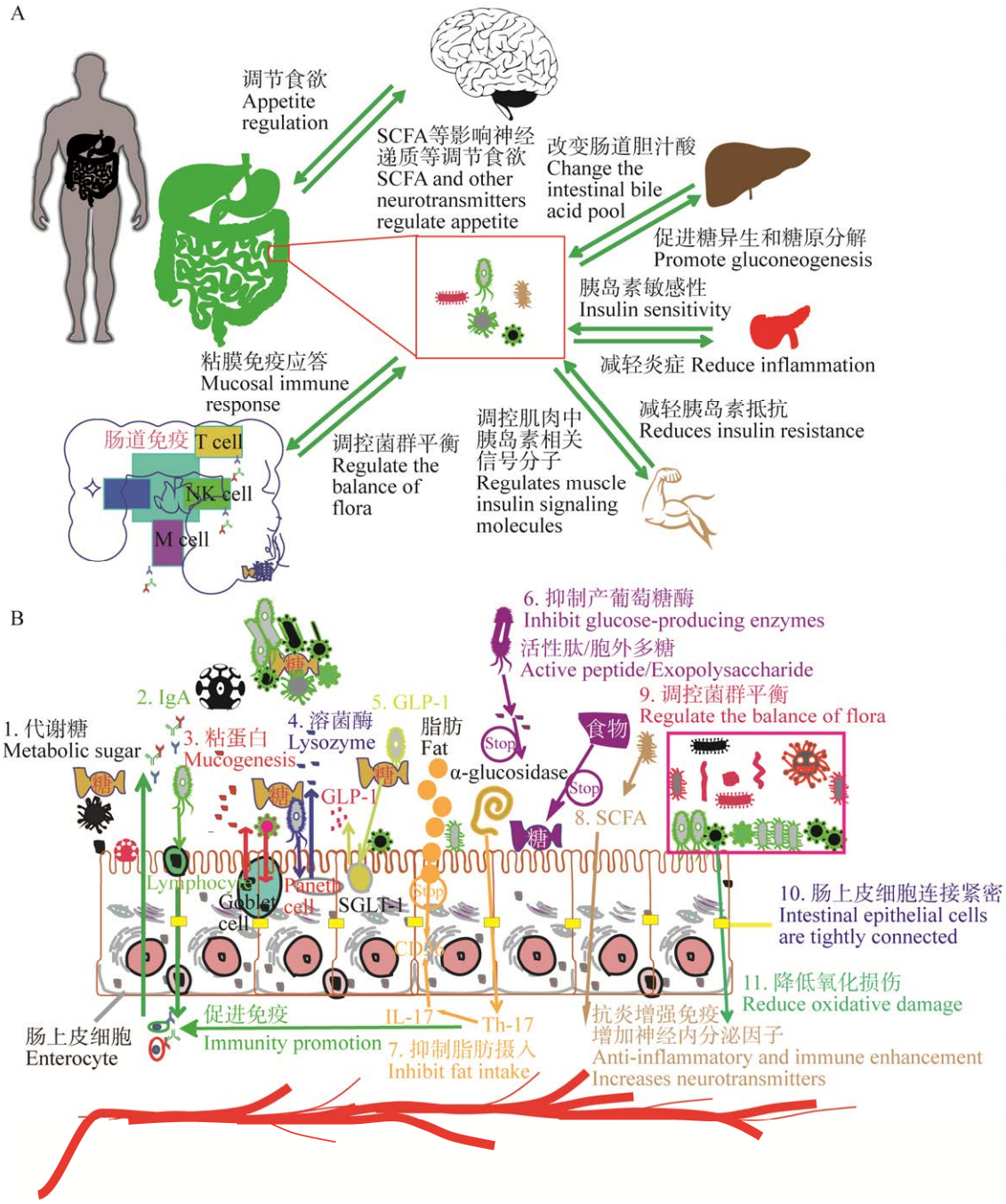

图 2　益生菌调控血糖的可能机制　A：益生菌通过调节肠道菌群平衡、改善肠道免疫、影响微生物-肠-脑轴和微生物-肠-肝轴等调控糖脂代谢，进而改善血糖. B：益生菌调控糖尿病的作用机制可能包括代谢糖、减少氧化应激、降低炎症、增强免疫、增加 GLP-1、产生抑制糖代谢相关酶和通过相关信号通路影响食欲等

Figure 2　Possible mechanisms by which probiotics regulate blood glucose. A: Probiotics regulate glucose and lipid metabolism by regulating the balance of intestinal flora, improving intestinal immunity, and affecting the microbial-gut-brain axis and microbial-gut-liver axis, thereby improving blood sugar. B: The mechanism of action of probiotics in regulating diabetes may include metabolizing sugar, reducing oxidative stress, reducing inflammation, enhancing immunity, increasing GLP-1, producing enzymes related to inhibiting sugar metabolism, and affecting appetite through related signaling pathways.

2.2 益生菌可以通过诱导胰高血糖素样肽-1分泌调节血糖

益生菌能够上调胰高血糖素原和前转化酶三分之一活性，通过葡萄糖触发胰高血糖素样肽-1 (glucagon-like peptide-1 receptor, GLP-1)分泌，从而增强胰岛素分泌来调控血糖[71]。粪菌移植干预后粪便中乙酸和丁酸水平显著升高，SCFA 激活 GLP-1 途径，结肠组织 GLP-1 蛋白表达升高改善糖脂紊乱[72]。植物乳杆菌 JY039 的胞外多糖和副干酪乳杆菌 JY062 促进肠道激素肽和 GLP-1 的分泌具有协同预防和缓解 T2DM 的潜力[73]。

2.3 益生菌可以通过改善胰岛素抵抗调节血糖

益生菌能够改善患者胰岛素敏感性[74-75]。益生菌产生的 SCFA 与受体结合，调节相关组织的胰岛素敏感性[76]。益生菌 LG2055 组动物胰腺胰岛素基因和胰岛素基因转录因子水平均升高，改善胰岛素分泌[77]。益生菌产生 SCFA 通过上调 G 蛋白偶联受体 43/41 保护胰腺免受细胞凋亡，这可能依赖于 PI3K/AKT 通路的上调[71]。益生菌治疗可以降低血浆中糖化血红蛋白(hemoglobin A1c, HbA1c)水平和空腹血糖，并改善胰岛素抵抗[78-81]。

2.4 益生菌可以通过降低炎症水平调节血糖

在糖尿病前期和 T2DM 患者中，益生菌通过减轻炎症和氧化应激来减轻机体症状[82]。益生菌产生 SCFA 调节白细胞介素-10 (interleukin-10, IL-10)和转化生长因子，发挥调控血糖的作用[76]。益生菌产生 SCFA 在 G 蛋白偶联受体 43 的参与下调节树突状细胞的功能、炎性小体的激活和白细胞介素-8 (interleukin-8, IL-8)的分泌调节肠道抗菌物质的产生[83]。益生菌 LG2055 组胰岛素分泌的增加与血清淀粉样蛋白水平和胰腺粒细胞集落刺激因子水平的降低有关[77]。约氏乳杆菌 MH-68 等可降低糖尿病患者的血糖水平和炎症细胞因子[84]。植物乳杆菌 JY039 胞外多糖和副干酪乳杆菌 JY062 通过平衡促炎因子白细胞介素-6 (interleukin-6, IL-6)、肿瘤坏死因子-α (tumor necrosis factor, TNF-α)和抗炎因子 IL-10 来减轻炎症缓解 T2DM[73]。副干酪乳杆菌调节肠道微生物群并通过降低血清脂多糖、游离脂肪酸、TNF-α、IL-6、IL-8 水平和升高 IL-10 水平，显著改善血清脂多糖诱导的炎症状态[85]。

2.5 益生菌可以通过增强免疫调节血糖

益生菌可能通过产生 SCFA 影响免疫系统调控血糖，通过 G 蛋白偶联受体信号传导通过 T 调节性细胞的分化调节免疫系统[76,83]。SCFA 通过中枢神经系统和 G 蛋白偶联受体调节肠内稳态和免疫应答信号调节血糖代谢[75,86-87]。

2.6 益生菌可以通过改善肠道菌群调节血糖

复合益生菌通过增加产 SCFA 细菌和 SCFA 的水平，降低大肠杆菌和脂多糖水平，改善肠道屏障功能[71]。复合益生菌导致小鼠肠道内的大肠埃希氏菌含量降低和双歧杆菌含量升高，改善菌群失调[81]。粪菌移植干预显著提高了均匀拟杆菌的相对丰度，梭状芽孢杆菌(*Clostridium* sp.)水平升高，沙氏粘螺旋体(*Mucispirillum schaedleri*)水平降低，粪便中乙酸和丁酸水平显著升高，进一步改善糖脂紊乱[72]。植物乳杆菌 JY039 的胞外多糖和副干酪乳杆菌 JY062 改变了肠道菌群的结构，厚壁菌门(*Firmicutes*)、毛螺球菌科(*Lachnospiraceae*)等占比降低，双歧杆菌(*Bifidobacterium* sp.)、粪杆菌(*Faecalibaculum* sp.)占比升高，协同预防和缓解 T2DM[73]。副干酪乳杆菌调节肠道微生物群并改善 T2DM 大鼠的炎症。拟杆菌属(*Bacteroides*)、梭状芽孢杆菌(*Clostridia* sp.)中瘤胃球菌(*Ruminococcus torques*)和副萨特氏菌属(*Parasutterella*)相对丰度显著减少，拟杆菌属(*Bacteroides*)、毛螺球菌科(*Lachnospiraceae*)和瘤胃菌科(*Ruminococcaceae*)

相对丰度则增加[85]。可见组合益生菌对血糖的调控效果比较明显，改善肠道产 SCFA 菌群，仅通过 SCFA 而发挥作用；植物乳杆菌、双歧杆菌、嗜酸乳杆菌、干酪乳杆菌、双歧杆菌、罗伊氏乳杆菌和乳酸片球菌等乳酸菌研究较多，效果显著。

实验和临床研究中益生菌可能通过几种途径综合调控 T2DM 的血糖，主要通过产生细菌素等物质、降低炎症、调节肠道菌群、增加短链脂肪酸含量、增强免疫和改善胰岛素抵抗等发挥作用，且适宜益生菌剂量为 10^9 CFU/d (表 1 和表 2)。目前大多研究结果支持益生菌通过降低炎症、调节肠道菌群和增加短链脂肪酸含量进一步发挥调控血糖的作用。

3 益生菌调控血糖的发展趋势及前景

3.1 益生菌及后生元将发挥重要作用

许多研究表明，组合益生菌调控糖尿病效果会更好，被认为是治疗大量慢性疾病和改善人类健康的一种经济、安全的替代品[15,88,100]。合成益生菌是指用于改善健康的益生元和益生菌的混合物，可以通过不同的作用机制改善 T2DM，如减少氧化应激和胰岛素抵抗等[15,101-102]。后生元不需要活细胞来诱导健康效应，组分包括微生物代谢物、蛋白质、脂类、碳水化合物、维生素、有机酸、细胞壁成分或其他复杂分子等，参与免疫调节或刺激肠道细胞发挥作用[103-104]。短链脂肪酸降糖功能不再赘述，其中醋酸盐已被证明可以通过调节空腹胰岛素和胰高血糖素水平来减少炎症和胰岛素敏感性(醋酸酯通过分泌 GLP-1)，并改善葡萄糖耐量[105-106]。细菌壁成分中的二肽可以调节 GLP-1 的分泌，通过 NOD2 受体改善饮食诱导的肥胖小鼠的胰岛素敏感性和葡萄糖耐量[107]。从嗜粘杆菌或巴氏灭菌细菌中纯化的膜蛋白可改善肥胖和糖尿病小鼠的代谢[108]。组合菌、合生菌、后生元具有良好的生物活性，对 T2DM 等代谢性疾病具有预防和缓解作用[75,100,103,109-111]。

3.2 合成生物学发展背景下基因工程菌崛起

随着合成生物学的发展，下一代微生物疗法聚焦于将益生菌改造成为能够自主复制、检测异常状况、在人体内部合成释放治疗因子的“药物合成工厂”。工程共生菌将肠细胞重编程为葡萄糖反应性胰岛素分泌细胞以治疗糖尿病[112]。口服型工程植物乳杆菌能够长效表达 GLP-1 发

表 1 益生菌对糖尿病的作用和机制的试验研究

Table 1 Experimental study on the effect and mechanism of probiotics on diabetes mellitus

益生菌 Probiotics	动物模型 Animal model	剂量 Dosage	主要效应 Main effects	参考文献 References
植物乳杆菌 CGMCC 8198 *Lactobacillus plantarum* CGMCC 8198	昆明小鼠，T2DM Kunming mice, type 2 diabetes	–	抑制有害菌群，代谢物能有效调节血糖、血脂等代谢指标，增强免疫 Inhibition of harmful bacteria, metabolites can effectively regulate blood sugar, blood lipids and other metabolic indicators, enhance immunity	[88]
乳酸片球菌 pA1c *Pediococcus acidilactici* pA1c	C57BL/6 雄性小鼠，T2DM C57BL/6 male mice, T2DM	1×10^{10} CFU/d	改善高脂饮食诱导的胰岛素抵抗和肠屏障完整性，降低体重 Improved high fat diet-induced insulin resistance and intestinal barrier integrity and reduced body weight	[89]

(待续)

(续表 1)

益生菌 Probiotics	动物模型 Animal model	剂量 Dosage	主要效应 Main effects	参考文献 References
植物乳杆菌 Y15 *Lactiplantibacillus plantarum* Y15	C57BL/6J 小鼠，T2DM C57BL/6J mice, T2DM	3×10^8 CFU/d	降低促炎因子和脂多糖(LPS)，增加产 SCFA 的细菌，调节炎症和胰岛素信号通路相关基因的表达 Decreased proinflammatory factors and lipopolysaccharide (LPS), increased SCFA-producing bacteria, and regulated the expression of genes related to inflammation and insulin signaling pathways	[90]
发酵乳杆菌 MCC2759 和 MCC2760 *Lactobacillus fermentum* MCC2759 and MCC2760	Wistar 雌性大鼠，T2DM Wistar female rat, T2DM	1×10^9 CFU/mL	肠屏障完整性(ZO-1)，TLR-4 受体和胰岛素敏感性(GLUT-4，GLP-1，脂联素)相关的标志物的正常化 Normalization of intestinal barrier integrity (ZO-1), TLR-4 receptor and markers associated with insulin sensitivity (GLUT-4, GLP-1, adiponectin)	[91]
植物乳杆菌 *Lactobacillus plantarum* HAC01	C57BL/6J 雄性小鼠，T2DM C57BL/6J male mice, T2DM	$1/4\times10^8$ CFU/d	通过调节肝脏葡萄糖代谢、保护胰岛 β 细胞团、恢复肠道微生物群和 SCFA 来缓解高血糖和 T2DM Alleviating hyperglycemia and T2DM by regulating liver glucose metabolism, protecting islet beta cell mass, and restoring gut microbiota and SCFA	[92]
沙克乳酸杆菌 Probio-65 和植物乳杆菌 Probio-093 *Lactobacillus sakei* Probio-65, *Lactobacillus plantarum* Probio-093	C57BL/6J 雄性小鼠，T2DM C57BL/6J male mice, T2DM	1×10^8 CFU/d	分别抑制 α-葡萄糖苷酶和 α-淀粉酶，调节血糖和肠道菌群，体重下降 They inhibited α-glucosidase and α-amylase, regulated blood sugar and intestinal flora, and decreased body weight	[93]
加氏乳杆菌和约氏乳杆菌 *Lactobacillus gasseri* and *Lactobacillus johnsonii*	C57BL/6J 雄性小鼠，T2DM C57BL/6J male mice, T2DM	1×10^9 CFU/d	菌作用于肝脏线粒体，导致脂质代谢的改善；调控血糖血脂；代谢组学分析显示还原型谷胱甘肽和胆红素可能介导这些作用 The bacteria act on the liver mitochondria, leading to the improvement of lipid metabolism; Regulate blood sugar and lipids; Metabolomics analysis suggested that reduced glutathione and bilirubin may mediate these effects	[94]
罗伊氏乳杆菌 GMNL-263 *Lactobacillus reuteri* GMNL-263	Wistar 雄性大鼠，T2DM Wistar male rat, T2DM	1×10^9 CFU/d	可激活糖尿病大鼠 IGF1R 细胞存活通路，降低高血糖诱导的 Fas 依赖性和线粒体依赖性凋亡通路 It can activate the survival pathway of IGF1R cells in diabetic rats and reduce the Fas-dependent and mitochondria-dependent apoptosis pathways induced by hyperglycemia	[95]
发酵乳杆菌 TKSN041 *Lactobacillus fermentum* TKSN041	Wistar 雄性大鼠，T2DM Wistar male rat, T2DM	–	降低血糖，减轻组织的损伤；降低体重、血脂和炎症水平；上调 AMP 依赖的蛋白激酶(denosine 5′-monophosphate (AMP)-activated protein kinase, AMPK)等通路分子 Lower blood sugar, reduce tissue damage; Reduced body weight, blood lipids and inflammation levels; Up-regulated pathway molecules such as activated protein kinase (adenosine 5′-monophosphate (AMP)-activated protein kinase, AMPK)	[96]

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表 2　益生菌对糖尿病的作用和机制的临床研究

Table 2　Clinical studies on the effect and mechanism of probiotics on diabetes

益生菌 Probiotics	剂量 Dosage	疗程 Treatment	病例 Clinical history	主要效应 Main effects	参考文献 References
乳酸双歧杆菌 BB-12 和嗜酸乳杆菌 La-5 *Bifidobacterium lactis* BB-12 and *Lactobacillus acidophilus* La-5	10^9 CFU	6 w	50 例 T2DM 50 patients with T2DM	改善 HbA1c 和 IL-10 水平 Improve HbA1c and IL-10 levels	[97]
双歧杆菌、乳酸菌和嗜热链球菌 *Bifidobacterium*, *Lactobacillus* and *Streptococcus thermophilus*	–	9 w	70 例 T2DM 70 patients with T2DM	改善 HbA1c、身体质量指数和微量白蛋白尿 Improved HbA1c, body mass index and microalbuminuria	[98]
副干酪乳杆菌 HII01 *Lactobacillus paracei* HII01	50×10^9 CFU/d	12 w	–	FBS、LPS、TNF-α、IL-6 和 hsCRP 下降 FBS, LPS, TNF-α, IL-6 and hsCRP decreased	[26]
嗜酸乳杆菌 *Lactobacillus acidophilus*	10^8 CFU	3 m	136 例 T2DM 136 patients with T2DM	适度提高抗氧化酶活性 Moderately increase the activity of antioxidant enzymes	[27]
嗜酸乳杆菌、干酪乳杆菌和双歧杆菌 *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum*	2×10^9 CFU	12 w	60 例 TDM 60 patients with TDM	降低血糖、改善胰岛素抵抗 Lower blood sugar and improve insulin sensitivity.	[99]

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–: There is no information in the citations.

挥调控血糖的作用[113]。通过合成生物学手段构建光遗传调控的工程乳酸菌，实现了在体外蓝光刺激下机体肠道中可控分泌 GLP-1，从而发挥调控血糖作用[114]。

3.3　益生菌协同药物、中药及功能物质兴起

益生菌与二甲双胍联合使用，通过调节肠道菌群，上调肠道中 SCFA 增强二甲双胍的降糖作用[115]。薏苡仁提取物和益生菌已被报道通过不同的作用模式调节糖脂代谢[116]。口服益生菌发酵红参可降低空腹血糖，改善糖耐量、缓解糖尿病小鼠症状[117]。

3.4　下一代益生菌将是“后起之秀”

许多报道表明，下一代益生菌(嗜粘蛋白阿克曼氏菌、普氏粪杆菌、拟杆菌属、哈利双歧杆菌和肺泡假杆菌等)在机体健康方面表现出积极的特性[118-119]。嗜粘蛋白阿克曼氏菌在治疗代谢紊乱疾病方面研究较多，与肠道器官的相互作用可减轻糖尿病[120-122]。嗜粘蛋白阿克曼氏菌能够改善胰岛素抵抗和肠道通透性、巴氏灭菌后增加肥胖小鼠的能量消耗[123-124]。从嗜粘杆菌中纯化的膜蛋白，与 toll 样受体 2 相互作用，可改善肥胖和糖尿病小鼠的代谢[108]。哈利双歧杆菌在糖尿病小鼠中，改善了胰岛素敏感性，同时增加了能量消耗可以增加丁酸盐的产生，调节肠道微生物群的组成[125]。均匀拟杆菌通过降低血清瘦素水平、空腹血糖浓度和改善葡萄糖耐量可预防代谢紊乱和肥胖[126]。考拉杆菌属、拟杆菌属、酸胺球菌在肥胖和 T2DM 患者

中的丰度明显高于对照组，因此被认为是 T2DM 患者的潜在治疗靶点[127]。

3.5 与时俱进，结合新技术的应用

粪便菌群移植作为人类和兽医学肠道菌群调节的新策略大有作用，在 T2DM 治疗方面会发挥重要作用[128]。新机制开拓也是与时俱进的，技术革新必将带来机制的深度解析。例如，色氨酸-犬尿氨酸通路可能成为寻找糖尿病预防和治疗干预措施的新靶点[129]。另外，全基因组测序技术迭代发展，将为益生菌的功能发现和机制研究带来突破性的进展。人工智能技术也将应用于菌株序列分析、工程菌设计等精准改造。脑科学迅速发展，技术革新，相信益生菌通过脑-肠轴调控血糖的机制将会更加明确。

针对胰岛素及现有降糖药物的局限性和副作用，益生菌降糖有很大的发展潜力和方向。随着生物信息学和大数据时代的到来，益生菌的遗传稳定性、安全性将更清晰，T2DM 机制将更加明确，靶向性、多向性和定制型的精准益生菌疗法时代肯定会到来。因此，基因工程菌为主的合成生物学以及益生菌组合物将是近年来益生菌调控血糖发展的大方向。推测肠道菌群与肠道免疫、益生菌-肠-脑轴、益生菌-肠-肝轴将是益生菌调控糖脂代谢的主流方向。

4 益生菌调控血糖的挑战

虽然肠道菌群被认为是未来 T2DM 治疗的新靶点，但目前这些新型的肠道菌群治疗方法应用于临床具有一定局限性，对免疫功能低下或危重患者、肠屏障功能障碍患者或新生儿和幼儿使用活微生物疗法存在一些担忧[130]。包括从肠道易位进入血液的风险，获得和转移抗生素耐药基因的风险以及干扰新生儿肠道微生物群正常定殖的风险[131]。肠道菌群的复杂性、新型治疗方法临床应用评估和临床大数据的缺乏等问题都需要未来进一步探索和研究。

(1) 益生菌定殖与存活问题，有些益生菌体外试验效果良好，进入机体后效果不理想。益生菌需要在菌株选择、适当的工艺和储存条件、细胞活力和功能以及目标部位的有效递送等方面进行综合考虑。由于益生菌是活的微生物，许多生物学和生物制药障碍限制了它们的临床应用[132]。通过基因工程改造和给药方式的革新是解决此类问题的根本[101,133]。益生菌加工、储存和模拟胃肠道条件对其活力和活性的影响很大，因此益生菌的靶向递送、益生菌胶囊化十分必要[134]。稳定的益生菌配方可克服各种物理化学、生物制药和生物学障碍，使其治疗效果和临床适用性最大化[132]。单细胞涂层由单宁酸和铁离子组成，被称为“纳米盔甲”，可以保护细菌免受抗生素的作用[135]。

(2) 益生菌在临床应用中存在诸多问题。尽管有些益生菌在体外和体内都取得了良好效果，但是由于对益生菌遗传信息、遗传稳定性和安全性等研究不深入，临床上的推广和广泛应用仍受到限制，需要更多的研究来了解肠道微生物群对糖尿病发展的影响。此外，需要更多的努力来标准化所使用的模型、浓度范围和解释工具，以进一步推进该领域[136]。精准医疗时代需要开发新的精准化益生菌治疗方法[100]。

(3) 尽管近年来在益生菌调控血糖方面的研究取得了一些进展，但有些机制研究尚不完善。研究已经从分子水平上升到基因水平，如应用全基因组 clustered regularly interspaced short palindromic repeats (CRISPR)技术发现了钙结合蛋白卷曲螺旋区 2 在调控 β 细胞功能和 2 型糖尿病风险中的作用[137]。然而，对于益生菌如何发挥作用以及其详细的机制研究仍然不完善，靶向性益生菌调控血糖的研究仍不完善[138]。因此，深入了解糖尿病发病机制及其调控机制，从基因和分子层

面进行研究，进一步开发靶向性强、精准调控血糖的益生菌开发是有所欠缺和有待提高的。

5 综合分析和讨论

益生菌被认为是治疗大量慢性疾病和改善人类健康的经济、安全的替代品[24-25]。尽管益生菌目前存在一定不足，但是随着研究的深入和科学技术的发展，这些不足将会被改善。机体存在完整的应激系统来调控机体内外环境的平衡。机体血糖平衡被破坏则需要新的系统来调节这种相对平衡，益生菌的作用显得格外重要，有研究已经表明益生菌能够在机体糖尿病预防、调控和治疗方面均发挥重要作用[43-44,53-57]。

随着糖尿病发病机制的深入研究，相应的调控机制将被阐明。多靶点治疗是一种很有前途的 T2DM 治疗方法，这包括多种途径。基因工程菌、益生菌联合使用、益生菌结合药物使用、益生菌结合中药、植物成分和更多可能的组合将会在糖尿病治疗过程中发挥重要作用。另外，全基因组测序及安全性评价体系的完善将带来安全有效的降糖益生菌组合，为治疗糖尿病发挥重要作用。

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