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Review of the Interaction between Gut Microbiota and IL-17 in Diabetic Immune Inflammation

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Abstract: ***The association between gut microbiota and host health has been increasingly recognized as research in this field progresses. This review is centered on the gut microbiome and its interplay with IL-17 in diabetes-associated immunoinflammatory disorders. Through a comprehensive examination of the composition, functional properties, and host-modulatory roles of gut microbiota, an analysis is conducted to elucidate how microbiota-derived perturbations are linked to IL-17 expression. The potential implications of this regulatory mechanism for the pathogenesis of diabetic immunoinflammatory conditions are further emphasized. These findings collectively demonstrate the bidirectional relationship between gut microbiota dynamics and IL-17-mediated inflammatory pathways, offering translational implications for diabetes immunotherapy development.***

Keywords: Diabetes, Gut microbiota, IL-17, Short chain fatty acids**.**

1. Introduction

The development of numerous diseases is attributed not only to genetic predisposition and lifestyle factors but also to the homeostasis of microbial ecosystems, particularly the gut microbiota. Recognized as the largest microbial reservoir in humans, the gut microbiota is intricately linked to host health through bidirectional interactions. In this field, research on gut microbiota has been extensively investigated, with particular emphasis placed on its interplay with host immune-inflammatory pathways. According to epidemiological data from the International Diabetes Federation (IDF), 536.6 million adults aged 20-79 years (representing 10.5% of the global population) were affected by diabetes in 2021, establishing it as a critical public health challenge [1]. Notably, the pathogenesis of diabetes mellitus — a chronic inflammatory metabolic disorder with a persistently rising global incidence — has been demonstrated to be profoundly modulated by gut microbiota.

Recent advancements in gut microbiology and inflammatory disease research have provided a foundation for this review, with specific emphasis placed on the mechanistic role of IL-17 in diabetic pathogenesis. The structural and metabolic perturbations of gut microbial ecosystems are systematically examined to demonstrate their association with IL-17 expression, while parallel alterations in host-derived inflammatory mediators are further characterized. Through a synthesis of compositional changes observed in the intestinal microbiota of diabetic patients, the regulatory capacity of microbial communities over host immune responses is clarified. These insights are ultimately translated into novel therapeutic perspectives for diabetes prevention and clinical management.

In this review, a systematic analysis of literature retrieved from PubMed and CNKI was conducted. This methodological approach has contributed to the advancement of theoretical frameworks elucidating gut microbiota - immune - inflammatory disease interactions. Furthermore, evidence - based foundations have been established to support the development of microbiota-modulating strategies, early diagnostic and therapeutic interventions for diabetes mellitus, and personalized clinical applications.

2. Immunoinflammatory Damage in Diabetes

2.1 Pathogenesis of Diabetes

Diabetes mellitus is defined as a spectrum of heterogeneous metabolic disorders primarily characterized by chronic hyperglycemia, which is caused by defective insulin secretion, impaired insulin action, or a combination of both mechanisms [2]. The pathogenesis of this condition has been shown to involve multifactorial interactions among genetic predisposition, environmental triggers, and lifestyle determinants. Reduced insulin secretion is primarily caused by pancreatic β-cell damage or depletion, while insulin resistance — characterized by diminished tissue sensitivity to insulin — leads to persistent hyperglycemia due to inefficient cellular glucose uptake. Concurrently, the following pathological processes have been identified: (1) hyperglucagonemia development; (2) elevated insulin resistance in peripheral tissues and hepatic systems; (3) impaired intestinal proinsulin processing; (4) enhanced lipolysis leading to increased circulating free fatty acids; and (5) upregulated renal glucose reabsorption. These mechanisms have been observed to synergistically interact with dysfunctional β-cell insulin synthesis and secretion throughout disease progression, collectively driving sustained diabetic deterioration [3].

The contribution of gut microbial dysbiosis to metabolic disorders, including diabetes mellitus, has been well-characterized. As the largest microbial ecosystem in humans, the gut microbiota is known to be critically involved

in food digestion, nutrient absorption, and metabolic/immune regulation through host-microbe interactions. Dysbiosis has been shown to induce intestinal barrier dysfunction with elevated permeability, subsequently leading to endotoxemia development, chronic inflammation exacerbation, and ultimately metabolic pathologies such as obesity [4]. Furthermore, intestinal barrier function and metabolite production (e.g., short-chain fatty acids [SCFAs]) are regulated by gut microbiota, which directly maintains intestinal integrity while indirectly modulating glucose-lipid metabolism through hormone synthesis and insulin sensitivity — mechanisms central to diabetic pathogenesis. Recent evidence has demonstrated that fecal microbiota transplantation (FMT) can effectively enhance insulin sensitivity, restore microbial diversity, and promote SCFAs biosynthesis. Notably, variations in gut microbial composition have been identified as potential early diagnostic biomarkers for type 2 diabetes mellitus (T2DM) in high-risk populations [5].

2.2 The Link between Diabetes and Immune Inflammation

To advance the understanding of diabetic pathophysiology, the relationship between diabetes and immune-inflammatory mechanisms must be systematically elucidated. In diabetic patients, abnormal immune activation — particularly the sustained low-grade inflammatory state — has been strongly correlated with pancreatic β-cell injury. Insulin, a hormone critical for glucose homeostasis, is synthesized and secreted by β-cells to facilitate cellular glucose uptake and suppress hepatic glucose production [6]. During early-stage diabetes, β-cell dysfunction and damage have been observed to trigger glucose metabolism dysregulation, ultimately progressing to overt diabetes. Notably, in prediabetic states, altered activity of immune cell subsets (e.g., Th17 cells) has been documented, with evidence suggesting these cells mediate inflammatory cascades through cytokine networks that drive the production of IL-6, IL-1β, and IL-17. Elevated IL-17 levels, a hallmark of autoimmune responses, have been mechanistically linked to intensified islet autoimmunity. Specifically, IL-17 has been implicated in two principal immunopathological pathways of T2DM: NF-κB pathway initiation, and the induction of inflammation-mediated insulin resistance coupled with β-cell dysfunction [7]. Concurrently, tissue damage and β-cell failure are further exacerbated by multiple stress pathways — including oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, and impaired autophagy — which are induced by glucolipotoxicity, amyloid deposition, and exosome/non-coding RNA alterations within the diabetic microenvironment [8]. Furthermore, diabetes-associated complications, especially diabetes-associated fatty liver cirrhosis, is closely associated with IL-17A [9].

3. Overview of Gut Microbiota

3.1 Composition and Function of Gut Microbiota

Prior to exploring the intricate interplay between gut microbiota and diabetic inflammation, this review is initiated by an analysis of microbial diversity and their multifunctional contributions to host physiology. The mammalian microbiota — a dynamic ecosystem established during infancy — is composed of bacteria, archaea, fungi, and viruses. Its density and compositional gradients are observed across the gastrointestinal tract's microenvironmental and physicochemical barriers, with site-specific functional specializations being executed [10]. These microbial dynamics are influenced by genetic predisposition, aging processes, and dietary patterns. While the mechanistic propagation of localized intestinal inflammation to systemic autoimmunity remains incompletely characterized, the gut microbiota has been identified as a pivotal modulator of both glucose homeostasis and immune regulation. Alterations in microbial composition or spatial distribution have been linked to metabolic dysregulation — a phenomenon implicated in the pathophysiology of diabetes mellitus and its complications [11]. Collectively, this vast and intricate microbial consortium has been widely acknowledged as a critical determinant of host health maintenance.

Recent investigations into gut microbiota have been predominantly focused on gut bacteria, which comprise approximately 500-1,000 distinct species. These microbial populations, collectively weighing 1-2 kilograms and exceeding human somatic cell counts by an order of magnitude, are dominated by the Firmicutes (thick-walled bacteria) and Bacteroidetes phyla, while Actinobacteria, Proteobacteria, and Fusobacteria constitute other major taxonomic groups distributed throughout the gastrointestinal tract, forming an essential component of the intestinal barrier [12, 13]. The functional repertoire of gut microbiota has been demonstrated to include micronutrient biosynthesis, nutrient digestion/metabolism (particularly of indigestible dietary fibers), and hepatic bile acid biotransformation from primary to secondary forms. Furthermore, these microbial communities regulate metabolic pathways through hormone-like signaling mechanisms and are critically involved in maintaining host immunometabolic homeostasis [14]. For instance, host-microbiota interactions have been shown to modulate the activity of intestinal submucosal immune cells and influence the development of gut-associated lymphoid tissues. Conversely, compromised bacterial barrier function results in translocation of bacterial lipopolysaccharide (LPS), which is recognized by Toll-like receptors, thereby triggering inflammatory signaling cascades and pro-inflammatory cytokine release.

The potential influence of gut microbiota dynamics across the human lifespan on host metabolic status has been increasingly elucidated through rigorous investigation. For instance, the establishment of immune system function during neonatal development has been demonstrated to be closely associated with gut microbiome maturation. In adulthood, specific microbial compositional alterations have been linked to the pathogenesis of metabolic disorders, including obesity and T2DM.

3.2 Gut Microbiota in Relation to Host Health

The bidirectional relationship between the gut microbiome and human physiology has been increasingly elucidated through advances in life sciences research. The profound influence of gut microbiota on host health, particularly in metabolic regulation and immune modulation, has been

established as a central focus of contemporary medical investigations. Gut microbiota are not only implicated in fundamental physiological functions such as nutrient digestion and metabolic homeostasis, but their regulatory role in host immune responses is now recognized as a critical determinant of systemic health outcomes.

In healthy individuals, the gut microbial community is established during infancy, initially being predominantly colonized by Bifidobacterium and Enterobacteriaceae. This microbial consortium undergoes progressive diversification and stabilization throughout development, ultimately achieving a complex yet relatively stable state in adulthood. A dynamic equilibrium between microbial phyla is maintained, which contributes to intestinal microbial homeostasis [15, 16]. The gut microbiota is mechanistically linked to host protection through multiple pathways: bacterial translocation into systemic circulation is prevented through the integrity of the intestinal barrier and immunoglobulin-mediated pathogen neutralization, while immune regulation and colonization resistance against pathogens are simultaneously ensured [17,18]. Disruption of this equilibrium by exogenous factors has been associated with compositional shifts in gut microbiota, which may precipitate diverse pathologies including inflammatory bowel diseases, allergic conditions, and immune-mediated disorders. Furthermore, gut dysbiosis has been increasingly linked not only to gastrointestinal dysfunction but also to metabolic derangements such as obesity and diabetes mellitus. For instance, SCFAs — microbial metabolites derived from dietary fiber fermentation — have been observed to accumulate in obesity due to excessive caloric intake, whereas SCFAs absorption has been reported to be impaired in diabetic states [19,20]. Consequently, SCFAs have been recognized as critical mediators in gut microbiota-host interactions, warranting focused investigation to elucidate their role in health maintenance. Dietary fiber is incompletely digested by human gastrointestinal enzymes, with SCFAs — primarily acetate (C2), propionate (C3), and butyrate (C4) — being produced through microbial fermentation. Among these metabolites, acetate is utilized as a substrate for lipogenesis and gluconeogenesis, whereas propionate and butyrate are implicated in the regulation of intestinal physiology and immune responses [21]. SCFAs are efficiently absorbed by the intestinal epithelium, where they serve as a fundamental energy source. The residual fraction enters systemic circulation via the portal vein, contributing to systemic homeostasis through multiple mechanisms: hormonal secretion is modulated, immune cell maturation / differentiation is regulated, and immune-inflammatory pathways are activated. The immunomodulatory effects of SCFAs are mediated through two primary mechanisms: intracellularly, histone deacetylase (HDAC) activity is inhibited; extracellularly, signaling cascades are initiated through binding to specific receptors (e.g., G protein-coupled receptors) [22]. Experimental evidence has demonstrated that gut microbiota-derived SCFAs induce colonic regulatory T (Treg) cell differentiation, thereby maintaining intestinal homeostasis [23-25]. These metabolites differentially modulate cytokine production and T cell functionality. Notably, butyrate has been shown to exert potent immunoregulatory effects by enhancing IL-10 synthesis while suppressing IL-17 production in T lymphocytes, mechanisms that collectively modulate inflammatory processes [23].

Immune-inflammatory dysregulation in diabetes has been closely linked to alterations in gut microbial composition and SCFAs profiles. Compared with non-diabetic individuals, diabetic patients have been shown to exhibit reduced abundances of Bifidobacterium and Faecalibacterium prausnitzii (F. prausnitzii), along with diminished populations of butyrate-producing bacteria such as Roseburia intestinalis. In contrast, elevated levels of Lactobacillus gasseri have been consistently observed in these patients [26]. These findings suggest the existence of sophisticated interaction mechanisms between gut microbiota and diabetic inflammatory pathways, thereby establishing a robust foundation for further investigation into microbial-mediated immunomodulatory strategies for diabetes management.

Metabolic abnormalities induced by microbial dysbiosis, particularly reduced SCFAs concentrations, have been associated with an increased propensity for pro-inflammatory responses. These perturbations are characterized by immune system activation, leading to elevated production of inflammatory cytokines such as IL-17, which has been implicated in the exacerbation of immune-inflammatory pathways in diabetes mellitus and related disorders. To address gut microbiota imbalance across disease states, therapeutic strategies involving dietary modulation have been explored. The composition of gut microbiota can be modified through rationally designed interventions, including high-fiber diets to promote probiotic proliferation, as well as prebiotic and probiotic supplementation. These approaches have been demonstrated to restore microbial equilibrium, enhance SCFAs biosynthesis, modulate immune reactivity, and improve glycemic control in diabetic patients [27].

In conclusion, human health status has been shown to be profoundly influenced by gut microbiota through intricate host-microbe interactions. The involvement of these microbial communities in diabetes-associated immune-inflammatory pathways has been increasingly recognized. These findings have provided novel therapeutic approaches for chronic metabolic disease management, ultimately establishing gut microbiota as a pivotal target for innovative disease interventions.

4. Role of IL-17 in Immunity

4.1 IL-17 Family and Signaling Pathways

The IL-17 family is recognized as a critical group of immunoregulatory cytokines through which downstream signaling pathways associated with host defense, inflammatory processes, and autoimmune pathologies are activated. In mammalian systems, this family has been identified to comprise six members (IL-17A to IL-17F), with IL-17A and IL-17F exhibiting the highest sequence homology [28-30]. These two isoforms have been specifically implicated in mediating immune-inflammatory responses during diabetic pathogenesis.

The IL-17 family has been demonstrated to activate critical signaling pathways — including NF-κB, MAPK, and C/EBP — through receptor binding, which are recognized as central regulators of immune defense and inflammatory homeostasis [29, 31, 32]. Mechanistically, NF-κB activator 1 (Act1) is

recruited via the SEF/IL17 receptor (SEFIR) domain of IL-17 receptors, followed by subsequent ubiquitination of tumor necrosis factor receptor-associated factor 6 (TRAF6). This cascade is ultimately responsible for the activation of NF-κB signaling pathways, leading to transcriptional upregulation of pro-inflammatory genes [33]. These molecular events have been shown to mediate inflammatory cell recruitment and activation, thereby amplifying immune responses through enhanced cytokine release at inflammatory sites.

4.2 IL-17 and Inflammatory Diseases

IL-17 (also designated IL-17A), initially characterized as a product of the herpesvirus saimiri open reading frame, was recognized as the founding member of the IL-17 cytokine family and has been extensively implicated in inflammatory pathologies due to its potent pro-inflammatory properties [34,35]. Production of IL-17 is predominantly mediated by Th17, though it is also secreted by γδ T cells, lymphoid tissue-inducing cells (LTi), type 3 innate lymphoid cells (ILC3s), and natural killer T (NKT) cells, reflecting its indispensable role in antimicrobial defense and immune regulation [36]. Under physiological conditions, IL-17 expression is restricted to barrier tissues, where it is required for microbiota homeostasis and infection resistance [37]. However, pathogen invasion through epithelial barriers has been shown to induce hyperactivation of IL-17 signaling pathways. This cascade triggers the synthesis of effector molecules (e.g., cytokines/chemokines) by target cells, which are essential for inflammatory response initiation and pathogen clearance. Notably, these mechanisms have been demonstrated to critically enhance host antimicrobial capacity during infection.

The potent immunomodulatory effects mediated by IL-17 are recognized to exert dual physiological roles. When dysregulated in expression or activated within ectopic tissues, autoimmune disorders and chronic inflammatory conditions are frequently initiated or exacerbated. Elevated IL-17 levels have been robustly correlated with pathological progression across multiple autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, psoriasis, and inflammatory bowel disease, as well as oncogenic processes [38-41]. In these pathological contexts, IL-17 has been demonstrated to not only amplify inflammatory cascades but also potentiate autoimmune responses, resulting in irreversible tissue damage and compromised regenerative capacity.

Diabetes mellitus, a metabolic disorder, has conventionally been attributed to β-cell dysfunction and insulin resistance (IR) driven by chronic inflammation, with the regulatory role of IL-17 in immune-inflammatory responses being well-documented [7]. Pathogenic effects mediated by IL-17-secreting Th17 cells have been demonstrated to involve the stimulation of pro-inflammatory cytokines/chemokines, recruitment and activation of immune cells, and suppression of immune tolerance through functional inhibition of Treg cells [42]. Under physiological conditions, a dynamic equilibrium between Treg and Th17 cells is maintained. However, exposure to pro-inflammatory cytokines (e.g., TGF-β, IL-1β, IL-6) has been shown to disrupt this balance, favoring Th17 cell dominance [43]. In diabetic states, this immune-inflammatory dysregulation is exacerbated, resulting in amplified Th17 differentiation and IL-17 overproduction. These pathological changes have been linked to pancreatic islet dysfunction, inflammatory infiltration, and disease progression. Emerging clinical evidence further indicates that IL-17 expression is elevated in both α- and β-cells isolated from T1D and T2D patients, with significantly higher levels observed in T2D cohorts. This cellular source of IL-17 has been proposed as a novel mechanism underlying its pathogenic role in diabetes [44].

The specific roles of IL-17 family members in inflammatory responses have been proposed as potential therapeutic targets. Through targeted modulation of IL-17 activation, its upstream differentiation factors, and associated signaling pathways, the maintenance of chronic inflammatory states may be reduced, thereby decelerating or reversing immune-mediated inflammatory progression in diabetes mellitus. Although therapeutic strategies targeting IL-17 have been successfully implemented in certain autoimmune disorders, their application in diabetes management remains investigational. Further clinical trials and experimental validation are required to establish efficacy and safety in this context.

5. Association of Gut Microbiota with IL-17 in Diabetes Mellitus

5.1 Effects of Gut Microbiota on IL-17 Expression

In recent years, the modulation of immune cells by gut microbiota and their metabolites (e.g., SCFAs) has been extensively investigated in the context of immune - inflammatory diseases. Dendritic cells (innate immunity) and conventional T lymphocytes (adaptive immunity) have been identified as key cellular targets, with particular emphasis placed on IL-17 expression regulation. However, the precise mechanisms through which these microbial components interact with the host immune system remain to be fully elucidated.

Gut microbiota, the resident microbial communities in the gastrointestinal tract, have been identified as physiological regulators of IL-17 production and function [45]. SCFAs have been demonstrated to enhance IL-10 secretion by Treg cells in the intestinal milieu while suppressing IL-17 production by γδ T cells in the spinal cord [46]. Furthermore, inhibition of IL-17 synthesis by cecal T cells has been attributed to gut microbiota activity, with microbial metabolites such as propionic acid directly shown to downregulate IL-17 and IL-22 production in γδ T cells [47]. Additionally, microbiota-derived SCFAs have been found to modulate the Treg/Th17 equilibrium through suppression of Th17 cell differentiation, thereby reducing IL-17 biosynthesis and secretion [48]. These findings collectively elucidate mechanistic pathways through which SCFAs regulate intestinal T-cell functionality, particularly their capacity to govern IL-17 expression dynamics.

A reciprocal relationship between gut microbial homeostasis and IL-17 expression has been established: balanced microbial communities are associated with physiological IL-17 regulation, whereas dysbiosis is linked to microbiota disruption. Under such imbalanced conditions, IL-17 production is upregulated through host immune

hyperactivation, exacerbating inflammatory cascades. These observations have laid the foundation for therapeutic strategies aimed at elucidating microbiota-IL-17 crosstalk. Through targeted restoration of microbial equilibrium in diabetic populations, inflammatory responses may be mitigated by modulating IL-17-mediated pathways.

5.2 Interaction of Gut Microbiota, IL-17 and Diabetes Mellitus

The interplay between gut microbiota and the IL-17 signaling pathway has been closely linked to host immune regulation and diabetes pathogenesis. IL-17A has been demonstrated to mediate protective immune responses against both commensal and pathogenic gut bacteria, thereby shaping microbial community composition [45, 49]. However, its excessive activation has been associated with disruption of gastrointestinal microbial homeostasis. Concurrently, IL-17 induction has been predominantly attributed to gut microbiota activity. Th17 cells have been observed to be enriched in gut-associated lymphoid tissues, particularly within the small intestinal lamina propria (SI-LP). Notably, intestinal Th17 cell development has been shown to depend on microbial composition, with segmented filamentous bacteria (SFB) proposed to drive Th17 differentiation and IL-17 synthesis through signaling mechanisms independent of TLR, NOD, and ATP pathways [50]. Under physiological conditions, the gut microbiota-IL-17 axis has been shown to mutually regulate immune homeostasis. Conversely, in metabolic disorders such as obesity, insulin resistance, or diabetes mellitus, persistent immune-inflammatory states have been associated with microbial dysbiosis characterized by pro-inflammatory strain dominance and anti-inflammatory species depletion. This dysregulation has been implicated in IL-17 pathway activation, which exacerbates glucolipid metabolic dysfunction and perpetuates inflammatory cascades [51,52]. Type 2 diabetes mellitus (T2DM) is pathologically associated with a systemic inflammatory state characterized by upregulation of pro-inflammatory immune cells, suppression of anti-inflammatory immune populations, and elevated pro-inflammatory cytokine levels across circulatory, adipose, hepatic, and pancreatic tissues. This condition has been consistently linked to significant gut microbiota dysbiosis [53]. The relationship between gut microbiota composition and T2DM-associated metabolic markers — including fasting blood glucose and serum IL-17 levels — has been experimentally confirmed in murine models [54]. Furthermore, targeted activation of the IL-17 signaling pathway has been demonstrated to restore microbial equilibrium in metabolic syndrome models while inducing neutrophil recruitment to the intestinal mucosa. This dual mechanism has been shown to mitigate pathological consequences of hyperglycemia, dyslipidemia, hyperinsulinemia, and insulin resistance [55].

6. Conclusion

The structural composition of gut microbial communities has been established as a critical determinant in diabetes-associated inflammatory responses. The host immune system is modulated by gut microbiota through diverse mechanisms, including the regulation of IL-17 expression — a process directly implicated in diabetic immunoinflammatory pathology. Furthermore, a significant correlation has been demonstrated between IL-17 (a pivotal mediator of inflammatory signaling) and gut microbial interactions, particularly their coordinated influence on the activation of inflammatory pathways in diabetes mellitus.

The interplay between gut microbiota and diabetes mellitus has been increasingly elucidated through modern scientific inquiry. In this review, the mechanisms through which gut microbial perturbations and elevated IL-17 levels influence diabetic pathogenesis have been systematically examined from an immunoinflammatory perspective, with particular emphasis on microbe-host crosstalk networks. Furthermore, the complex relationship linking gut microbiota dynamics, IL-17 regulation, and diabetes progression has been delineated. These insights provide novel perspectives for deciphering inflammatory mechanisms underlying diabetes and developing targeted interventions against immune-inflammatory pathways in diabetic pathology.

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