

Review

The GLP-1–Gut Microbiota–Autoimmunity Axis in Type 1 Diabetes: Emerging Evidence and Mechanistic Perspectives

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Abstract

Type 1 diabetes (T1D) is an autoimmune disease in which genetic susceptibility interacts with environmental and immunometabolic factors. Growing evidence implicates gut dysbiosis, impaired intestinal barrier integrity, and altered microbial metabolites in the loss of immune tolerance and β -cell autoimmunity. Microbiota-derived metabolites regulate enteroendocrine glucagon-like peptide-1 (GLP-1) secretion, epithelial barrier function, and immune responses. Conversely, GLP-1 signaling and incretin-based therapies may modify the intestinal environment and microbial composition. Overall, the GLP-1–gut microbiota axis is a promising therapeutic target. Activation of the GLP-1 receptor suppresses pro-inflammatory pathways while promoting anti-inflammatory ones; all these effects may protect β -cells. Caveolin-1 may represent a molecular hub linking the GLP-1–gut microbiota–autoimmunity axis in T1D. This narrative review examines the bidirectional relationship between GLP-1 signaling and the gut microbiota and its potential relevance to T1D.

Keywords: type 1 diabetes; gut microbiota; GLP-1; autoimmunity; SCFA; incretins; immune regulation; caveolin-1; beta-cell preservation

1. Introduction

Type 1 diabetes (T1D) is an autoimmune disease characterized by immune-mediated destruction of pancreatic β -cells, leading to insulin deficiency and chronic hyperglycemia [1]. Although T-cell destruction of pancreatic β -cells is central in T1D pathogenesis, its precise etiology remains unclear [1]. Disease development is currently considered multifactorial and results from a complex interaction between genetic susceptibility, environmental factors, metabolic alterations, and immune dysregulation [1]. The global incidence of T1D is rising, especially in children and young adults, suggesting that early-life exposure to environmental factors plays a crucial role in triggering autoimmune responses in genetically predisposed individuals [1,2]. Among these environmental factors, the gut microbiota has emerged as a key regulator in maintaining immune homeostasis [3]. Conversely, gut dysbiosis has been associated with impaired barrier function and aberrant immune cell activation [4].



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Glucagon-like peptide-1 (GLP-1) is an incretin hormone that regulates glucose homeostasis primarily by enhancing glucose-dependent insulin secretion and suppressing glucagon release [5,6]. The broad expression of the GLP-1 receptor (GLP-1R), extending from the pancreas to immune cells and other tissues, reflects the pleiotropic nature of GLP-1 signaling and suggests a link between metabolism and immunity [7]. Several studies have shown a bidirectional relationship between the gut microbiota and GLP-1. On one hand, the microbiota modulates the response to GLP-1 receptor agonists (GLP-1RAs) and, on the other hand, GLP-1 may affect gut microbiota composition [8]. Interestingly, gut microbiota may influence both GLP-1 secretion and immune regulation, leading to the concept of a GLP-1–gut microbiota axis, which may contribute to the regulation of both metabolic and immune homeostasis [7,9]. Considering that the microbiota is altered in T1D, and that the gut microbiota influences both GLP-1 secretion and immune regulation, targeting the GLP-1–gut microbiota axis may represent a novel therapeutic strategy to modulate autoimmunity and disease progression [7,10].

The therapeutic efficacy of GLP-1RAs is well established in type 2 diabetes (T2D), whereas their relevance in T1D remains unclear [10,11]. This narrative review provides an updated overview of the current evidence on the bidirectional relationship between GLP-1 signaling and the gut microbiota, with particular emphasis on the potential mechanisms through which the GLP-1–microbiota axis may influence immune regulation, β -cell preservation, and the development and progression of autoimmunity in T1D.

2. Materials and Methods

We conducted a literature search in the PubMed database to identify studies addressing the relationships among T1D, gut microbiota, incretin signaling, and immune regulation. The following keywords and their combinations were used: type 1 diabetes mellitus, T1DM, type 1 diabetes, T1D, gut microbiota, autoimmunity, immune system, GIP, glucose-dependent insulintropic polypeptide, GLP-1, glucagon-like peptide-1. We collected scientific articles, including case reports, original articles, reviews, systematic reviews, meta-analyses, guidelines, and consensus statements published in the English language from 1975 to June 2026. We eliminated duplicates, non-English articles, and publications not relevant to the scope of the review.

We selected studies according to their relevance to the GLP-1–gut microbiota–immune axis and their potential implications for T1D. When available, priority was given to human evidence (longitudinal cohort studies, randomized controlled trials, systematic reviews, and meta-analyses). In addition, evidence from individuals with T2D, obesity, or other metabolic conditions was used when it provided information on biological mechanisms potentially applicable to the GLP-1–microbiota axis. Given the limited availability of human studies directly addressing this interaction in T1D, preclinical animal studies and in vitro or molecular mechanistic studies were also included. These preclinical findings were interpreted as mechanistic support and were not considered direct evidence of efficacy or disease modification in human T1D.

3. GLP-1 Biology

GLP-1 was first identified and characterized in the early 1980s as a product of the proglucagon gene [5,12], which is expressed in the pancreas, intestine, and brain. The post-translational processing of proglucagon depends on the tissue-specific expression of prohormone convertase (PC) isoforms, which generate different peptides [13]. In pancreatic α -cells, the expression of isoform PC2 leads to the synthesis of glucagon, whereas the expression of isoform PC1/3 in intestinal and specific neuronal populations processes

proglucagon into GLP-1 together with glicentin, oxyntomodulin, glucagon-like peptide-2 (GLP-2), and other biologically active peptides [13].

The best-known effect of GLP-1 is to enhance glucose-dependent insulin secretion from pancreatic β -cells and suppress glucagon release from α -cells [6]. Due to its ability to stimulate insulin secretion in the presence of hyperglycemia, it was defined as an incretin hormone.

The majority of circulating GLP-1 is produced by the intestinal L cells, epithelial endocrine cells (EECs), which are located in the distal ileum and colon [14]. Although the selective cleavage of proglucagon in L-cells produces two biologically active forms, GLP-1(7–37) and GLP-1(7–36)NH₂, released in response to food ingestion of GLP-1, GLP-1(7–36)NH₂ represents the majority of circulating GLP-1 in humans [15]. Once released into the circulation, GLP-1 is rapidly inactivated by the ubiquitous proteolytic enzyme dipeptidyl peptidase-4 (DPP-4), that cleaves GLP-1 at the N-terminal (GLP-1 9–36) [16]. Consequently, native GLP-1 has a half-life of less than 2 min in the circulation [17].

GLP-1 release is regulated differently in EECs and preproglucagon-expressing neurons of the nucleus tractus solitarius, and its magnitude is correlated with the rate of gastric emptying [18,19]. In EECs, GLP-1 secretion is triggered by nutrients derived from food ingestion [20]: glucose uptake by the sodium-coupled glucose transporters leads to membrane depolarization, with consequent opening of the voltage-gated Ca²⁺ channels and exocytosis of GLP-1 vesicles. However, studies in vitro demonstrated that chronic high levels of glucose may affect viability, function, and insulin sensitivity of the GLP-1 secreting cells [21]. At the central level, GLP-1 is secreted by the preproglucagon-expressing neurons in response to peripheral metabolic, inflammatory, and gastrointestinal signals transmitted through vagal afferents [19,22]. Peripheral GLP-1 released by intestinal EECs may activate vagal afferents and thereby modulate preproglucagon neurons in the brain, potentially contributing to central GLP-1 signaling [23]. This supports an integrated gut–brain GLP-1 axis that coordinates gastrointestinal signals with energy balance, appetite, gastric emptying, and glucose homeostasis.

The biological effects of GLP-1 are mediated through binding to its specific receptor, GLP-1R, a G protein-coupled receptor characterized by seven transmembrane domains, widely expressed in several tissues, including the endocrine pancreas, gastrointestinal tract, brain, heart, kidney, and immune cells, highlighting the pleiotropic nature of GLP-1 signaling [24]. Activation of GLP-1R is regulated by trafficking [25]. Upon stimulation, GLP-1R internalizes through both a clathrin-dependent and a caveolin-dependent mechanism and may finally be recycled [25]. At the cellular level, GLP-1R localizes in caveolae, specialized cholesterol-rich invagination of the plasma membrane involved in regulating receptor trafficking and in assembling signaling complexes [26]. Consequently, the coordination of the intracellular pathways activated by GLP-1R depends on the assembly of different downstream effectors and is regulated by caveolin-1, the principal component of caveolae [27].

Upon ligand binding, GLP-1R primarily couples to the stimulatory G protein (G α s), leading to activation of adenylyl cyclase, increased intracellular cyclic AMP (cAMP) production, and subsequent activation of protein kinase A (PKA) as well as exchange protein directly activated by cAMP (EPAC) [28,29]. These events lead to insulin granule exocytosis, improved β -cell function, regulation of cellular metabolism, and protection from hyperglycemic damage [30–32]. In addition, GLP-1R can recruit β -arrestins, which regulate receptor desensitization and endocytosis while activating alternative signaling cascades, such as extracellular signal-regulated kinase 1/2 (ERK1/2), phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), and mitogen-activated protein kinase (MAPK) pathways [33]. These pathways contribute to insulin secretion, β -cell function, cellular metabolism, survival, proliferation, and mitochondrial function.

The metabolic effects of GLP-1 extend beyond glucose homeostasis and include delaying gastric emptying and reducing appetite [34]. These effects led to the development of long-acting GLP-1RAs resistant to DPP-4 cleavage for the treatment of T2D [11,35]. Cardiovascular, renal, neuroprotective, anti-inflammatory, and cytoprotective actions have also increased interest in the relationship between GLP-1 signaling, immune regulation, and host-microbiota interactions [5,36,37].

4. Gut Microbiota in T1D

Among the environmental factors involved in T1D initiation and progression, the gut microbiota has emerged as a potential modulator of immune tolerance and autoimmunity [38]. Its composition is influenced by host genetics, diet, geographical location, environmental exposures, pet ownership, health status, and medications such as antibiotics, anti-inflammatory drugs, and immunosuppressive therapies [39].

Metagenomic analyses of individuals with T1D have consistently revealed a dysbiotic gut profile marked by diminished microbial diversity, a loss of butyrate-producing bacteria, notably *Faecalibacterium prausnitzii* and *Roseburia*, and an overrepresentation of pro-inflammatory species [40]. Similar findings have been reported in pediatric and adult populations [40–44].

The gut microbiota contributes to immune homeostasis through continuous interaction with the intestinal barrier and mucosal immune system [45]. Commensal bacteria contribute to immune tolerance through multiple, interconnected mechanisms. Microbial-derived signals and metabolites promote the differentiation and expansion of regulatory T cells (Tregs), which suppress excessive inflammatory responses and help maintain mucosal immune homeostasis [46]. At the same time, commensal microorganisms reinforce epithelial barrier function and regulate innate immune signaling through pattern-recognition pathways [45], thereby limiting inappropriate immune activation. Together, these mechanisms maintain intestinal immune homeostasis and may reduce the likelihood of aberrant immune responses against host antigens. Dysbiosis may disrupt intestinal barrier integrity, leading to increased intestinal permeability, commonly referred to as “leaky gut”. This impaired barrier function may facilitate the translocation of microbial products, such as lipopolysaccharides (LPS), from the intestinal lumen into the systemic circulation. These microbial signals can subsequently activate innate and adaptive immune pathways, thereby contributing to chronic low-grade systemic inflammation [4]. These observations support the existence of a gut-immune-islet axis, whereby alterations in gut microbial composition and intestinal barrier function influence systemic immune responses and pancreatic β -cell autoimmunity. This combination of impaired immune regulation and enhanced systemic inflammation may ultimately favor autoimmune responses directed against pancreatic β -cells.

Most evidence supporting a direct role of the microbiome in autoimmune diseases derives from animal models. Loss of gut barrier integrity in transgenic mice carrying a T-cell receptor specific for a β -cell autoantigen triggers the activation of islet-reactive T cells within the gut mucosa and the onset of autoimmune diabetes, in a process dependent on the presence of commensal microbiota [4]. Germ-free mouse models have shown that the absence of microbial colonization leads to immune defects, including a marked reduction in colonic ROR γ t⁺ (retinoic acid receptor-related orphan receptor γ t) peripheral Tregs and an expansion of invariant natural killer T (iNKT) cells [47]. Microbial reconstitution restores normal immune cell populations only when performed during the neonatal period, but not in adulthood, highlighting the existence of a critical early-life window during which microbial signals are essential for the proper development of immune tolerance [2].

Molecular mimicry between microbial antigens and pancreatic islet antigens has also been proposed as a potential trigger of islet autoimmunity [48]. Certain gut microbes produce peptides that resemble pancreatic β -cell autoantigens, potentially triggering cross-reactive T-cell responses through molecular mimicry. For example, a peptide derived from *Parabacteroides distasonis* shares homology with the insulin B-chain epitope insB:9–23 and can activate insulin-reactive T cells, suggesting a potential link between gut microbial antigens and β -cell autoimmunity [49].

The immune system recognizes these microbial peptides and activates peptide-specific T lymphocytes. Due to their structural similarity, these activated T cells can cross-react against β -cell antigens, leading to the development of islet autoantibodies and the expansion of autoreactive T-cell populations. Over time, the resulting autoimmune process contributes to β -cell destruction and the onset of T1D [50].

Further support for this hypothesis comes from longitudinal population-based investigations. Within the DIABIMMUNE cohort, the presence of microbiota producing the hprt4–18 peptide was associated with a significantly increased risk of seroconversion, defined as the emergence of at least two islet autoantibodies [51]. Beyond insulin and its immunodominant insB:9–23 epitope, several additional β -cell autoantigens, including GAD (glutamic acid decarboxylase), IA-2 (islet cell antigen 2), zinc transporter 8 (ZnT8), and hybrid insulin peptides (HIPs), have been implicated as potential targets of microbial mimicry and subsequent cross-reactive immune reaction [52].

Experimental manipulation of the gut microbiota through antibiotics, probiotics, dietary interventions, and fecal microbiota transplantation has been shown to modify autoimmune responses, delay diabetes onset, and reduce disease incidence in several animal models, whereas evidence in humans remains limited and largely exploratory [53,54]. Although substantial progress has been made in understanding the role of the gut microbiota in T1D, the causal links between dysbiosis and disease onset remain incompletely defined. While the gut–immune–islet axis is increasingly recognized as a key contributor to disease pathogenesis, microbiota-targeted therapies are still considered experimental [55,56].

5. Microbiota-Derived Metabolites and Immune Regulation

The risk of islet autoimmunity is affected by several factors, including diet, infections, antibiotic exposure, and microbiome maturation [57]. The gut microbiome can affect T cell development, differentiation, activation, and exhaustion by producing metabolites that are sensed by host cells, thus acting as potent regulators of T cell function [58]. Microbiota-derived metabolites are small molecules produced by intestinal microorganisms through the fermentation of dietary components or the transformation of host-derived substrates [59,60]. Over the last decade, they have emerged as key mediators of communication between the gut microbiota and the immune system, therefore connecting nutrition, intestinal microbes, and the immune system [61]. Interestingly, many of these metabolites act as molecular messengers entering the circulation and influencing immune responses both locally and systemically [62,63]. The major microbiota-derived metabolites involved in immune regulation are short-chain fatty acids (SCFAs), tryptophan metabolites, and secondary bile acids.

5.1. Short-Chain Fatty Acids (SCFAs)

SCFAs are organic fatty acids produced in the distal gut through fermentation of macrofibreous material, such as dietary fiber, sugars, unabsorbed or undigested proteins, and endogenous substrates, like mucus and other secretions [64], which reach the colon by escaping gastrointestinal digestion. SCFAs are mainly produced in the colon, where the microbial concentration is higher, by members of the phyla Firmicutes and Bacteroidetes [65].

Interestingly, the rate and ratio of SCFA production are influenced by diet: increased SCFA production is favored by ingestion of fermentable dietary fibers, whereas a high-fat diet (HFD) reduces the formation of SCFAs [66]. Acetate, propionate, and butyrate account for approximately 90–95% of colonic SCFAs [67]. Propionate and acetate are mainly produced by fermentation of dietary fibers, whereas butyrate is also generated through cross-feeding and transformation of other SCFAs [68]. Despite the intraluminal concentrations of acetate reaching around 60%, the major energy source for the colonic epithelium is constituted by butyrate, which is oxidized at a higher rate than acetate and propionate [69]. On the contrary, propionate enters the portal circulation and is primarily utilized in gluconeogenesis in the liver, whereas acetate enters systemic circulation and reaches peripheral tissues [67]. SCFAs are predominantly absorbed via a facilitated process involving transmembrane transport proteins such as monocarboxylate transporters: MCT1 and MCT4 [70].

The metabolic and immunoregulatory effects of SCFAs have been mainly investigated in diabetes. It has been shown that children with T1D have lower levels of fecal butyrate and acetate [40], whereas increased SCFA production has been associated with improved glycaemic control in both T2D and T1D [71,72]. Interestingly, in patients with T1D, the increased concentrations of SCFAs were also associated with changes in systemic immune activity [72]. Beyond providing an energy source for colonocytes, SCFAs have a significant impact on intestinal homeostasis and immune regulation [73]. Following absorption, the action of SCFAs may be mediated by two main mechanisms: interactions with G-protein-coupled receptors (GPCRs) or acting as histone deacetylase (HDAC) inhibitors [74,75]. Through these mechanisms, SCFAs contribute to preserving intestinal homeostasis, by reducing intestinal permeability, microbial translocation, and chronic inflammation, as well as protecting against a wide range of metabolic, inflammatory, and immune-mediated diseases [72,74,75]. Interaction of SCFAs with GPCRs results in induction of anti-inflammatory responses through modulation of cytokine levels [76,77]. On the contrary, inhibition of HDACs leads to promotion of expression of genes involved in cellular protection, regulatory T-cell differentiation, cell metabolism regulation, epithelial barrier maintenance, improvement of antioxidant defenses, and suppression of several pro-inflammatory pathways [78,79].

It is well known that gut microbiota play a central role in maintaining intestinal barrier function [80,81]. The presence of epithelial cells, tight junction proteins, and intestinal secretions in the intestinal epithelial barrier prevents passage of luminal substances and antigens through the paracellular space [82]. Therefore, its integrity is essential for the maintenance of normal intestinal function, whereas its dysfunction is associated with a variety of gastrointestinal diseases. SCFAs contribute to preserving the integrity of the epithelial barrier by regulating the expression and localization of the tight junction (TJ) proteins [72] and stimulating goblet cells to produce and secrete mucus and antimicrobial peptides [83]. In particular, butyrate has been shown to strengthen epithelial barrier function and to reduce intestinal permeability by enhancing the expression of tight junction proteins, including occludin, claudins, and zonula occludens-1 (ZO-1), mainly through the activation of adenosine monophosphate (AMP)-kinase (AMPK) pathways [84,85].

Moreover, SCFAs may contribute to promoting immune tolerance by modulating the balance between Tregs and macrophages, and suppressing inflammatory responses [76,78,86]. Tregs are a specialized subpopulation of T cells that modulate immune responses, characterized by the expression of the transcription factor Foxp3 [87]. They play a central role in maintaining immune homeostasis, especially tolerance to self-antigens, through the production of anti-inflammatory cytokines such as interleukin-10 (IL-10), TGF- β , and IL-35 [88]. The imbalance between Tregs and Th17 cells is implicated in autoimmune diseases, including T1D [89]. Interestingly, butyrate promotes Treg differentiation by en-

hancing histone H3 acetylation at the Foxp3 promoter [86,90], while inhibiting Th17 cell differentiation [91], therefore favoring regulatory T cells that produce anti-inflammatory IL-10. Moreover, administration of butyrate reduces Th17 cell frequencies in a mouse model of T1D [91]. In addition, SCFAs promote the release of IL-35, an anti-inflammatory cytokine able to reverse T1D in a non-obese diabetic mouse [92]. This evidence highlights the therapeutic relevance of SCFAs in the preservation of immune tolerance in T1D.

5.2. Tryptophan Metabolites

Tryptophan is an essential aromatic amino acid characterized by an indole group [93]. Under normal physiological conditions, most of tryptophan enters the gastrointestinal tract, where a small fraction is metabolized by microbiota, whereas the other is adsorbed and enters the portal circulation for hepatic metabolism [94,95]. In the intestine, tryptophan may be metabolized through 3 distinct pathways: (1) direct conversion into indole derivatives by gut microbiota; (2) the kynurenine pathway in immune and epithelial cells; and (3) the serotonin production pathway in enterochromaffin cells [95,96]. Besides direct transformation of Tryptophan, gut microbiota can also affect the two other pathways. As results, microbiota-derived tryptophan metabolites play an important role in immune homeostasis, as they serve as key molecular mediators between gut microbes and host signaling communication.

Several bacterial taxa, such as *Escherichia coli*, *Bacteroides* species, and *Lactobacillus* species, convert tryptophan into metabolites, which function as active ligands of the aryl hydrocarbon receptor (AHR) in epithelial and immune cells [94]. AHR is a ligand-activated transcriptional factor, expressed by intestinal epithelial cells, dendritic cells, macrophages, and T lymphocytes, that regulates immune cells by affecting intra- and intercellular signaling and cytokine secretion [97]. Consequently, activation of AHR by microbial tryptophan metabolites maintains intestinal homeostasis, as it promotes barrier integrity and epithelial regeneration, and induces immune cells to produce cytokines that support mucosal defense, tissue repair, and protection against pathogenic microorganisms [97].

In particular, indoles such as indole-3-aldehyde (IAld), indole-3-acetic acid (IAA), indole-3-propionic acid (IPA), and their acid derivatives have anti-inflammatory activity, which results in immune regulatory effects [98,99]. Once activated via an AHR-dependent mechanism, they exert anti-inflammatory and immunoregulatory effects, which include alleviation of inflammation caused by the innate immune response, regulation of intestinal homeostasis through expression of IL-22, IL-17, and increased expression of tight junctions and the anti-inflammatory mediator IL-10, induction of Treg cells, and prevention of Th17 cell polarization [65]. In addition, these metabolites can inhibit activation of antigen-presenting cells and restrict their ability to activate T cells [100,101]. Among the indole derivatives, IAA is considered one of the most important metabolites of tryptophan. It maintains epithelial homeostasis, enhances barrier function, and suppresses macrophage-mediated inflammatory responses, thereby inhibiting MCP-1-mediated migration [102–104]. Similarly, IPA reduces levels of pro-inflammatory cytokines and inhibits NF- κ B activation, whereas it upregulates expression of tight junction proteins [105]. Furthermore, melatonin, another bioactive molecule produced through the tryptophan metabolic pathway, acts by reducing the expression of components of the NOD-like receptor protein 3 (NLRP3) inflammasome, such as NLRP3, caspase-1, IL-1 β , and IL-18 [106].

5.3. Secondary Bile Acids

Bile acids (BAs) are cholesterol-derived natural surfactants, produced in the liver and released into the duodenum, which aid in eliminating cholesterol and increase intestinal permeability [107]. Primary BAs, including cholic acid (CA) and chenodeoxycholic acid

(CDCA), contribute to lipid absorption, antibacterial defense, glucose metabolism, and GLP-1 secretion [107]. Approximately 95% of BAs are reabsorbed in the small intestine and recirculated to the liver [108], where the remainder reaches the colon and is converted by various bacterial species, including *Clostridium*, *Bacteroides*, *Lactobacillus*, and *Eubacterium*, into secondary bile acids [108,109]. The most studied are deoxycholic acid (DCA), lithocholic acid (LCA), ursodeoxycholic acid (UDCA), and their derivatives.

Secondary BAs modulate innate and adaptive immune responses through multiple receptors, including the Farnesoid X Receptor (FXR) and the G protein-coupled bile acid receptor 1 (TGR5), which are expressed by intestinal epithelial cells, macrophages, dendritic cells, and other immune cells [110,111]. TGR5 activation promotes anti-inflammatory responses by inhibiting NF- κ B signaling and reducing the production of pro-inflammatory cytokines such as tumor necrosis factor α (TNF- α), IL-1 β , and IL-6. In a murine enteroendocrine cell line, activation of TGR5 promotes GLP-1 secretion [107]. Secondary bile acids also regulate macrophage polarization, favoring anti-inflammatory phenotypes and limiting excessive innate immune activation, while LCA and its derivatives enhance Treg differentiation while inhibiting Th17 cell differentiation [112]. Moreover, dysregulation of bile acid metabolism has been associated with autoimmune conditions, inflammatory bowel disease, obesity, and T2D [108].

6. Bidirectional Crosstalk Between the Gut Microbiota and GLP-1

The gut microbiota can influence GLP-1 secretion and activity, whereas GLP-1 signaling and incretin-based therapies can modify the intestinal environment and gut microbial composition [8,9,100–102].

6.1. Effects of the Gut Microbiota on GLP-1

The gut microbiota can modulate GLP-1 secretion, mainly through the production of bioactive metabolites, such as SCFAs and secondary bile acids (BAs), and the regulation of enteroendocrine L-cell function through microbial metabolites, such as 2-oleoyl glycerol (2-OG) and indole [113–116]. SCFAs stimulate GLP-1 release through G-protein-coupled receptor-dependent mechanisms [116–118]. In particular, activation of GPR43/FFAR2 (G-protein-coupled receptor 43/Free fatty acid receptor 2) in L cells increases GLP-1 secretion in the human and rat colon and terminal ileum [119] (Figure 1).

In GPR43 knockout mice, GLP-1 secretion does not occur [120], while in humans intravenous or rectal SCFA infusion has been demonstrated to increase GLP-1 secretion [121]. In parallel, human and animal studies indicate that the baseline composition of the gut microbiota may influence postprandial GLP-1 dynamics, supporting the concept that gut microbiota contributes to individual variability in intestinal hormone responsiveness [122,123].

Also, secondary BAs have a regulatory effect on GLP-1 secretion [124,125], activating the TGR5 on intestinal L cells to stimulate GLP-1 secretion [126,127] and FXR to inhibit GLP-1 secretion [118,128]. The gut microbiota may also affect L-cell differentiation, epithelial sensing, gut–brain communication, and local inflammatory responses [114,115,129]. Tryptophan-derived compounds may influence enteroendocrine cell maturation and function, whereas microbiota-derived hydrogen sulfide may impair host metabolism, at least in part through reduced GLP-1 levels [129,130].

Microbial composition may also influence the response to GLP-1RAs, particularly in patients with obesity and T2D [114]. In patients with T2D who exhibited varying responsiveness to GLP-1RA therapy, the composition of the gut microbiota differed significantly between responders and non-responders, highlighting how the gut microbiota signature can predict the efficacy of such drugs [131]. Prebiotic supplementation, probiotic administration, fecal microbiota transfer, and antibiotic-driven microbiota alteration have all

been associated with changes in GLP-1 secretion and function [117,132–135]. However, the available literature is heterogeneous, and further studies are needed to establish the effects and underlying mechanisms [8,114,136].

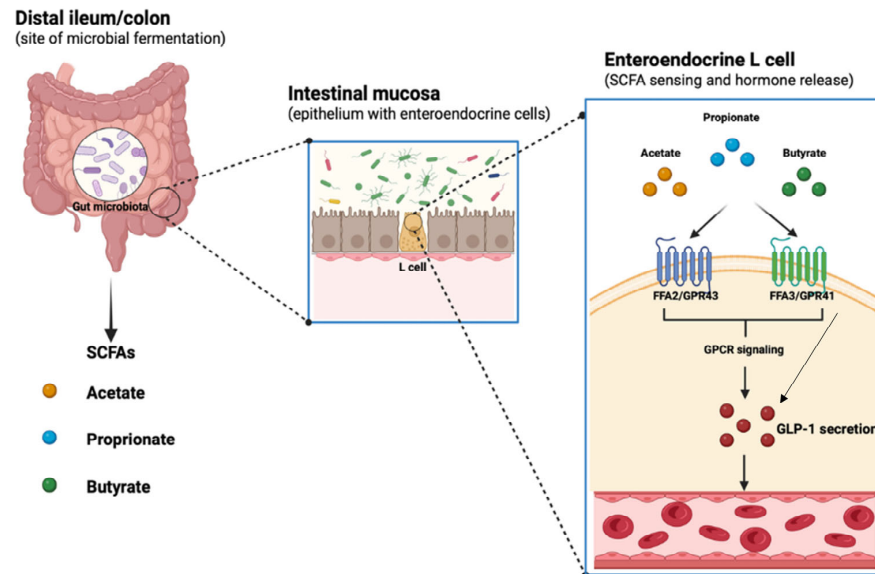


Figure 1. GLP-1 secretion by microbiota-derived metabolites. Microbiota-derived short-chain fatty acids (SCFAs) promote GLP-1 secretion through enteroendocrine L-cell signaling. Dietary substrates reaching the distal ileum and colon are metabolized by the gut microbiota, leading to the production of short-chain fatty acids, mainly acetate, propionate, and butyrate. SCFAs interact with G protein-coupled receptors (GPCRs) expressed on enteroendocrine L cells, including FFA2/GPR43 and FFA3/GPR41, thereby activating GPCR-dependent signaling and promoting GLP-1 secretion into the circulation. This mechanism represents one of the major pathways through which the gut microbiota may regulate host enteroendocrine function and contribute to the bidirectional GLP-1–gut microbiota axis. (created with BioRender).

6.2. Effects of GLP-1 Signaling and Incretin-Based Therapies on the Gut Microbiota

GLP-1 signaling may itself contribute to modifying the gut environment and, indirectly, the microbiota [136–139]. GLP-1RAs have been associated with changes in gut microbiota composition, including modifications in community structure, richness, diversity, and microbiome-related metabolic pathways [136–139]. Liraglutide may shift the microbiota from obesity-associated configurations toward profiles of improved metabolic status, involving some bacteria related to glucolipid metabolism and intestinal inflammation [137,138]. Preclinical studies suggest that both liraglutide and semaglutide may modulate the gut microbial structure in parallel with metabolic improvement [139]. GLP-1 signaling, thought to be a cAMP-dependent pathway, may affect the inflammatory responses: intestinal intraepithelial lymphocytes express GLP-1R, and exendin-4, a GLP-1RA, significantly inhibits inflammatory cytokines and macrophage infiltration [140]. Observed microbial changes may reflect direct effects of GLP-1 signaling on the intestinal environment, but they may also arise secondarily from reduced food intake, delayed gastric emptying, altered nutrient delivery to the distal gut, weight loss, improved glycemic control, or attenuation of intestinal inflammation [8,136].

Growing data indicate that GLP-1RAs and, in particular, the dual GIP/GLP-1 receptor agonist tirzepatide can partially restore gut microbial dysbiosis [141]. In experimental models, tirzepatide increased beneficial taxa, particularly *Akkermansia*, and reduced bacteria associated with obesity and metabolic dysfunction, such as *Erysipelatoclostridium* [141]. These microbial changes were accompanied by improvements in intestinal barrier integrity, bile acid metabolism, insulin resistance, hepatic steatosis, and liver injury. Importantly,

depletion of the gut microbiota with broad-spectrum antibiotics markedly attenuated the beneficial hepatic effects of tirzepatide, suggesting that an intact microbiota is required for the full therapeutic response [141]. Additional evidence indicates that these microbiota-mediated effects may extend to the restoration of intestinal homeostasis. In a murine model combining obesity, T2D, and menopause, treatment with tirzepatide markedly improved intestinal barrier integrity by increasing the expression of key TJ proteins, including occludin (*Ocln*), claudin-12 (*Cldn12*), and junctional adhesion molecule A (*JamA*), while also modulating *MUC2*, the major intestinal mucin involved in epithelial protection [142]. These structural changes were accompanied by attenuation of intestinal inflammation, characterized by increased IL-10 expression together with reduced IL-17 and suppression of the CD14/TLR4 (toll-like receptor 4) signaling pathway, suggesting reduced lipopolysaccharide-mediated endotoxemia. At the microbial level, tirzepatide induced a remodeling of gut microbial composition, reducing the Firmicutes/Bacteroidetes ratio, a hallmark of obesity-associated dysbiosis, while increasing the abundance of *Bacteroidetes*, *Actinobacteria*, *Bifidobacterium*, *Bacteroides*, *Clostridium*, and particularly *Akkermansia muciniphila*, whose expansion was most pronounced in obese diabetic ovariectomized mice [142]. The ability of *Akkermansia muciniphila* to strengthen epithelial barrier function, enhance tight junction protein expression, and dampen intestinal inflammation supports the hypothesis that modulation of the gut microbiota contributes to the intestinal and systemic benefits of tirzepatide. Restoration of microbial homeostasis may modify SCFA production, thereby promoting endogenous GLP-1 secretion through FFAR2/FFAR3 (free fatty acid receptor 2/free fatty acid receptor 3) signaling and amplifying the anti-inflammatory and metabolic effects of incretin therapy [142]. However, this mechanism remains unclear [142].

Whether similar microbiota-mediated mechanisms contribute to the metabolic or immunomodulatory effects of incretin-based therapies in T1D remains unknown. The available findings derive mainly from models of obesity and T2D and therefore cannot be directly transferred to autoimmune diabetes. However, these findings strengthen the concept of a gut–microbiota–metabolism axis and support further investigation of incretin therapies as modulators of host–microbiota interactions in T1D.

7. GLP-1 and Autoimmunity in T1D

GLP-1 is an important regulator of both innate and adaptive immunity [13,143–145]. It exerts immunomodulatory effects by regulating activation, differentiation, and polarization of immune cells, contributing to the maintenance of immune homeostasis and linking metabolic status with immune function.

7.1. Potential Immunological Mechanisms

Interest in GLP-1 in autoimmune and inflammatory diseases has increased because incretin-based therapies may modulate inflammatory responses, immune-cell activity, and tissue damage [143–145]. Endogenous GLP-1 may participate in host response, reducing the production of inflammatory cytokines and limiting the recruitment and infiltration of immune cells [146,147]. GLP-1-based therapies, including GLP-1RAs and DPP-4 inhibitors, have been associated with downregulation of pro-inflammatory responses in several organs through modulation of several intracellular signaling pathways. Activation of GLP-1R inhibits activation of protein kinase C (PKC) and nuclear factor- κ B (NF- κ B) signaling and subsequent expression of inflammatory mediators, such as NLRP3, IL-1 β , TNF- α , IL-6, vascular cell adhesion molecule-1 (VCAM-1), interferon- γ (IFN- γ), and monocyte chemoattractant protein-1 (MCP-1) [148–150]. This is associated with increased levels of anti-inflammatory cytokines, like IL-10 [151,152]. Furthermore, GLP-1R signaling activates cAMP/Ca²⁺, Ca²⁺/calmodulin-dependent protein kinase kinase β (CAMKK β), and

AMPK, which contribute to its anti-inflammatory effects by reducing monocyte adhesion and leukocyte recruitment [149,153]. Growing evidence has also demonstrated that GLP-1R activation exerts beneficial effects in retinal inflammatory diseases by attenuating neuroinflammation, reducing oxidative stress, protecting retinal neurons and vascular cells from diabetes-associated damage, and preserving blood–retinal barrier integrity [147]. These findings reflect the broader cytoprotective effects of GLP-1 on the vascular endothelium. Since endothelial dysfunction is a hallmark of microvascular complications of diabetes and atherosclerosis [154], preserving endothelial barrier integrity represents a key mechanism through which GLP-1 exerts its beneficial effects. Indeed, several studies Rho/ROCK (rho-associated protein kinase) and MAPK signaling pathways, thereby leading to reduced inflammation, oxidative stress, and endothelial permeability [37,155–157].

At the level of innate immunity, GLP-1 promotes macrophage polarization toward an anti-inflammatory M2 phenotype [7,134,135], through activation of transcription factor 3 (STAT3) [158], while inhibiting NF- κ B signaling, suppressing the NLRP3 inflammasome, and activating the cAMP/PKA and AMPK pathways, thereby inhibiting the M1 phenotype and decreasing production of pro-inflammatory cytokines, like IL-6 and TNF- α [158]. Thus, overall shifting macrophage responses toward a tissue-repairing phenotype. Through these actions, GLP-1 contributes to limiting tissue inflammation and reducing oxidative stress in several organs, including adipose tissue, liver, kidney, cardiovascular tissues, and the retina. GLP-1 may also modulate the function of dendritic cells, essential for the link between innate and adaptive immunity [159]. Indeed, GLP-1 reduces the expression of major histocompatibility complex class II (MHC-II) molecules and costimulatory proteins, such as CD80 and CD86, thus reducing the ability of dendritic cells to activate naive T lymphocytes and initiate inflammatory immune responses [159]. Moreover, GLP-1 decreases the production of inflammatory cytokines by dendritic cells, thus promoting a more tolerogenic phenotype [159]. GLP-1 may also affect the function of neutrophils by reducing the expression of endothelial adhesion molecules and, consequently, recruitment of neutrophils into inflamed tissues, thereby attenuating oxidative stress and limiting inflammatory activation [159].

GLP-1R activation may also influence adaptive immunity. Activation of the GLP-1R receptor influences T-cell differentiation and cytokine secretion [159,160]: GLP-1 promotes the expansion and function of Tregs, which suppress excessive immune activation through the production of IL-10 and transforming growth factor- β (TGF- β) [160], and decreases the differentiation and activity of pro-inflammatory T helper 1 (Th1) and T helper 17 (Th17) cells, reducing the secretion of IFN- γ , IL-17, and other inflammatory cytokines [161]. In an experimental model, exenatide reduced progressive IL-17 and T-cell infiltration of pancreatic islets and restored systemic Th17/Treg balance via regulating the PI3K/Akt/FoxO1 (forkhead box protein O1) pathway [161]. These mechanisms are relevant to T1D, in which autoreactive CD8+ T cells are principal effectors of β -cell destruction and the imbalance between Th1/Th17 cells and Tregs is a central pathogenic feature. Infiltrating immune cells release cytokines that amplify β -cell dysfunction and apoptosis, while β -cell NF- κ B activation can sustain a cycle of inflammation and injury. By attenuating these pathways, GLP-1 signaling may contribute to preserving β -cell viability.

An indirect link may also involve the gut microbiota. Dysbiosis can reduce immunoregulatory metabolites, particularly SCFAs, impair Treg differentiation, and promote immune activation [41,43]. Because GLP-1 signaling interacts bidirectionally with the gut microbiota, its immunomodulatory effects may also involve changes in microbial homeostasis, intestinal-barrier integrity, and microbiota-derived metabolites. However, most mechanistic evidence derives from T2D, experimental models, or other inflammatory conditions.

Direct evidence that GLP-1 protects pancreatic β -cells from human T1D autoimmunity remains limited [143].

7.2. Preclinical and Clinical Evidence in Autoimmune Diabetes

Experimental studies in non-obese diabetic (NOD) mice support a potential role for GLP-1-related pathways in autoimmune diabetes. Continuous stimulation of GLP-1 signaling has been reported to delay the onset of autoimmune diabetes, and combination approaches involving GLP-1-related pathways have shown beneficial effects on glycaemic status and beta-cell preservation [162,163]. Combining liraglutide with other therapies, such as anti-IL-21 treatment or mesenchymal stem cell therapy, has suggested that GLP-1RAs may enhance protection against autoimmune beta-cell injury in severe experimental settings [164,165]. Moreover, stimulation of endogenous GLP-1 secretion may confer protection against autoimmune diabetes in NOD models [166], supporting the hypothesis that GLP-1-related signaling may modulate the inflammatory environment in autoimmune diabetes. Oral administration of exopolysaccharide from *Leuconostoc pseudomesenteroides* XG5 increased colonic SCFA levels, especially butyrate, together with circulating GLP-1 and colonic proglucagon gene expression. In vitro, butyrate directly stimulated GLP-1 secretion, suggesting that the protective effect may be mediated, at least in part, by microbiota-derived butyrate-dependent enhancement of endogenous GLP-1 production [166]. The immunomodulatory role of GLP-1RAs has also been demonstrated in other experimental models of autoimmune diseases, such as autoimmune encephalomyelitis [167–170], where liraglutide, dulaglutide, and semaglutide have been associated with delayed disease onset, reduced neuroinflammation, attenuation of demyelination, and modulation of pathogenic immune-cell responses [167–170].

Clinical evidence regarding the use of GLP-1RAs in T1D remains heterogeneous, although their metabolic effects appear relatively consistent. The role of GLP-1RAs as an addition to insulin therapy in T1D patients is gaining more recognition, mainly due to their possible benefits in reducing glycaemic variability, beta-cell stress, inflammation, and body weight [10]. A recent systematic review and meta-analysis of 21 randomized controlled trials including 3417 individuals with T1D treated with five different GLP-1RAs reported that GLP-1RAs, used as adjunctive therapy to insulin, can lead to important improvements in other cardiometabolic risk factors [171]. The multicentre, randomized, placebo-controlled, phase 2 trial (REPAIR-T1D) assessed the combined use of sitagliptin and lansoprazole in patients with recent-onset T1D, evaluating the C-peptide response to the mixed-meal tolerance test; it found no statistically significant differences compared with the placebo group in terms of the preservation of beta-cell function [172]. The effect of GLP-1RAs in delaying progression or preserving β -cell function prior to overt clinical onset has also been investigated; however, the definitive results have not yet been published [173]. Case reports have described possible benefits of semaglutide in autoimmune diabetes phenotypes, particularly in latent autoimmune diabetes in adults (LADA), where favorable effects on glycaemic control, insulin requirements, and the preservation of residual β -cell function have been reported [174]. Despite these results, evidence is insufficient to establish a disease-modifying effect on in vivo T1D autoimmunity.

Although the supposed anti-inflammatory and potentially protective effects are promising, isolated case reports have described possible immune-mediated adverse events during GLP-1RA treatment, including autoimmune hepatitis [175], lupus-like syndromes [176], and pemphigus vulgaris [177].

The hypothetical bidirectional gut microbiota–GLP-1 axis and its potential role in regulating immune homeostasis and contributing to T1D pathogenesis are summarized in Figure 2.

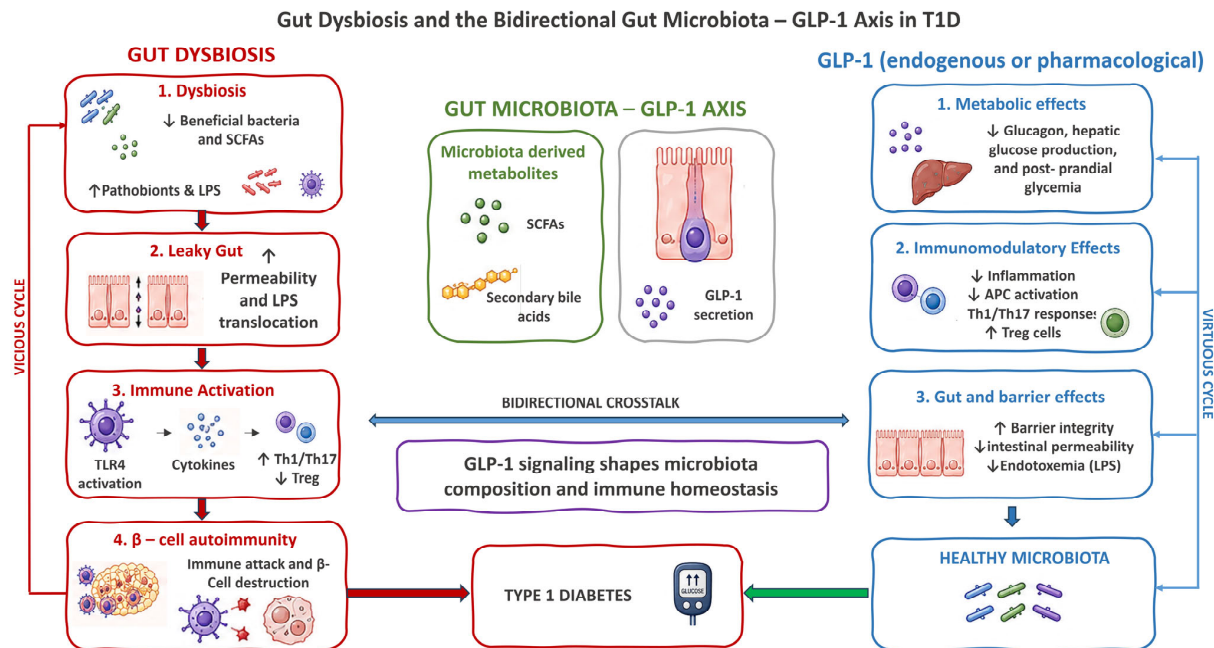


Figure 2. Hypothetical bidirectional gut microbiota–GLP-1 axis in type 1 diabetes. The gut microbiota and GLP-1 form a bidirectional signaling axis that integrates metabolic, intestinal, and immune functions. Gut dysbiosis impairs intestinal homeostasis, reducing SCFA production and increasing intestinal permeability (“leaky gut”), facilitating the translocation of microbial products into the systemic circulation. The resulting activation of innate immune pathways promotes the release of pro-inflammatory cytokines and drives adaptive immune dysregulation, leading to autoreactive T- and B-cell activation, pancreatic β-cell destruction, and the development of T1D. Gut microbiota-derived metabolites promote endogenous GLP-1 secretion. In turn, GLP-1 signaling may reciprocally influence gut microbial composition and function, establishing a bidirectional crosstalk that contributes to the maintenance of intestinal homeostasis. Endogenous or pharmacological GLP-1 exerts well-established metabolic actions, preserves intestinal barrier integrity, promotes the expansion of beneficial and SCFA-producing bacteria, and exerts immunomodulatory effects favoring immune tolerance. These mechanisms may contribute to protection against β-cell autoimmunity through a putative protective pathway, in which enhancement of the gut microbiota–GLP-1 axis promotes intestinal and immune homeostasis, thereby potentially limiting autoimmune progression. The evidence supporting these interactions derives predominantly from studies in type 2 diabetes, animal models, and in vitro systems, with limited direct evidence in T1D. Thus, the proposed axis represents a conceptual framework integrating findings across experimental models rather than an established causal pathway in T1D.

8. Future Perspectives

Several important questions remain regarding the temporal and mechanistic relationship between gut dysbiosis and endogenous GLP-1 signaling during T1D development. It is currently unclear whether microbiota alterations precede changes in GLP-1 levels or GLP-1R signaling, including whether such alterations are already detectable before seroconversion. Future research should integrate gut microbiome analysis with metabolomics and immune profiling to clarify the causal relationships between microbial alterations, incretin signaling, and autoimmune responses, and to identify novel therapeutic targets. Particular attention should be devoted to early-life microbiota-targeted interventions in individuals at risk of T1D, as well as to combination therapies targeting both the gut microbiota and incretin pathways. Defining microbiota signatures that predict the response to GLP-1RAs could provide insight into patient-specific therapeutic responses. Moreover, it remains to be determined whether GLP-1RAs can directly modulate antigen-specific T-cell responses independently of their effects on body weight, food intake, and glycemic control. Similarly, whether GLP-1RA-induced changes in the gut microbiota reflect a direct pharmacological

effect or are secondary to altered nutrient intake and gastrointestinal motility remains unresolved. Addressing these questions through longitudinal and mechanistic studies will be essential to determine whether the microbiota–GLP-1–immune axis contributes causally to T1D progression and whether it can be therapeutically targeted.

Caveolin-1: A Putative Molecular Linker of the GLP-1–Gut Microbiota–Autoimmunity Axis

Caveolin-1 (Cav-1) is not a genetic determinant of T1D susceptibility; however, accumulating experimental data support its function as an important regulator at the intersection of microbiota-derived signals, GLP-1 signaling, epithelial barrier integrity, and immune activation [178]. Therefore, Cav-1 may constitute a molecular platform integrating several pathways implicated in disease progression.

Firstly, Cav-1 may directly regulate the GLP-1 signaling pathway and connect microbiota-derived signals with GLP-1. Considering that GLP-1R localizes within caveolar lipid rafts and physically interacts with Cav-1, Cav-1 may influence the quality and the magnitude of the GLP-1R signaling pathway by regulating trafficking, membrane compartmentalization, and internalization of GLP-1R [26,179]. Another mechanistic link between microbial metabolites and GLP-1 signaling may be related to the organization of membrane signaling complexes by Cav-1. For instance, butyrate increases Cav-1 expression through HDAC inhibition and simultaneously enhances AHR, which is physically associated with Cav-1 [67,120]. Interestingly, FXR signaling is reduced in Cav-1-deficient mice, suggesting that Cav-1 may be necessary for optimal bile acid sensing and downstream immune regulation [180]. FXR signaling exerts anti-inflammatory effects largely through reciprocal interactions with the NF- κ B pathway, suppressing transcription of inflammatory genes, whereas chronic inflammation in turn impairs FXR activity [181]. Therefore, these observations suggest that Cav-1 contributes to maintaining the balance between inflammatory and anti-inflammatory responses downstream of microbiota-derived bile acids. Considering that GLP-1 receptor activation exerts anti-inflammatory effects on macrophages, dendritic cells, and lymphocytes and improves intestinal barrier function [182], Cav-1-dependent regulation of GLP-1R signaling may represent a mechanism through which the gut microbiota shapes autoimmune responses in T1D. Further, the association of DPP-4 with Cav-1 in antigen-presenting cells provides an additional point of convergence between incretin biology and immune regulation [183]. The interaction between Cav-1 and NF- κ B signaling further supports this hypothesis. Although Cav-1 has often been described as a negative regulator of NF- κ B activation, its overall effects appear highly context-dependent [184–186]. Indeed, rather than acting as a simple inhibitor of inflammation, Cav-1 appears to modulate inflammatory responses in a context-dependent manner: on the one hand, it can directly interact with TLR4, limiting LPS-induced cytokine production; on the other hand, it has also been associated with activation of pro-inflammatory pathways [184,185]. Interestingly, experimental blockade of TLR4 prevents diabetes development in NOD mice [186], supporting the hypothesis that innate immune pathways may be modulated by Cav-1.

Beyond innate immunity, Cav-1 has also been implicated in several processes directly relevant to T1D pathogenesis, including regulation of cytokine-induced β -cell apoptosis, B-cell tolerance, and T-cell activation. These findings suggest that Cav-1 may influence both innate and adaptive immune responses.

Finally, the intestinal epithelial barrier represents another potential interface where Cav-1 may integrate microbiota-derived signals with immune regulation. Cav-1 directly interacts with tight junction proteins, including claudins and occludin, while functioning in concert with ZO-1 to preserve epithelial integrity [187,188]. Loss or dysregulation of Cav-1 compromises occludin expression and tight junction function, potentially facilitating

exposure of the immune system to microbial antigens. On the other hand, many pathogens use caveolin machinery to invade host cells [189,190].

Overall, these observations support a conceptual model in which Cav-1 functions as a membrane signaling hub linking gut microbiota-derived metabolites, GLP-1 receptor biology, bile acid signaling, immune regulation, and epithelial barrier integrity. In this system, alterations in microbial composition may influence GLP-1 secretion and signaling not only through changes in SCFAs and bile acids, but also through Cav-1-dependent organization of membrane signaling complexes. Although direct evidence supporting this model in T1D remains limited, this hypothesis provides a mechanistic framework that unifies several apparently independent pathways discussed in this review. As the saying goes, “One coincidence is just a coincidence, two coincidences are a clue, three coincidences are proof.” However, future experimental studies should investigate whether modulation of Cav-1-dependent signaling contributes to the immunometabolic effects of GLP-1 receptor agonists, microbiota-targeted interventions, or combined therapeutic strategies in individuals with T1D (Figure 3).

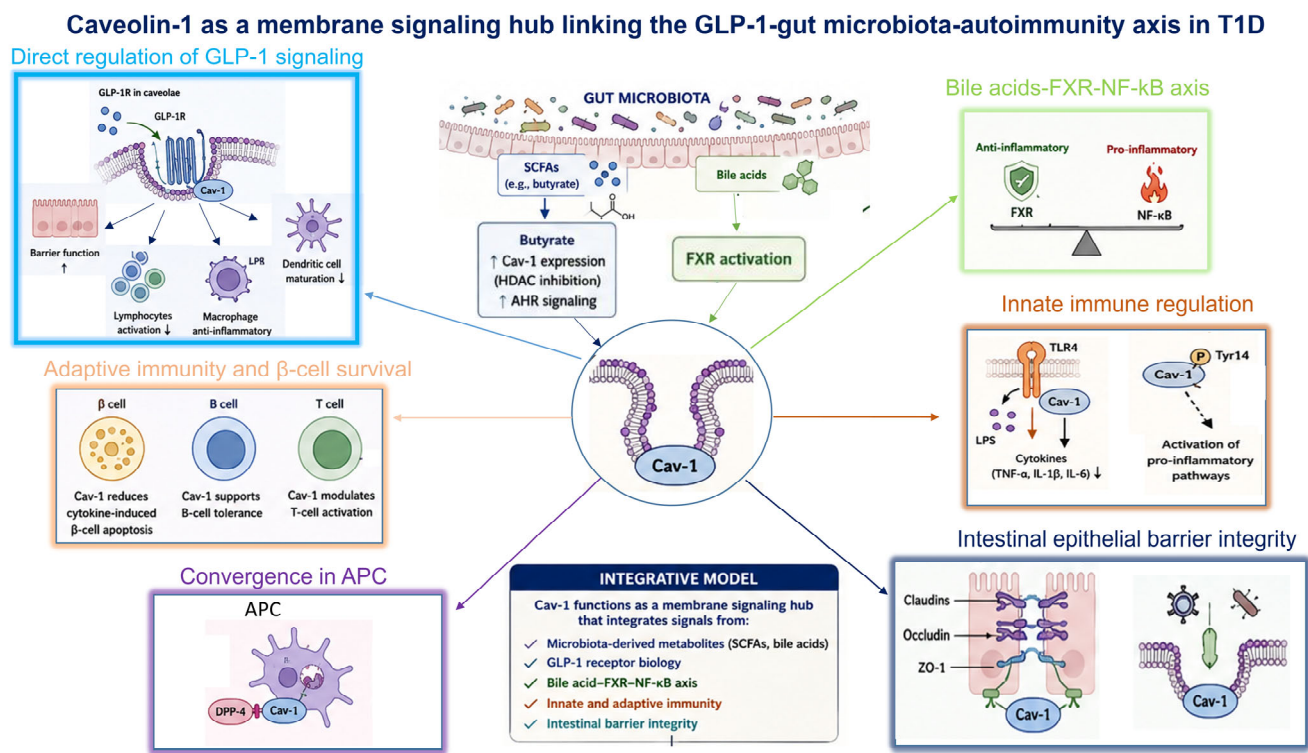


Figure 3. Caveolin-1 as a membrane signaling hub linking GLP-1 signaling, gut microbiota, and immune regulation in T1D. Cav-1 may be a central membrane signaling platform integrating metabolic, microbial, and immune pathways implicated in the pathogenesis of T1D. Through the integration of these pathways, Cav-1 may regulate GLP-1 secretion and receptor signaling, modulate inflammatory and immune responses, and preserve epithelial barrier function. Collectively, these mechanisms suggest that Cav-1 may contribute to maintaining immune tolerance and limiting autoimmune β-cell destruction in T1D.

9. Conclusions

The link between gut microbiota, GLP-1 signaling, and immune regulation may represent a biologically plausible framework linking metabolism and autoimmunity. Although substantial evidence supports the individual components of this axis, the strength of evidence differs considerably across these components, and a direct role of the integrated axis in T1D pathogenesis remains to be established. Relatively robust evidence supports gut dysbiosis, altered SCFA availability, intestinal barrier dysfunction, and immune dysregulation

in T1D, whereas direct evidence that microbiota-driven changes in GLP-1 signaling modify human T1D autoimmunity or disease progression remains limited. Microbial dysbiosis and reduced production of immunoregulatory metabolites may impair intestinal-barrier integrity, promote inflammation and β -cell autoimmunity, while GLP-1 signaling may improve immune responses, epithelial function, and gut microbial composition. Although preclinical findings suggest potential anti-inflammatory and β -cell-protective effects of GLP-1RAs, these effects are supported predominantly by experimental studies, and a consistent disease-modifying effect in human T1D has not yet been demonstrated.

Caveolin-1 may represent a signaling platform linking GLP-1 receptor signaling, microbial metabolites, immune activation, and barrier integrity, but this hypothesis remains to be validated. Further mechanistic and clinical studies are needed to determine whether targeting the GLP-1–gut microbiota axis can safely modulate autoimmunity, preserve residual β -cell function, or improve outcomes in individuals with or at risk of T1D (Table 1).

Table 1. Evidence supporting individual components of the proposed GLP-1–microbiota–autoimmunity axis in T1D. Despite evidence shown in the table, several important questions remain regarding the temporal and mechanistic relationship between gut dysbiosis and endogenous GLP-1 signaling during T1D development. Associations between SCFA-producing taxa and T1D are heterogeneous across cohorts, and reduced SCFA production has not been established as a direct cause of disease, while human interventional evidence remains limited. Similarly, the microbiota–GLP-1 relationship has been investigated predominantly in obesity, T2D, and experimental models, and a direct causal pathway linking microbiota-derived signals to GLP-1 secretion and subsequent modulation of T1D autoimmunity has not been demonstrated in humans. It is therefore unclear whether microbiota alterations precede changes in GLP-1 levels or GLP-1R signaling, including whether such alterations are already detectable before seroconversion. Increased intestinal permeability is not specific to T1D, and its temporal relationship with islet autoimmunity remains unresolved; likewise, evidence for GLP-1-mediated restoration of intestinal barrier integrity is largely preclinical. Although microbiota-derived signals may influence Treg responses, Treg alterations can also reflect broader autoimmune inflammation, and it remains unclear whether microbiota-mediated Treg modulation is sufficient to prevent human T1D. Evidence for molecular mimicry is similarly limited to specific microbial peptides, such as those derived from *P. distasonis*, and does not establish this mechanism as a general driver of human T1D, while associations with seroconversion do not demonstrate causality. Defining microbiota signatures that predict responses to GLP-1 receptor agonists (GLP-1RAs) could provide insight into patient-specific therapeutic responses. Moreover, it remains to be determined whether GLP-1RAs can directly modulate antigen-specific T-cell responses independently of their effects on body weight, food intake, and glycaemic control, and whether GLP-1RA-induced changes in the gut microbiota reflect direct pharmacological effects or are secondary to altered nutrient intake and gastrointestinal motility. Finally, current evidence is insufficient to establish a direct connection between caveolin-1 (Cav-1), gut microbiota, GLP-1 signaling, and T1D autoimmunity; thus, Cav-1 should currently be considered a putative mechanistic component rather than an established element of this axis.

Component	Key Findings	Evidence Type	Clinical Implications
SCFAs	Reduced abundance of SCFA-producing bacteria and altered microbial metabolic activity in T1D Dysbiosis [40–44] Support intestinal epithelial integrity and contribute to immune regulation [76–79,84–86] Stimulate intestinal GLP-1 secretion [116–119] In NOD mice, delayed onset of diabetes [92]	Human + animal/in vitro	SCFA-producing microbiota and microbial metabolite pathways represent potential targets for restoring intestinal and immune homeostasis. Their therapeutic relevance in T1D remains investigational.

Table 1. Cont.

Component	Key Findings	Evidence Type	Clinical Implications
GLP-1 secretion	Stimulated by microbiota-derived metabolites [107,113–118,126,127] GLP-1R activation has anti-inflammatory effects [143–147,159] In NOD mice, sustained GLP-1 reduced insulinitis, β -cell apoptosis, and delayed diabetes onset [162,163,166]	Human + animal/in vitro	GLP-1 signaling may have immunomodulatory effects in addition to its metabolic actions, but a disease-modifying effect in T1D has not been established.
Intestinal barrier integrity	Commensal microbiota and microbial metabolites contribute to epithelial barrier maintenance [4,79,81,97–99] GLP-1 signaling may improve intestinal and endothelial barrier integrity [142,182] Dysbiosis may increase intestinal permeability, facilitating translocation of microbial products and potentially promoting systemic inflammation [4]	Human + animal/in vitro	Preservation of intestinal barrier integrity could reduce exposure to microbial inflammatory signals and potentially contribute to immune homeostasis. Barrier-targeted interventions remain experimental in T1D.
Tregs	SCFAs promote Treg differentiation and function [76,86,90] GLP-1 signaling has been associated with increased Treg responses and reduced Th1/Th17 activity [159–161] Exenatide restored the Th17/Treg balance and reduced IL-17 ⁺ T-cell infiltration into pancreatic islets [161]	Animal + human/in vitro	Support microbiota-dependent maintenance of immune tolerance. GLP-1 and microbiota-derived metabolites could attenuate autoimmune inflammation, enhancing Treg-mediated immune regulation. Confirmation in human T1D is required.
Molecular mimicry	Microbial peptides may structurally resemble β -cell autoantigens and activate cross-reactive T cells [50] A peptide derived from <i>Parabacteroides distasonis</i> homologous to insulin B:9–23 activated insulin-reactive T cells and accelerated diabetes in NOD mice [49]. Its presence was also associated with islet autoantibody seroconversion in the DIABIMMUNE cohort.	Human + animal + ex vivo	Support microbial molecular mimicry as a potential trigger of islet autoimmunity.
Caveolin-1 (Cav-1)	Cav-1 may participate in endothelial and membrane signaling, including pathways involved in vascular permeability, inflammation, and cellular responses to metabolic stress [26,179,183–188]	Predominantly animal/in vitro; indirect evidence in T1D	It could represent a potential downstream link between GLP-1-mediated vascular/barrier protection and inflammatory signaling. Cav-1 should be considered a putative mechanistic component.

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Abbreviations

The following abbreviations are used in this manuscript:

2-OG	2-oleoyl glycerol
AHR	aryl hydrocarbon receptor
Akt	Protein kinase B
AMP	adenosine monophosphate
AMPK	AMP-activated protein kinase
BAs	bile acids
CA	cholic acid
CAMKK β	Ca ²⁺ /calmodulin-dependent protein kinase kinase β
cAMP	cyclic AMP
Cav-1	caveolin-1
CD	cluster of differentiation
CDCA	chenodeoxycholic acid
DCA	deoxycholic acid
DPP-4	dipeptidyl peptidase-4
EECs	epithelial endocrine cells
EPAC	exchange protein directly activated by cAMP
ERK1/2	extracellular signal-regulated kinase 1/2
FFAR2	free fatty acid receptor 2
FFAR3	free fatty acid receptor 2
FOXP3	forkhead box protein P3
FoxO1	forkhead box protein O1
FXR	Farnesoid X Receptor
GAD	glutamic acid decarboxylase
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1RAs	GLP-1 receptor agonists
GLP-1R	GLP-1 receptor
GLP-2	glucagon-like peptide-2
GPCRs	G-protein-coupled receptors
G α s	stimulatory G protein
H3	histone H3
HDACs	histone deacetylases
HDAC6	histone deacetylase 6
HDAC9	histone deacetylase 9
HFD	high-fat diet
HIPs	hybrid insulin peptides
IA-2	islet cell antigen 2
IAA	indole-3-acid-acetic
IAld	indole-3-aldehyde
IFN- γ	interferon- γ
IL	interleukin
iNKT	invariant natural killer T
IPA	indole-3-propionic acid
JamA	junctional adhesion molecule A
LADA	latent Autoimmune diabetes in adults
LCA	lithocholic acid

LPS	lipopolysaccharides
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemoattractant protein-1
MCT1	monocarboxylate transporter 1
MCT4	monocarboxylate transporter 4
MHC-II	major histocompatibility complex class II
NF- κ B/NF- κ B	nuclear factor- κ B
NLRP3	NOD-like receptor protein 3
NOD	non-obese diabetic
NTS	nucleus tractus solitarius
PC1/3	prohormone convertase 1/3
PC2	prohormone convertase 2
PI3K	phosphoinositide 3-kinase
PKA	protein kinase A
PKC	protein kinase C
ROCK	Rho-associated protein kinase
ROR γ t	retinoic acid receptor-related orphan receptor γ t
SCFA/SCFAs	short-chain fatty acid/short-chain fatty acids
STAT3	Signal Transducer and Activator of Transcription 3
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes
TGF- β	transforming growth factor- β
TGR5	Takeda G protein-coupled receptor 5
Th1	T helper 1
Th17	T helper 17
TJ	tight junction
TLR4	toll-like receptor 4
TNF- α	tumor necrosis factor α
Tregs	regulatory T cells
UDCA	ursodeoxycholic acid
VCAM-1	vascular cell adhesion molecule-1
ZnT8	zinc transporter 8
ZO-1	zonula occludens-1

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