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Exploring the Molecular Biological Mechanisms of Type 2 Diabetes Mellitus Based on Intestinal Flora Metabolites that Affect Host-Associated Signaling Pathways

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Abstract: *Alterations in gut flora composition and function of the host have become a crucial area in the pathogenesis of type 2 diabetes. This paper aims to discuss the molecular biological mechanisms of type 2 diabetes, including glucose metabolism, inflammation, intestinal barrier function, and immunomodulation. It reviews studies on the signaling pathways related to the metabolites of the intestinal flora affecting the host. This will provide the basis for subsequent clinical targeted therapy and an outlook on future research.*

Keywords: *gut flora; signaling pathway; type 2 diabetes mellitus*

1. Introduction

Epidemiological studies indicate that over 500 million people worldwide suffer from diabetes, with a prevalence of 11.4% for type 2 diabetes in China[1]. Diabetes is frequently associated with complications such as cardiovascular disease, neuropathy, eye disease, kidney disease, and lower limb vasculopathy, placing a significant burden on public health. Currently, there is mounting evidence that the intestinal microbiota plays a crucial role in the development and progression of type 2 diabetes mellitus. This paper aims to comprehensively review recent research progress on the metabolite-host-related signaling pathways of gut microbiota and type 2 diabetes, providing a reference and insights for related studies in this field.

2. The development of type 2 diabetes mellitus is influenced by the metabolic axis between the host and gut microbiome

The human gut contains trillions of microorganisms, including over 1014 bacteria from six major phyla: Bacteroides, Firmicutes, Verrucomicrobia, Proteus, Clostridium, and Actinobacteria[2]. The microbial community in the gut interacts with the host and produces metabolites that promote the adaptive evolution of the host. This is known as the host-microbe metabolic axis[3]. Within these metabolic pathways, multiple bacterial genomes can sequentially regulate metabolic reactions that enable the microbiome and host genome to synthesize substrates such as bile acids (BA), lipopolysaccharide (LPS), and short-chain fatty acids (SCFA), among others. Multiple effective signaling pathways regulate mechanisms involving various classes of molecules in this process for delivery and metabolite interactions that affect the development and metabolism of the host health system. Patients diagnosed with Type 2 diabetes mellitus (T2DM) often exhibit an increase in pathogenic bacteria, such as Clostridium, Symbiotic clostridium, and Coli bacillus, while healthy controls have a high abundance of butyrate-producing bacteria[4]. The alterations in the composition and function of the intestinal flora have an impact on the metabolic processes of glucose and fatty acid metabolic pathways. This, in turn, affects the development of type 2 diabetes mellitus[5]. Secondly, disruption of gut microbiota is also significant in the development of type 2 diabetes. This is often

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caused by immune system stimulation, increased permeability of the gut barrier, and elevated levels of lipopolysaccharides, which in turn alter glucose metabolic processes. Finally, diabetes alters the host intestinal flora, leading to a decrease in the abundance of butyrate bacteria. This alteration results in high expression of inflammatory cytokines (interleukin IL-1β and NADPH oxidase NOX4) in the colonic tissues of diabetic mice, which increases the risk of various complications[6].

3. Influence of the metabolite-host-associated signaling pathway of intestinal flora on type 2 diabetes mellitus

3.1. Inflammation-related signaling pathways

Inflammation-related signaling pathways are crucial in the formation and development of type 2 diabetes. Elevated levels of inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin 6, hurt insulin signaling cascades. Lipopolysaccharide, a metabolite of the intestinal microbiota, triggers inflammation of the intestinal mucosa, which can result in insulin resistance or direct damage to pancreatic β-cells, further exacerbating the severity of type 2 diabetes. Therefore, interventions targeting inflammatory signaling pathways have the potential to be effective treatments for diabetes and its complications.

TLR4/NF-κB signaling pathway. Lipopolysaccharide is a potent virulence factor of gram-negative bacterial species and plays a major role in acute and chronic infections. Changes in the gut microbiota determine plasma LPS concentrations and are one of the mechanisms involved in metabolic disorders. It was demonstrated that a high-fat diet induced an increase in intestinal permeability and a decrease in the number of certain Gram-positive and Gram-negative bacteria, such as Lactobacillus, Bifidobacterium, and Bacteroidetes-Prevotella et. This alteration in the gut microbiota led to a significant increase in plasma LPS levels[7]. The ability of LPS to recognize the receptor TLR4 with the help of CD14 leads to macrophage aggregation and activation of the NF-κB inflammatory signaling pathway, which is characterized by an increase in the production of inflammatory factors such as TNF-γ, IL-1β, IL-6, and TNF-α, followed by aberrant phosphorylation of insulin receptor substrates and insulin resistance[8]. However, regulating the TLR4/NF-κB signaling pathway and medication rationally can attenuate the inflammatory response of type 2 diabetes caused by LPS. For instance, acupuncture combined with the acupoint technique can effectively regulate the balance of intestinal microbes and the structure of the intestinal tract, thereby repairing the damage to the intestinal mucosal barrier. Additionally, this technique can inhibit the activity of the TLR4/NF-κB signaling pathway. This inhibition can help reduce the local and systemic immune-inflammatory response and improve glucose-lipid metabolism disorders. As a result, it can reduce the damage caused by T2DM to the intestine[9]. Therefore, when treating lipopolysaccharide, a metabolite of the intestinal flora, it is important to consider its dual role comprehensively. On one hand, moderate lipopolysaccharide production can be maintained through dietary modifications such as increasing the intake of dietary fiber and probiotics to maintain a healthy gut flora composition. On the other hand, if an individual is at risk for chronic inflammatory diseases, it may be necessary to control lipopolysaccharide production to minimize the inflammatory response.

3.2. Bile acid-related signaling pathway

The bile acid signaling pathway plays a crucial role in the regulation of energy and glucolipid metabolism, as well as the absorption of saturated fatty acids and cholesterol. The bile acid signaling pathway plays a crucial role in the regulation of energy and glucolipid metabolism, as well as the absorption of saturated fatty acids and cholesterol. The bile acid signaling pathway plays a crucial role in the regulation of energy and glucolipid metabolism, as well as the absorption of saturated fatty acids and cholesterol. This is achieved by altering the production of metabolites such as short-chain fatty acids and oxalic acid by the gut flora-bile acid axis. These effects improve not only the intestinal inflammatory response but also reduce the incidence of diseases, such as type 2 diabetes and its complications.

FXR/TGR5 signaling pathway. The gut microbiota may play a role in the development of T2DM by affecting bile acid metabolism in the intestinal lumen and regulating energy and lipid metabolism. Anaerobic bacteria of the genera Anabaena, Eubacterium, and Clostridium transform primary bile acids secreted into the gut, metabolizing them into secondary bile acids, such as deoxycholate and lithocholate, through deconjugation and 7-dehydroxylation[10]. These bile acid metabolites, formed

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through metabolic interactions between mammals and intestinal microbes, are major ligands for nuclear hormone receptors. They strongly activate the Farnesol X receptor (FXR), an important member of the family, as well as the plasma membrane-bound bile acid receptor Thiol guanosine receptor-5（TGR5). Under normal physiological conditions, activation of intestinal FXR maintains efficient efflux of bile acids into the portal vein, controls the reuptake of bile acids into intestinal epithelial cells, and limits intracellular bile acid levels[13]. Furthermore, FXR signaling impacts numerous target genes, such as those related to bile acid synthesis and transport, as well as lipid and carbohydrate metabolism. It also plays a role in regulating intestinal innate immunity and triggers the release of fibroblast growth factor 19/15 (FGF19/15). FGF19/15, as a ligand, enhances insulin sensitivity and glucose tolerance. TGR5 is a G protein-coupled cell surface receptor that exerts anti-inflammatory effects, protects cholangiocytes from BA-induced toxicity, promotes cholangiocyte secretion and proliferation, mediates gallbladder filling, promotes muscular energy expenditure, and stimulates intestinal L-cells to secrete glucagon-like peptide-1 (GLP-1). Additionally, TGR5 rescues insulin resistance and abnormal glucose metabolism. A recent study suggests that antibiotic treatment can alter gut microbiota, reduce intestinal tissue inflammation, improve insulin signaling in basal and stimulated states, and enhance glucose metabolism in obese and diabetes-prone C57BL/6J mice on a high-fat diet (HFD). These physiological changes are closely associated with changes in levels of serum bile acids and the anti-inflammatory bile acid receptor TGR5 (G protein-coupled receptor 5) [11].

3.3. Glucose metabolism-related signaling pathways

The host's glucose metabolism can be influenced by gut flora through various pathways, including changes in metrics such as the glucose load test, fasting blood glucose, and insulin sensitivity. The gut microbiota can also break down and use polysaccharides and oligosaccharides, resulting in the production of short-chain fatty acids (SCFAs). These SCFAs play important roles in promoting insulin secretion and improving insulin sensitivity, which indirectly affects the control of blood glucose levels. Furthermore, the gut microbiota can impact the production and secretion of intestinal hormones, such as GLP-1, that are crucial in regulating insulin secretion and sensitivity.

SCFA/GPR43/GLP-1 signaling pathway. The signaling pathway of SCFA/G protein-coupled receptors 43 (GPR43)/GLP-1 plays a crucial role in the onset and development of diabetes mellitus. SCFA, which is a metabolite of the intestinal flora, including propionic acid, butyric acid, and valeric acid, can affect host-microbe signaling and colonic pH control. In turn, it impacts the composition of the microbiota, intestinal motility, and proliferation of epithelial cells. The gut microbiota produces short-chain fatty acids (SCFAs), including butyric acid, which can improve the progression of type 2 diabetes mellitus (T2DM) through several mechanisms. These microorganisms, such as Clostridium, fungi, and Roseobacter, help maintain the integrity of the intestinal epithelial barrier, facilitate hepatic glycogen metabolism, and modulate mitochondrial functions[12]. Studies have shown that short-chain fatty acids (SCFAs) can activate GPR43 in adipocytes, inhibiting insulin signaling. Additionally, SCFAs can promote GLP-1 secretion from L cells, improving glucose tolerance and insulin sensitivity. They also help maintain the integrity of the intestinal mucosal barrier, protecting intestinal health[13]. The SCFA/GPR43/GLP-1 signaling pathway plays a crucial role in regulating glucose metabolism and immune system function to prevent and treat type 2 diabetes and its complications. Coix lacrymal polysaccharide has been shown to reduce glucose levels and increase GLP-1 concentration in diabetic mice[14]. Flavopiridol combined with senna glycosides may regulate intestinal health and glucose metabolism in db/db mice through the colonic SCFA-GPR43/GLP-1 pathway. This combination can also reduce hepatic insulin resistance and gluconeogenesis, resulting in hypoglycemic effects. The study suggests that this treatment has the potential to manage diabetes in mice[15]. Therefore, when treating and rehabilitating diabetic patients, it is important to prioritize intestinal health and promote the normal function of the SCFA/GPR43/GLP-1 signaling pathway.

PI3K/AKT signaling pathway. Branched-chain amino acids are essential amino acids that cannot be synthesized by the body and must be obtained from the diet. Branched-chain amino acids are mainly composed of leucine, isoleucine, and valine. Studies on animals have shown that synthetic Branched-chain amino acids can induce insulin resistance, decrease glucose tolerance, and increase plasma Branched-chain amino acid levels in a mouse model of fecal microbiota transplantation. The main driver bacteria of branched-chain amino acids are Prevotella and Mycobacterium avium, which increase the oxidation of free fatty acids and activate phosphatidylinositol 3 kinase[16]. Activation of PI3K can induce insulin resistance through phosphorylation of protein kinase B (AKT). In a study of the therapeutic process, it was found that perilla oil reduced the abundance of Aerococcus aeruginosa, promoted the abundance of cyanobacteria in the gut, and accelerated the restoration of intestinal flora

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diversity by activating the expression of glucose transporter protein 4 (Glut4) and phosphorylated AKT serine/threonine kinase (p-AS160) in the liver, via the PI3K / AKT signaling pathway in type 2 diabetic KKAy mice[17]. Cinnamaldehyde regulates the insulin receptor substrate 1 (IRS1)/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway, promotes insulin secretion, reduces insulin resistance, inhibits inflammation, regulates intestinal flora, and plays a role in preventing and controlling diabetes through antioxidant response and other pathways[18].EGCG, also known as epically catechin-3-gallate, has been shown to inhibit hepatic gluconeogenesis and increase glucose uptake in skeletal muscle tissues. This is achieved by enhancing insulin sensitivity and activating the PI3K/Akt insulin signaling pathway. Additionally, EGCG has been found to significantly increase the abundance of Eckermannia spp. in the intestinal tract of diabetic rats and modulate the intestinal barrier function, leading to a direct improvement in insulin resistance[19].

3.4. Signaling Pathways Related to Intestinal Barrier Function

The gut barrier function is the defense mechanism of the intestinal mucosa against external environmental invasion. The intestinal microbiota can influence the intestinal barrier function through various pathways, which in turn directly or indirectly affects the development of type 2 diabetes mellitus. Research has demonstrated that signaling pathways related to gut flora can impact the expression of Tight junctions and Adherens junctions in intestinal mucosal endothelial cells, which in turn affects the intestinal barrier function. A decrease in barrier function can lead to toxins and inflammatory factors from the intestinal lumen entering the circulatory system through the intestinal mucosa, promoting a systemic inflammatory response and reducing insulin sensitivity. Dysfunction of the intestinal barrier can increase the leakage of bacteria or bacterial products, leading to chronic inflammation and metabolic disease. This can be detrimental to the body's overall health and well-being.

AMPK signaling pathway. The AMPK signaling pathway regulates intracellular energy metabolism by modulating the structure of the intestinal microflora and the production of SCFAs, particularly propionic acid and butyric acid. These SCFAs activate the AMPK signaling pathway, increasing the efficiency of cellular energy metabolism. The AMPK signaling pathway regulates energy metabolism and has been linked to factors such as intestinal flora imbalance and intestinal mucosal barrier disruption. Its activation has been the subject of extensive research. For instance, the mechanism of diabetic diarrhea induced by highly digestible protein diets is thought to be related to the AMPK signaling pathway associated with intestinal flora. Recent studies have shown that the AMPK signaling pathway plays a role in the onset and development of type 2 diabetes. Activation of the AMPK signaling pathway helps to maintain energy homeostasis and balance energy metabolism in the body. Diabetic patients often experience metabolic disorders, such as insulin resistance and hyperglycemia, which cause an imbalance in energy metabolism. The activation of the AMPK signaling pathway can regulate these metabolic abnormalities[20]. Activation of the AMPK signaling pathway can improve glucose uptake by intestinal epithelial cells, insulin resistance, and lower blood glucose levels to alleviate the symptoms of diabetic complications. Additionally, it can regulate the metabolic activity of the intestinal flora, promoting the growth of beneficial bacteria and inhibiting the propagation of harmful bacteria, thereby maintaining the balance of the intestinal flora and decreasing the risk of developing diabetic complications[21].AMPK is activated in response to impaired energy metabolism. This activation inhibits fatty acid and cholesterol synthesis while promoting fatty acid oxidation and glucose uptake. Activation of the AMPK signaling pathway can alter the community structure of gut microbes and influence the production of SCFAs. Additionally, it promotes the repair of the intestinal mucosal barrier, enhances its stability, and reduces the occurrence of diabetic complications. This pathway also improves metabolic abnormalities, regulates the balance of intestinal flora, and promotes the repair of the intestinal mucosal barrier. These effects can reduce the risk of developing type 2 diabetes mellitus and its complications[22]. Thus, the activation of the AMPK signaling pathway can be considered a novel target for treating diabetes, offering more practical therapeutic options for individuals with diabetes. For instance, natural volatile oils from plants and their active ingredients can inhibit IR by protecting pancreatic β-cells, inhibiting α-glucosidase activity, regulating the abundance and diversity of intestinal flora, and modulating glucose transporter protein 4 (GLUT4) and adenylate-activated protein kinase (AMPK) signaling pathways. They can also improve diabetic complications through multiple mechanisms of action[23]. The group administered with Pueraria Mirifica Scutellaria Tang showed a significant increase in the relative abundance of glucolipid metabolism, lipopolysaccharide metabolism, MARK signaling pathway, and insulin signaling pathway metabolism. It is important to note that these findings are objective and not based on subjective evaluations[24]. Nigella sativa reduces inflammation, liver injury, and insulin resistance induced by a

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high-fat diet and streptozotocin (STZ) in C57BL/6J mice. It also ameliorates disorders of glucose-lipid metabolism through the activation of the AKT and adenosine 5'monophosphate-activated protein kinase (AMPK) signaling pathways and modulates the intestinal microbiota in mice with type 2 diabetes mellitus[25]. Activation of the AMPK signaling pathway plays a crucial role in preventing and treating type 2 diabetes and its complications.

3.5. Immunomodulation-related signaling pathways

The host immune system can be modulated by the gut microbiota, which can have an indirect impact on glucose metabolism and the development of type 2 diabetes and its complications in vivo. The metabolites of gut flora can affect the differentiation and function of immune cells, including T cells, B cells, and macrophages. They can also regulate the secretion of cytokines and anti-inflammatory molecules by immune cells, promoting a balanced and healthy immune system. This information is supported by Sommer and Bäckhed. For instance, SCFAs have various functions such as providing energy, regulating blood glucose levels, promoting fatty acid oxidation, and reducing weight gain. Additionally, they can modulate the immune system, and promote intestinal epithelial cell repair and proliferation. It is important to maintain a balanced and objective tone when discussing the effects of SCFAs.

Notch signaling pathway. Research has shown that there is an interactive relationship between the Notch signaling pathway and intestinal flora. The Notch signaling pathway regulates the differentiation, proliferation, and self-renewal of intestinal epithelial cells, which in turn affects the intestinal mucosal barrier function. The intestinal flora can indirectly regulate the activation of the Notch signaling pathway and downstream gene expression through the production of metabolites such as short-chain fatty acids, the activation of Toll-like receptors, and the induction of immune responses. The Notch signaling pathway is a highly conserved signaling pathway that regulates T cell development, proliferation, and differentiation. It influences the function and phenotype of T cells by regulating T cell transcription factors, thereby affecting the strength and specificity of the immune response[26]. Research has found that the Notch signaling pathway plays a role in regulating insulin synthesis and secretion, as well as glucose metabolism and insulin resistance. Specifically, the pathway regulates pancreatic β-cell proliferation, differentiation, and maintenance of function to impact glucose metabolism and insulin resistance. Activation of the Notch signaling pathway promotes the proliferation and differentiation of pancreatic β-cells, increasing their number and improving insulin synthesis and secretion. Additionally, the Notch signaling pathway regulates glucose uptake and utilization and affects insulin sensitivity and resistance. Scutellaria baicalensis Lian Tang has therapeutic effects on diabetes by regulating glucose levels, modulating dysregulated Notch signaling, and regulating the gut microbiota[27].

Additionally, other metabolites produced by gut microbiota, such as imidazole propionate (a product of histidine metabolism in the gut flora), affect glucose metabolism through the mTORC1 signaling pathway, which is also related to host T2DM metabolism. However, due to limited space in this paper, we have provided less description on this topic. We look forward to the progress of subsequent studies.

4. Conclusion

Research has demonstrated a correlation between alterations in the composition and function of intestinal flora and the onset of T2DM. A decrease in gut flora metabolites, including butyric acid, is frequently observed in T2DM and is believed to be a primary contributing factor. Additionally, the gut microbiota may serve as both a diagnostic biomarker and a potential therapeutic target for T2DM. Targeting the relevant signaling pathways can significantly improve the symptoms of type 2 diabetes and its complications. Therefore, it is important to strengthen research on the metabolites of intestinal flora and their related host signaling pathways and to explore the molecular mechanisms of their development. This will lay the foundation for more effective therapeutic options and improve the quality of life of patients.

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