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# Research progress of probiotics intervention in insulin resistance

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**Abstract**: Insulin resistance (IR) refers to a pathological condition in which the body's sensitivity to insulin decreases. The resulting disorders of glucose and lipid metabolism can lead to the onset and progression of various chronic diseases, such as type 2 diabetes mellitus (T2DM), coronary heart disease, metabolic syndrome, etc. The pathogenesis of IR is complex, but with in-depth research, accumulating evidence has suggested that gut microbiota can affect the development and progression of IR by regulating energy metabolism and inflammatory responses. Probiotics not only regulate gut microbiota and impact energy intake, but also promote health by activating immune responses. Therefore, the use of probiotics to modulate gut microbiota and intervene in the development of IR has garnered increasing attention. This review summarizes the current research advancements regarding the pathogenesis of IR, as well as the related mechanisms by which gut microbiota, especially probiotics, affect IR.

**Keywords**: Insulin resistance; Type 2 diabetes mellitus; Gut microbiota; Probiotics; Inflammation; Energy metabolism

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Over the past few decades, type 2 diabetes mellitus (T2DM) has emerged as a major global public health concern [1]. Approximately 1.6 million deaths occur annually due to diabetes, making it the ninth leading cause of mortality worldwide. The primary pathological basis of T2DM is insulin resistance (IR), which is physiologically defined as a state in which insulin-targeted tissues exhibit reduced responsiveness to high physiological insulin levels. IR serves as a common pathogenic factor in the development and progression of numerous metabolic disorders [2]. With the advancement of research, a growing body of evidence has demonstrated that the gut microbiota plays a crucial role in the onset and progression of IR. The gut microbiota can influence host glucose and lipid metabolism, thereby inducing IR, through mechanisms such as triggering chronic inflammation, altering bile acid metabolism, and producing short-chain fatty acids [3]. Therefore, targeted regulation of the host gut microbiota may represent an effective strategy for preventing and treating IR, among which probiotic intervention has been proven to hold promising application prospects [4]. This review summarizes the current understanding of the pathogenesis of IR, the mechanisms underlying probiotic-mediated regulation of IR, and the progress in their application, while also discussing future development trends and prospects, aiming to provide a theoretical basis for the subsequent development of microbial agents to ameliorate IR.

## 1 Pathogenesis of Insulin Resistance

The pathogenesis of IR is highly complex, involving multiple factors and signaling pathways. As the core pathway maintaining normal host metabolism, disruption of the insulin-insulin receptor binding signaling pathway is considered a primary cause of IR [5]. Currently, IR is mainly believed to be associated with the following aspects.

### *1.1 Inflammatory Factors*

Studies have shown that chronic low-grade inflammation is a key pathological feature of IR. These inflammatory mediators can interfere with insulin signal transduction through multiple signaling pathways: (1) Activating the inhibitor of nuclear factor kappa-B kinase β/nuclear factor kappa-B (IKKβ/NF-κB) and c-Jun N-terminal kinase (JNK) pathways to suppress the expression of the glucose transporter type 4 (GLUT4) gene [6]; (2) Mediating serine phosphorylation of insulin receptor substrate 1 (IRS-1) via JNK, thereby blocking the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway [7]; (3) Activating the diacylglycerol/protein kinase C (DAG/PKC) pathway to inhibit insulin-stimulated tyrosine phosphorylation of IRS-1 and directly interfere with the insulin signaling cascade [8].

### *1.2 Adipokines*

Adipokines are bioactive molecules secreted by adipocytes, including key members such as adiponectin and leptin. Adiponectin can bind to its receptors AdipoR1 and AdipoR2, mediating the phosphorylation of adenosine 5'-monophosphate-activated protein kinase (AMPK) and enhancing the activity of peroxisome proliferator-activated receptor α (PPARα). This process further activates fatty

acid oxidation and glucose uptake, thereby participating in the regulation of host glucose metabolism [9]. Leptin, on the other hand, exerts functions in regulating food intake, body weight, energy expenditure, and neuroendocrine activity, primarily through the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway [10].

### *1.3 Oxidative Stress*

Under normal physiological conditions, free radicals are involved in various host physiological processes. However, when the production of free radicals exceeds the physiological threshold, oxidative stress occurs. Oxidative stress impairs glucose homeostasis and promotes IR through multiple mechanisms: (1) Damaging pancreatic β-cell function and ATP-sensitive potassium channels, leading to decreased insulin secretion [11]; (2) Reducing GLUT4 expression and impairing the binding of nuclear proteins to insulin response elements within the GLUT4 promoter; (3) Activating multiple transcription factors to induce the expression of inflammation-related genes [11], thereby promoting inflammatory responses that contribute to IR.

### *1.4 Endoplasmic Reticulum Stress (ERS) and Mitochondrial Dysfunction*

The endoplasmic reticulum is a key organelle responsible for protein synthesis, folding, and modification. Dysfunction of the endoplasmic reticulum leads to the accumulation of misfolded proteins within its lumen [12]. Such stress induces excessive activation of JNK and subsequent serine phosphorylation of IRS-1, thereby inhibiting insulin receptor signal transduction, triggering inflammation and lipid accumulation, and exerting adverse effects on insulin biosynthesis and pancreatic β-cell function [13].

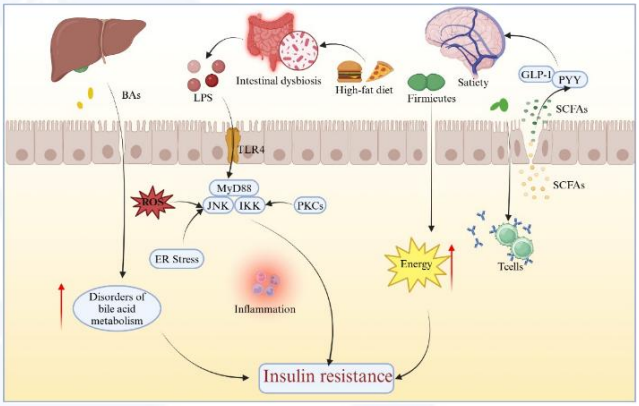
Mitochondria are the primary source of reactive oxygen species (ROS) production. Moderate levels of ROS generated by mitochondria can regulate protein tyrosine phosphatases and insulin receptors through redox reactions, thereby enhancing insulin sensitivity [14]. Meanwhile, insulin can maintain the integrity of the mitochondrial electron transport chain by inhibiting forkhead box protein O1/heme oxygenase 1 (FoxO1/HO-1) and preserving the NAD+/NADH ratio within mitochondria [15].

## 2 Potential Mechanisms by Which Gut Microbiota Influence Host Insulin Sensitivity

Studies have found that germ-free mice fed a high-fat diet exhibit less weight gain and do not develop IR compared with conventional mice on the same diet [16]. This indicates that diet-induced obesity may promote IR through a gut microbiota-dependent mechanism, which is currently believed to be associated with energy metabolism, inflammation, and microbial metabolites (see **Figure 1**).

### *2.1 Energy Metabolism*

The presence, composition, and metabolic activities of the gut microbiota exert a significant impact on host energy harvest, mainly through the following aspects: (1) Fermenting undigested food residues to produce short-chain fatty acids (SCFAs), which can be absorbed by host intestinal epithelial cells to provide additional energy; (2) Upregulating the expression of sodium-glucose cotransporter 1 (SGLT-1) in the small intestine and increasing the capillary density beneath the small intestinal villous epithelium, thereby promoting glucose absorption and supplying more energy to the host [17]; (3) Regulating the production of appetite- and satiety-related hormones such as peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) in the gut, thereby modulating food intake [18].




**Note:** TLR4 stands for toll-like receptor 4; GLP-1 stands for glucagon-like peptide-1; MyD88 stands for myeloid differentiation primary response 88; IKK stands for IκB kinase.

**Fig.1** Possible mechanisms for the involvement of gut microbiota in IR

### *2.2 Inflammation*

A high-fat diet can induce the enrichment of gut microbiota that produce lipopolysaccharide (LPS), a key factor triggering inflammation. When LPS levels in the body rise to a certain threshold, metabolic endotoxemia occurs. Endotoxins bind to the CD14 receptor on the surface of immune cells such as monocytes and macrophages, activating these cells and stimulating the expression of pro-inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which contribute to the development of obesity, IR, and diabetes [19]. LPS produced by the gut microbiota can also induce the activation of the Toll-like receptor 4 (TLR4) pathway, exacerbating ERS, and triggering the activation of JNK and IKK, which target and inhibit the insulin signaling pathway.

### *2.3 Metabolites*

The main metabolites involved include SCFAs and bile acids. SCFAs are the primary end products of the fermentation of indigestible carbohydrates by the gut microbiota. They can enhance intestinal barrier function by upregulating tight junction proteins, thereby inhibiting

inflammatory responses [21]. Additionally, SCFAs can bind to G protein-coupled receptors (GPCRs) to regulate the activity of peroxisome proliferator-activated receptor γ (PPARγ) and modulate the expression of lipid metabolism-related genes [22]. Bile acid synthesis is regulated by the gut microbiota, a process dependent on the farnesoid X receptor (FXR). Furthermore, bile acids themselves are metabolized by the gut microbiota in the intestine. Dysregulation of this process leads to an imbalance in the ratio of primary to secondary bile acids, which further disrupts signaling and metabolic pathways, thereby promoting the occurrence and progression of metabolic disorders such as obesity [23].

## 3 Possible Mechanisms of Probiotics in Regulating Insulin Resistance

Numerous studies have demonstrated that probiotics can ameliorate host IR. Although the specific regulatory pathways remain to be fully elucidated, probiotics are generally believed to improve IR through mechanisms such as regulating gut microbiota balance, preserving the integrity of intestinal epithelial tight junctions, modulating immunity, and alleviating oxidative stress.

### *3.1 Regulating Gut Microbiota Balance*

Dramatic changes in the composition and function of the gut microbiota are defined as gut dysbiosis, which not only reduces the stability of the mucosal barrier but also disrupts the immune system, triggering oxidative stress and inflammation. Probiotics can regulate gut microbiota balance through the following two main mechanisms: (1) Directly inhibiting the proliferation of pathogenic bacteria. Most probiotics, such as Lactobacillus and Bifidobacterium, are anaerobic bacteria. Their massive local proliferation creates an oxygen-depleted microenvironment, which inhibits the growth and reproduction of pathogenic bacteria that are predominantly aerobic; (2) Inhibiting the growth of pathogenic bacteria through their metabolic products. For example, probiotics produce organic acids to lower intestinal pH, generate hydrogen peroxide, and synthesize natural antibiotics, thereby reducing the production of toxic substances such as ammonia and amines in the gut and restoring gut microecological balance [24].

### *3.2 Modulating Intestinal Mucosal Barrier Function*

The intestinal mucosal barrier serves as the first line of defense against pathogen invasion, playing a critical role in preventing the translocation of intestinal bacteria and toxins into the bloodstream and other organs, as well as maintaining host homeostasis. Elevated levels of certain pro-inflammatory cytokines in the body can impair intestinal epithelial cell function, leading to the degradation of tight junction proteins, damage to the intestinal mucosal barrier, and increased intestinal permeability [25]. Upon entering the gut, probiotics colonize the intestinal mucosa and form a natural barrier on the intestinal surface through adhesion and competitive inhibition, physically separating pathogenic bacteria from intestinal epithelial tissues. This inhibits or reduces the invasion and colonization of pathogenic bacteria, thereby enhancing host defense mechanisms [26]. In addition, SCFAs, the metabolic products of probiotics, can enhance the integrity of intestinal epithelial tight junctions by promoting the synthesis of antimicrobial peptides and mucus, as well as regulating epithelial cell growth, thereby maintaining the function of the intestinal mucosal barrier.

### *3.3 Regulating Intestinal Immune Function*

The gut is the largest immune organ in the human body, harboring over 70% of the body's immune cells. Probiotics exert their immunomodulatory effects through mechanisms such as enhancing macrophage activity, regulating the release of immunoglobulins and cytokines, strengthening intestinal epithelial barrier function, adjusting mucus secretion, and competitively inhibiting the colonization of pathogenic bacteria. Within the intestinal mucosal immune system, probiotic cells or their metabolic products can be recognized by certain pattern recognition receptors (PRRs), activating corresponding signaling pathways to induce the production of cytokines, chemokines, and other effector molecules, thereby triggering host immune responses [27]. Toll-like receptors (TLRs) are an important class of PRRs. Probiotics can regulate the activation of TLR signaling pathways. TLRs recognize and bind to pathogen-associated molecular patterns (PAMPs), promoting the coordinated activation of downstream signaling molecules and transcription factors, which in turn induces the expression of antimicrobial substances, chemokines, cytokines, and co-stimulatory molecules, initiating both innate and adaptive immune responses [28].

### *3.4 Regulating Glucose and Lipid Metabolism*

Dysregulated glucose and lipid metabolism is one of the hallmark features of T2DM patients. Severe gut microbiota dysbiosis may affect glucose homeostasis and IR status in key metabolic organs such as the liver, muscle, and adipose tissue, thereby inducing abnormal changes in the expression of glucose metabolism-related genes. Probiotics can interact with bile acids in the gut to alter bile acid metabolism, which in turn affects cholesterol absorption and ameliorates host lipid metabolism disorders to a certain extent [29]. Additionally, probiotics can regulate glucose metabolism by downregulating the expression of gluconeogenesis-related genes such as glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) in the liver, as well as reducing the expression of SGLT-1 and GLUT2 in the α-glucosidase pathway [30]. Furthermore, SCFAs, the metabolic products of probiotics, can improve the efficacy of insulin by activating AMPK or regulating intracellular fatty acid synthesis, thereby helping to modulate blood glucose levels and energy metabolism [31].

### *3.5 Regulating Oxidative Stress*

Gut dysbiosis can also alter the metabolism of bile acids and choline, increasing the production of endogenous ethanol in the gut. All these events can induce inflammation and oxidative stress, exacerbating IR. Probiotics can alleviate intestinal oxidative stress by increasing the levels of superoxide dismutase (SOD) and plasma glutathione peroxidase, reducing malondialdehyde (MDA) content, promoting SCFA production, and lowering hepatic triglyceride levels [32]. Gao et al. [33] found that Lactobacillus plantarum NCU116 can enhance host antioxidant capacity by increasing the levels of SOD, catalase (CAT), and glutathione peroxidase in the liver and kidney of T2DM rats, reducing inflammation and oxidative stress in diabetic rats, and elevating serum insulin levels.

## 4 Current Status of Clinical Studies on Probiotics for Improving Insulin Resistance

Given the diverse physiological functions of probiotics and their metabolic products, as well as evidence that gut microbiota can ameliorate inflammation and metabolic disorders in diabetic mice, researchers have proposed that probiotics can be used as an adjuvant therapy to improve IR, leading to the implementation of a series of clinical trials (see **Table 1**). Different types of probiotics exhibit distinct mechanisms of action and efficacy. Therefore, when selecting probiotic supplements, it is necessary to consider their species and strain-specific characteristics. Currently, Lactobacillus, Bifidobacterium, and Akkermansia muciniphila are the most extensively studied and reported probiotics in this field.

Lactobacillus is a common type of lactic acid bacteria, classified as Gram-positive bacilli, and is found in various fermented foods such as yogurt, fermented cheese, and pickles. As a probiotic, it has been widely used in health-related fields including improving gut health, inhibiting inflammatory responses, and regulating glucose and lipid metabolism [41]. Bifidobacterium is a group of Gram-positive anaerobic bacteria and is one of the earliest microorganisms to naturally colonize the human gut. The abundance and diversity of Bifidobacterium in the colon are closely associated with host health, and these bacteria possess homeostasis-promoting and anti-inflammatory immunomodulatory properties. Bifidobacterium can regulate immune responses at the intestinal mucosal level; their cell surface polysaccharides can promote the production of forkhead box protein P3 (Foxp3) and regulatory T cells (Treg cells). The increase in Treg cells helps inhibit excessive activation of the immune system, reduce inflammatory responses, and maintain immune homeostasis [42]. Bifidobacterium can also assist certain butyrate-producing bacteria in increasing butyrate production, which helps improve insulin sensitivity, regulate blood glucose levels, and exert a protective effect against diabetes and metabolic disorders [43]. Akkermansia muciniphila is a strictly anaerobic Gram-negative bacterium that acts as a symbiont of the intestinal mucus layer, holding significant value in improving host metabolic function and immune responses. Akkermansia muciniphila not only participates in host immune regulation but also enhances the integrity of intestinal epithelial cells and the thickness of the mucus layer, thereby promoting gut health [44].

**Tab.1** Clinical trials using probiotics to improve IR

| Probiotic | Dosage/Duration | Participant Characteristics | Primary Effects | Reference |
|---|---|---|---|---|
| ***Lactobacillus salivarius UBL S22*** | $4 \times 10^9$ CFU/day, 6 weeks | 45 healthy participants, aged 20–25 years, BMI 18.5–24.9 kg/m² | In the probiotic group, HDL-C was significantly increased; total cholesterol, LDL-C, triglycerides, and inflammatory markers (hs-CRP, IL-6, IL-1β, TNF-α) were significantly decreased; HOMA-IR was reduced | [34] |
| ***Akkermansia muciniphila*** | $1 \times 10^{10}$ CFU/day, 12 weeks | 32 obese/overweight participants, aged 18–70 years, BMI >25 kg/m² | Total cholesterol, LDL-C, AST, and HOMA-IR were decreased | [35] |
| ***Lactobacillus acidophilus La-5 and Bifidobacterium animalis subsp. lactis BB-12*** | $1 \times 10^{10}$ CFU/day, 6 weeks | 50 patients with T2DM | Total cholesterol and LDL-C levels were significantly decreased; acetic acid production was increased; TNF-α and resistin levels were reduced | [36] |
| ***Bifidobacterium breve BR03 and B632*** | $2 \times 10^9$ CFU/day, 8 weeks | 6–18 years old, obese, HOMA-IR > 2.5 or insulin > 15 mU/ml | Probiotics improved insulin sensitivity during fasting and OGTT | [37] |
| ***Composite Probiotic "Symbiter"*** | – | 53 patients with T2DM | The probiotic supplementation group significantly reduced HOMA-IR, as well as TNF-α and IL-1β | [38] |
| ***Lactobacillus reuteri ADR-1 or ADR-3*** | *Lactobacillus reuteri* ADR-1: $4 \times 10^9$ CFU/day; *Lactobacillus reuteri* ADR-3: $2 \times 10^{10}$ CFU/day, 24 weeks | 68 patients with T2DM, aged 25–70 years, BMI >18.5 kg/m² | ADR-1 treatment reduced HbA1c and cholesterol; ADR-3 group reduced blood pressure and inflammatory cytokine IL-1β | [39] |
| ***Bifidobacterium pseudocatenulatum CECT 7765*** | $10^{10}$ CFU/day | 48 obese children, aged 10–15 years, all with IR | CRP and MCP-1 were significantly decreased; HDL-C was increased | [40] |

**Note:** BMI stands for body mass index; HDL-C stands for high-density lipoprotein cholesterol; LDL-C stands for low-density lipoprotein cholesterol; hs-CRP stands for high-sensitivity C-reactive protein; HOMA-IR stands for homeostasis model assessment of insulin resistance; AST stands for aspartate aminotransferase; OGTT stands for oral glucose tolerance test; HbA1c stands for glycated hemoglobin; MCP-1 stands for monocyte chemoattractant protein-1.

## 5 Development Trends of Probiotic Products

### *5.1 Inactivated Probiotics*

Although the gut microbiota is considered a promising new target for alleviating IR and even treating T2DM in the future, the clinical application of these novel gut microbiota-based therapeutic strategies carries potential risks, such as inducing immunosuppression, causing systemic infections in critically ill patients, or facilitating the transmission of antibiotic resistance genes. To mitigate these risks, there has been a growing interest in non-viable probiotics or probiotic cell extracts, such as heat-inactivated probiotics (including those inactivated by other methods) or their purified components (e.g., lipocholic acids, metabolites, and bacteriocins), which can serve as effective alternatives to viable probiotics. Studies have shown that industrially cultured and heat-treated probiotics, including bacterial extracts and supernatants in most cases, can retain their key probiotic properties at the intestinal level, enabling the development of safer formulations with superior pharmaceutical characteristics [45].

### *5.2 Prebiotics*

Prebiotics are a class of non-digestible food components, the main types of which include fructooligosaccharides (FOS), inulin, and galactooligosaccharides (GOS). Prebiotics can selectively promote the growth and metabolism of beneficial probiotics such as Bifidobacterium and Lactobacillus [46], thereby inhibiting the proliferation of pathogenic bacteria and improving the gut ecological environment. In clinical practice, strategies involving the addition of specific prebiotics are often employed to enhance the competitive advantage of probiotics within the gut microbial community. Despite the diversity of prebiotic types, further in-depth research is required to determine which prebiotics can most effectively synergize with probiotics to regulate IR.

### *5.3 Genetically Engineered Probiotics*

With continuous research efforts, the genetic stability and safety of probiotics have been further improved. Meanwhile, the mechanisms underlying various metabolic disorders have become increasingly clear. The development of targeted precision probiotic therapies using probiotics as chassis cells, or engineered live bacterial therapies for delivering drug molecules, has gradually become a research hotspot in the fields of biomedical engineering and synthetic biology. For example, Duan et al. [47] utilized engineered commensal bacteria to reprogram intestinal cells into glucose-responsive insulin-secreting cells that can secrete GLP-1 to ameliorate diabetes. Russell et al. [48] genetically engineered Escherichia coli to express bile salt hydrolase and IL-10, which improved insulin sensitivity and glucose tolerance in mice in vivo.

## 6 Conclusions and Prospects

With the advancement of research, the efficacy and mechanisms of action of probiotics have become increasingly well-known. However, the clinical application of gut microbiota-based therapies still faces numerous challenges. Firstly, individuals with IR exhibit differences in the pathophysiological mechanisms underlying the disease, meaning that different patient subgroups may respond differently to the same treatment. The gut microbiota is highly susceptible to external factors and individual variations, resulting in relatively unstable therapeutic effects. Secondly, probiotics are generally regarded as dietary supplements rather than drugs, subject to less stringent market regulation, leading to a lack of sufficient evidence to confirm their efficacy and safety. Finally, although most studies have demonstrated the beneficial effects of probiotics during administration, there is a paucity of long-term follow-up data after discontinuation of use. The long-term colonization ability of probiotics remains to be further investigated. Moreover, most commercially available probiotic products are general-purpose formulations, lacking specificity for targeted therapeutic effects. A crucial prerequisite for the application of probiotic therapy is to clarify the pathogenic mechanisms and baseline levels of gut microorganisms, which also forms the basis for the successful personalized colonization of microorganisms.

**Conflict of interest** None

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·研究进展·

# 益生菌干预胰岛素抵抗的研究进展

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**摘要：**胰岛素抵抗（IR）是指机体对胰岛素敏感性下降的一种病理状态，由此引起的糖脂代谢紊乱可导致2型糖尿病、冠心病、代谢综合征等多种慢性疾病。IR的发病机制较为复杂，而随着研究深入，许多证据表明，肠道微生物可以通过调控机体能量代谢和炎症反应影响IR的发生发展。益生菌不仅能够调节肠道菌群、影响能量摄入，还能通过激活免疫应答促进机体健康。因此，通过益生菌来调节肠道菌群进而干预IR的发生，引发了越来越多的关注。本文围绕IR的发病机制、肠道菌群尤其是益生菌调节影响IR的相关机制作一综述。

**关键词：**胰岛素抵抗；2型糖尿病；肠道菌群；益生菌；炎症；能量代谢
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## Research progress of probiotics intervention in insulin resistance

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**Abstract:** Insulin resistance (IR) refers to a pathological condition in which the body's sensitivity to insulin decreases. The resulting disorders of glucose and lipid metabolism can lead to the onset and progression of various chronic diseases, such as type 2 diabetes mellitus (T2DM), coronary heart disease, metabolic syndrome, etc. The pathogenesis of IR is complex, but with in-depth research, accumulating evidence has suggested that gut microbiota can affect the development and progression of IR by regulating energy metabolism and inflammatory responses. Probiotics not only regulate gut microbiota and impact energy intake, but also promote health by activating immune responses. Therefore, the use of probiotics to modulate gut microbiota and intervene in the development of IR has garnered increasing attention. This review summarizes the current research advancements regarding the pathogenesis of IR, as well as the related mechanisms by which gut microbiota, especially probiotics, affect IR.

**Keywords:** Insulin resistance; Type 2 diabetes mellitus; Gut microbiota; Probiotics; Inflammation; Energy metabolism
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近几十年来，2型糖尿病（type 2 diabetes mellitus，T2DM）已经成为全球范围内的重大公共卫生问题[1]，每年因糖尿病致死约有160万人，已经成为死亡的第九大病因。T2DM的主要病理学基础是胰岛素抵抗（insulin resistance，IR），IR在生理学上被定义为胰岛素靶向组织对高生理性胰岛素水平反应性降低的状态，是许多代谢类疾病发生发展的共因[2]。随着研究深入，越来越多的证据显示肠道菌群在IR的发生和发展中具有重要作用。肠道菌群可以通过引发机体慢性炎症、改变胆汁酸代谢、产生短链脂肪酸等方式影响人体糖脂代谢，进而诱导IR[3]。所以，靶向调控机体肠道菌群可能成为防治IR的有效手段，其中，采用益生菌干预已被证明具有良好的应用前景[4]。本文总结了当前有关IR的发病机制、益生菌调控IR的机制研究及应用进展，并探讨了其发展趋势与前景，以期为后续开发改善IR的微生物制剂提供理论基础。

### 1 IR的发病机制

IR的发病机制非常复杂，涉及多种因子和多条信号通路，而胰岛素及其受体结合信号通路作为维持机体正常代谢的核心，对此通路的干扰可能是导致IR的主要原因[5]。目前主要认为与以下几个方面有关。

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1.1　炎症因子　研究表明，慢性低度炎症是IR的重要病理特征，这些炎症介质可以通过多条信号通路干扰胰岛素信号传导：(1) 通过激活抑制性κB激酶β/核因子κB和c-Jun氨基末端激酶(c-Jun N-terminal kinase，JNK)通路，抑制葡萄糖转运蛋白4(glucose transporter type 4，GLUT4)基因的表达[6]；(2) 通过JNK介导胰岛素受体底物1(insulin receptor substrate 1，IRS-1)丝氨酸磷酸化，阻断磷脂酰肌醇-3激酶/蛋白激酶B通路[7]；(3) 通过激活二酰甘油/蛋白激酶C(protein kinase C，PKC)通路，阻止胰岛素刺激的IRS-1酪氨酸磷酸化并直接干扰胰岛素信号通路[8]。

1.2　脂肪因子　它们是由脂肪细胞分泌的生物活性分子，包括脂联素与瘦素等关键成员。脂联素可以通过与其受体AdipoR1和AdipoR2结合，介导AMP活化的蛋白激酶(adenosine 5'-monophosphate-activated protein kinase，AMPK)磷酸化和过氧化物酶体增殖物激活受体α活性的增加，从而激活脂肪酸氧化和葡萄糖摄取，参与调节机体糖代谢[9]。而瘦素具有调节食物摄入、体质量、能量消耗和神经内分泌等功能，主要通过Janus激酶/信号转导与转录激活因子(Janus kinase-signal transducer and activator of transcription，JAK-STAT)途径介导其作用[10]。

1.3　氧化应激　在正常情况下，自由基参与机体多种生理过程，但当自由基的生成超过生理范围时，就会导致氧化应激。氧化应激通过多种方式破坏葡萄糖稳态，促进IR：(1) 损害β细胞功能及ATP敏感钾通道，导致胰岛素分泌减少[11]；(2) 降低GLUT4表达，使核蛋白与GLUT4启动子中胰岛素反应元件的结合受损；(3) 激活多种转录因子诱导炎症通路相关基因的表达[11]，促进炎症反应参与IR。

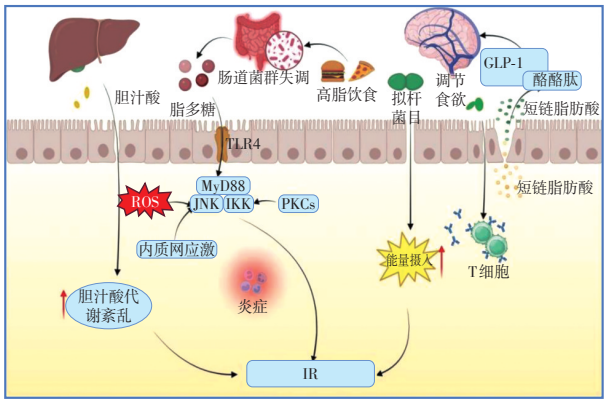
1.4　内质网应激(endoplasmic reticulum stress，ERS)和线粒体功能障碍　内质网是蛋白质合成、折叠和修饰的关键细胞器，其功能紊乱会导致错误折叠的蛋白质在内质网中积累[12]。这种应激会通过JNK的过度激活和随后IRS-1的丝氨酸磷酸化进而导致胰岛素受体信号传导的抑制，引发炎症和脂质积累，对胰岛素生物合成和β细胞功能产生不良影响[13]。

线粒体是产生活性氧(reactive oxygen species，ROS)的主要部位，它可以通过产生适度的ROS并通过氧化还原反应调节蛋白酪氨酸磷酸酶和胰岛素受体，增强胰岛素敏感性[14]；同时，胰岛素可以通过抑制叉头框蛋白O1/血红素加氧酶1和维持线粒体中$NAD^+$/NADH的比率来维持线粒体电子传输链的完整性[15]。

## 2　肠道菌群影响宿主胰岛素敏感性的潜在机制

研究发现食用高脂饮食的无菌小鼠比食用同样食物的对照组小鼠体质量增加更少，并且不会产生IR[16]，这表明饮食诱导的肥胖可能通过依赖于肠道微生物群的机制促进IR，目前主要认为与能量代谢、炎症和代谢产物有关。见图1。

2.1　能量代谢　肠道微生物群的存在、组成和代谢作用对能量摄取具有明显的影响，主要包括以下几个方面：(1) 发酵未被吸收的食物残渣，产生短链脂肪酸(short-chain fatty acids，SCFAs)，这些SCFAs可以被宿主肠道上皮细胞吸收，并提供额外的能量；(2) 增加小肠中钠-葡萄糖共转运体1(sodium glucose cotransporter 1，SGLT-1)的表达和小肠绒毛上皮下毛细血管密度，促进葡萄糖吸收，为宿主提供更多能量[17]；(3) 通过影响肠道内肠源性饱腹激素酪酪肽和GLP-1等调节食欲和饱腹感相关激素的产生，调节食物摄入[18]。




注：TLR4为Toll样受体4；GLP-1为胰高血糖素样肽-1；MyD88为髓样分化因子88；IKK为IκB激酶。

**图1**　肠道菌群参与IR的可能机制

**Fig.1**　Possible mechanisms for the involvement of gut microbiota in IR

2.2　炎症　高脂饮食可以诱导富含脂多糖(lipopolysaccharide，LPS)的肠道菌群富集，而LPS是诱发炎症的一个重要因素。当体内的LPS上升到一定水平时，就会造成代谢性内毒素血症。内毒素通过与单核细胞、巨噬细胞等免疫细胞表面受体CD14结合激活免疫细胞，刺激白细胞介素(interleukin，IL)-6、肿瘤坏死因子(tumor necrosis factor，TNF)-α等促炎因子的表达，影响肥胖、IR及糖尿病的发生发展[19]。肠道菌群产生的LPS还会诱导TLR4通路激活，导致ERS加剧[20]，诱导JNK和IKK的激活，靶向并抑制胰岛素信号通路。

2.3　代谢产物　主要包括SCFAs和胆汁酸。SCFAs是一类由肠道菌群利用不可消化碳水化合物发酵的主要最终产物，可以通过上调紧密连接蛋白增强肠道屏障功能，抑制炎症反应[21]，也可以通过结合G蛋白偶联受体，调控过氧化物酶体增殖物激活受体γ活性，调节脂代谢基因表达[22]。胆汁酸的合成受肠道微生物组的调控，这一过程依赖于法尼醇X受体。此外，胆汁酸本身也在肠道中被微生物群代谢。其失调会导致初级胆汁酸与次级胆汁酸比例失衡，胆汁酸比例失衡将进一步导致信号代谢通路紊乱，从而促进肥胖等代谢性疾病的发生与发展[23]。

## 3　益生菌参与调节IR的可能机制

许多研究发现，益生菌具有改善机体IR的作用，虽然其具体调控途径有待进一步深入了解，但一般认为，益生菌可以调节菌群平衡、保护肠上皮紧密连接的完整性、调节免疫及氧化应激等改善IR。

3.1　调节肠道菌群平衡　肠道微生物组成和功能的剧烈变化被定义为肠道微生态失调，这不仅会降低黏膜屏障的稳定性，还会破坏免疫系统，诱发氧化应激和炎症。益生菌可通过以下两个方面调节肠道菌群平衡：(1) 直接抑制有害菌繁

殖。大多数益生菌如乳酸杆菌、双歧杆菌多为厌氧菌，其在局部大量繁殖会形成缺氧微环境，而致病菌多为需氧菌，它们在缺氧环境下生长繁殖受到抑制。(2) 通过代谢产物抑制致病菌的生长。例如产生有机酸、降低肠道pH值或产生过氧化氢和天然抗生素，减少肠道内氨、胺等有毒物质的产生等，从而达到重建肠道微生态平衡的目的[24]。

3.2 调节肠道黏膜屏障 肠道黏膜屏障是宿主抵御病原体入侵的第一道防线，在阻止肠腔内的细菌和毒素入侵血液和其他器官、维持内环境稳态方面起着重要作用。当机体内一些细胞炎性因子水平升高时，就会损伤肠上皮细胞功能，使紧密连接蛋白降解、肠道黏膜屏障受损，肠道通透性增强[25]。益生菌进入肠道中，定植于肠道黏膜上，通过自身的黏附和竞争性抑制作用，在肠道表面形成一道天然屏障，将致病菌与肠上皮组织隔离开来，可以抑制或减少病原菌的侵染和定植，增强机体防御作用[26]。此外，益生菌代谢产物SCFAs可以通过促进合成抗菌肽、黏液合成、调节上皮细胞生长等方式提升紧密连接肠上皮细胞的致密性，维持肠道黏膜屏障的功能。

3.3 调节肠道的免疫功能 肠道是人体最大的免疫器官，超过70%的免疫细胞位于肠道。益生菌可通过提高巨噬细胞活性、调控免疫球蛋白及细胞因子的释放，或增强肠道上皮屏障功能、调整黏液分泌量，以及竞争性抑制致病菌定植等机制来实现其功能。在肠道黏膜免疫系统中，益生菌菌体或其代谢产物可通过被某些模式识别受体(pattern recognition receptors，PRRs)识别并激活相应的信号通路诱导细胞因子、趋化因子和其他效应分子的产生，从而激活宿主的免疫反应[27]。TLR是PRRs中重要的一种，益生菌可调节TLR信号通路的活化，TLR识别并结合病原相关分子模式，促进下游信号和转录因子的协调激活，从而诱导抗菌物质、趋化因子、细胞因子及共刺激分子的表达，引发天然免疫和适应性免疫[28]。

3.4 调节糖脂代谢 糖脂代谢异常是T2DM患者的典型特征之一，肠道微生物群的严重失衡，可能影响肝脏、肌肉及脂肪组织等关键代谢器官中的葡萄糖平衡与IR状态，进而引发糖代谢相关基因表达的异常变化。益生菌可以通过与肠道内胆汁酸相互作用，改变胆汁酸代谢，进而影响胆固醇吸收，一定程度上可以改善人体脂质代谢紊乱[29]；也可以通过降低肝脏糖异生相关的*G6Pase*和*PEPCK*基因的表达、降低α-葡萄糖苷酶途径中SGLT-1和GLUT2的表达来调控糖代谢[30]。此外，益生菌代谢产物SCFAs可以通过激活AMPK或调节细胞内脂肪酸合成等途径，改善胰岛素的作用效果，从而有助于调节血糖水平和能量代谢[31]。

3.5 调节氧化应激 肠道微生态失调还会改变胆汁酸和胆碱的代谢，增加肠道内源性乙醇的产生。所有这些事件都会引起炎症和氧化应激，加剧IR。益生菌可以通过增加超氧化物歧化酶(superoxide dismutase，SOD)和血浆谷胱甘肽过氧化物酶的水平和降低丙二醛的含量，促进SCFAs的产生，降低肝脏三酰甘油的水平，缓解肠道氧化应激[32]。Gao等[33]发现植物乳杆菌NCU116具有提升机体抗氧化的能力，可以提高T2DM大鼠肝肾中SOD、过氧化氢酶和谷胱甘肽过氧化物酶水平，降低糖尿病大鼠的炎症和氧化应激，提高血清胰岛素水平。

## 4 益生菌用于改善IR的临床研究现状

鉴于益生菌及其代谢产物丰富的生理功能，以及肠道微生物改善糖尿病小鼠炎症和代谢紊乱的证据，有研究者提出益生菌可以作为一种辅助手段来改善IR，并由此开展了一系列临床试验(表1)。不同类型的益生菌具有不同的作用机制和效果，因此在选择益生菌补充剂时需要考虑其种类和菌株的特性，目前研究和报道较多的是乳杆菌、双歧杆菌和嗜黏蛋白阿克曼菌。

乳杆菌是一种常见的乳酸菌，属于革兰阳性菌，具有杆状形态，存在于许多发酵食品中，如酸奶、发酵奶酪、泡菜等。作为一种益生菌，它已被广泛应用于改善肠道健康、抑制炎症反应和调节糖脂代谢等相关健康领域[41]。双歧杆菌是一类革兰阳性厌氧菌，是最早在人体肠道内自然定植的微生物之一，其在结肠中的丰度和多样性与宿主的健康密切相关，具有促稳态和抗炎免疫调节特性。双歧杆菌可以在肠道黏膜水平上调节免疫反应，它们的细胞表面多糖可以促进叉头框蛋白P3以及调节性T细胞(regulatory T cell，Treg)的产生，这种Treg的增加有助于抑制免疫系统的过度激活，减轻炎症反应，并维持免疫平衡[42]。双歧杆菌还可以帮助一些产丁酸盐细菌增加丁酸盐产量，这有助于改善胰岛素敏感性，调节血糖水平，对糖尿病和代谢性疾病具有一定的保护作用[43]。嗜黏蛋白阿克曼菌是严格厌氧的革兰阴性菌，作为一种肠道黏液层的共生菌，在改善宿主代谢功能和免疫应答方面具有重要价值。嗜黏蛋白阿克曼菌不仅参与宿主免疫调节，还能增强肠道上皮细胞的完整性和黏液层的厚度，从而促进肠道健康[44]。

## 5 益生菌产品的发展趋势

5.1 灭活益生菌 虽然肠道菌群被认为是未来缓解IR甚至是治疗T2DM的新靶点，但目前这些新型的益生菌肠道菌群治疗方法应用于临床具有潜在风险，例如有可能引起免疫功能低下或导致危重患者全身性感染或传播抗生素耐药基因等。为了避免这些风险，人们对于非活性益生菌或益生菌细胞提取物的兴趣日益增加，如使用热灭活(包括其他方式灭活)益生菌，或其纯化组分如脂质胆酸、代谢物和细菌素等，都可以在替代活益生菌方面发挥重要作用。研究发现，经过工业培养、热处理的益生菌，包括大多数情况下的细菌提取物和上清液在肠道水平上可以保持其主要的益生菌特性，从而允许开发更安全的制剂，具有更优的药物特性[45]。

5.2 益生元 益生元是一类非消化性食品成分，主要类型包括低聚果糖、菊粉和半乳低聚糖。益生元能够通过选择性地促进益生菌如双歧杆菌、乳酸杆菌的生长代谢[46]，从而抑制有害细菌的繁殖，改善肠道生态环境。在治疗实践中，常采用添加特定益生元的策略，以增强益生菌在肠道微生物群落中的竞争优势。尽管益生元类型多样，但关于哪种益生元能最有效地协同益生菌调节IR，仍需进一步深入探索。

5.3 基因工程菌 随着不断探索，益生菌的遗传稳定性、安

**表 1**　益生菌改善人群 IR 的临床研究

**Tab.1**　Clinical trials using probiotics to improve IR

| 益生菌 | 剂量/时间 | 参与者特征 | 主要效应 | 参考文献 |
|---|---|---|---|---|
| 唾液乳杆菌 UBL S22 | $4\times10^9$ CFU/d，持续 6 周 | 45 名健康受试者，20~25 岁，BMI 18.5~24.9 kg/m$^2$ | 益生菌组 HDL-C 显著升高，总胆固醇、LDL-C、三酰甘油和炎症标志物 hs-CRP、IL-6、IL-1β、TNF-α显著降低，HOMA-IR 降低 | ［34］ |
| 嗜黏蛋白阿克曼菌 | $1\times10^{10}$ CFU/d，持续 12 周 | 32 名肥胖/超重受试者，18~70 岁，BMI>25 kg/m$^2$ | 总胆固醇、LDL-C、AST、HOMA-IR 降低 | ［35］ |
| 嗜酸乳杆菌 La-5 和动物双歧杆菌乳亚种 BB-12 | $1\times10^{10}$ CFU/d，持续 6 周 | 50 名 T2DM 患者 | 总胆固醇、LDL-C 水平均显著降低，乙酸产量均增加，TNF-α和抵抗素水平均降低 | ［36］ |
| 短双歧杆菌 BR03 和 B632 | $2\times10^9$ CFU/d，持续 8 周 | 6~18 岁，肥胖，HOMA-IR>2.5 或胰岛素>15 mU/L | 益生菌改善了空腹时和 OGTT 期间的胰岛素敏感性 | ［37］ |
| 复合益生菌“Symbiter” | _ | 53 名 T2DM 患者 | 补充益生菌组可显著降低 HOMA-IR、TNF-α和 IL-1β | ［38］ |
| 罗伊乳杆菌 ADR-1 或 ADR-3 | 罗伊乳杆菌 ADR-1 $4\times10^9$ CFU/d 或罗伊乳杆菌 ADR-3 $2\times10^{10}$ CFU/d，持续 24 周 | 68 名 T2DM 患者，25~70 岁，BMI>18.5 kg/m$^2$ | ADR-1 处理组 HbA1c 和胆固醇均降低，ADR-3 组降低血压和炎症细胞因子 IL-1β | ［39］ |
| 假小链双歧杆菌 CECT 7765 | $10^{9\text{-}10}$ CFU/d | 48 名肥胖儿童，10~15 岁，均伴有 IR | CRP 和 MCP-1 显著降低，HDL-C 增加 | ［40］ |

注：身体质量指数（BMI）；高密度脂蛋白胆固醇（HDL-C）；低密度脂蛋白胆固醇（LDL-C）；超敏 C 反应蛋白（hs-CRP）；胰岛素抵抗指数（HOMA-IR）；天冬氨酸氨基转移酶（AST）；口服葡萄糖耐量试验（OGTT）；糖化血红蛋白（HbA1c）；单核细胞趋化蛋白-1（MCP-1）。

全性得到进一步提升。同时，各类代谢性疾病的机制将更加明确，将益生菌作为底盘细胞开发靶向性更强的精准益生菌疗法或传递药物分子的工程活细菌疗法逐渐成为生物医学工程和合成生物学领域的研究热点。例如 Duan 等[47]利用工程共生菌将肠细胞重新编程为葡萄糖响应性胰岛素分泌细胞，可以分泌 GLP-1 来改善糖尿病；Russell 等[48]利用基因工程改造大肠杆菌来表达胆盐水解酶和 IL-10，在体内能够改善小鼠的胰岛素敏感性和葡萄糖耐量等。

## 6　总结与展望

随着研究进展，益生菌的功效与作用也越来越为人们所熟知，但目前，肠道菌群治疗应用于临床存在许多困难。首先，在 IR 个体中发现不同群体在发病机制上的病理生理存在差异，不同的患者亚群对同样的治疗可能有不同的反应；肠道菌群易受外界因素及个体差异影响，治疗相对不稳定。其次，益生菌一直被认为是膳食补充剂，而不是药物，受到的市场监管较少，所以没有足够的证据来证明其疗效或安全性。最后，虽然大部分研究表明益生菌在使用过程中具有改善作用，但停止使用后缺乏对其长期的追踪过程，益生菌的长期定植能力仍有待考究，且市面上大多数的益生菌产品具有普适性，缺乏具体效用的针对性。应用益生菌治疗的重要前提是明确致病机制和肠道内微生物的基线水平，这也是成功地以个体化方式定植微生物的基础。

**利益冲突**　无

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