

Cross - Kingdom Dialogue of Microbial Messengers: Multi - Target Regulatory Mechanisms and Therapeutic Strategies of Gut Microbiota - Derived Extracellular Vesicles in Metabolic Diseases

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Abstract: Gut microbiota-derived extracellular vesicles (GMEVs) serve as pivotal mediators of cross-communication between microorganisms and their hosts, playing a complex and central role in the onset and progression of metabolic diseases. This review systematically summarizes the biological characteristics, molecular composition, and regulatory mechanisms of GMEVs in metabolic disorders such as obesity, diabetes, and non-alcoholic fatty liver disease. GMEVs facilitate dialogue along the “gut-organ axis” by transporting active molecules such as lipopolysaccharides (LPS), flagellin, nucleic acids, and metabolic products, thereby mediating bidirectional regulation of host metabolic homeostasis. GMEVs derived from pathogenic bacteria promote metabolic inflammation and insulin resistance by compromising the intestinal barrier, activating inflammatory pathways, and inhibiting insulin signaling. Conversely, GMEVs originating from probiotics exert protective effects by enhancing tight junction functionality, modulating immune responses, and improving lipid metabolism. Notably, the dynamic fluctuations of GMEVs are closely linked to disease progression, and their microbiota-specific molecular characteristics offer novel biomarkers for the early diagnosis of metabolic diseases. Despite the challenges posed by standardization of isolation and elucidation of underlying mechanisms, the potential applications of GMEVs in the precise prevention and treatment of metabolic diseases are vast, providing a theoretical foundation for the development of novel microbiome-based intervention strategies. Future research should further elucidate the heterogeneity of GMEVs and their spatiotemporal dynamics in host interactions, facilitating the transition from fundamental research to clinical application.

Keywords: gut microbiota-derived extracellular vesicles, metabolic diseases, gut-organ axis, microbial-host interactions, precision therapy

Introduction

The gut serves as the core site for digestion and absorption within the human body, functioning as a highly intricate microbial ecosystem.¹ Recent studies increasingly indicate that the gut microbiota not only maintains local homeostasis within the intestinal environment but also influences the physiological functions and disease progression of distant organs through regulatory mechanisms of the “gut-organ axis”.² As a crucial regulator of internal environmental stability, the interplay between gut microbiota and host metabolism has emerged as a focal point in metabolic disease research. Existing evidence suggests that dysbiosis of the gut microbiota may contribute to the onset and progression of metabolic diseases such as obesity, diabetes, and its complications, as well as metabolic associated fatty liver disease (MAFLD), through mechanisms that regulate host insulin resistance, low-grade inflammatory responses, and disturbances in lipid metabolism.^{3,4} Given its extensive regulatory functions, the gut microbiota is regarded as a unique endocrine dynamic

ecosystem, participating in the maintenance of host energy metabolic homeostasis through molecular crosstalk between microorganisms and the host.⁵ As research into the “gut-organ axis” deepens, the mechanisms by which gut microbiota and their metabolic products influence metabolic diseases are gradually being elucidated. Studies indicate that the gut microbiota may participate in the pathological processes of metabolic diseases by affecting intestinal barrier function, immune regulation, and the secretion of metabolites.⁶ However, the molecular mechanisms by which the gut microbiota “remotely controls” metabolic diseases such as obesity and diabetes remain unclear, particularly regarding the pathways of information transfer between the gut microbiota and distant tissues. In this context, gut microbiota-derived extracellular vesicles (GMEVs) have garnered significant attention as novel mediators of microbial-host interactions.

GMEVs are membrane-bound vesicles, approximately 30–300 nm in diameter, actively secreted by the gut microbiota, capable of stably carrying and delivering a wealth of bioactive molecules, including nucleic acids (such as bacterial deoxyribonucleic acid [DNA] and non-coding ribonucleic acid [RNA]), proteins (such as enzymes and virulence factors), and metabolites (such as short-chain fatty acid derivatives).⁷ Compared to free molecules, GMEVs possess unique biological advantages: their lipid bilayer membrane structure effectively protects their contents from degradation by the harsh intestinal environment (such as low potential of hydrogen [pH] and digestive enzymes), ensuring the intact delivery of active molecules;^{8,9} simultaneously, the specific adhesion molecules expressed on the surface of GMEVs confer tissue-targeting capabilities, enabling precise recognition and interaction with specific host cells.^{10,11} These characteristics suggest that GMEVs may play a pivotal messenger role between the gut microbiota, regarded as an “endocrine organ”, and distant target organs, thereby participating in the regulation of metabolic diseases such as obesity, diabetes, and MAFLD. In summary, this study focuses on the role of GMEVs in the relationship between gut microbiota and metabolic diseases, analyzing their biological origins, functional components, delivery mechanisms, and the influences of dietary factors. It also summarizes the regulatory mechanisms and advancements in the application of GMEVs in the treatment of metabolic diseases, aiming to provide a theoretical basis and novel intervention strategies for GMEV-targeted therapies in metabolic disorders (Figure 1).

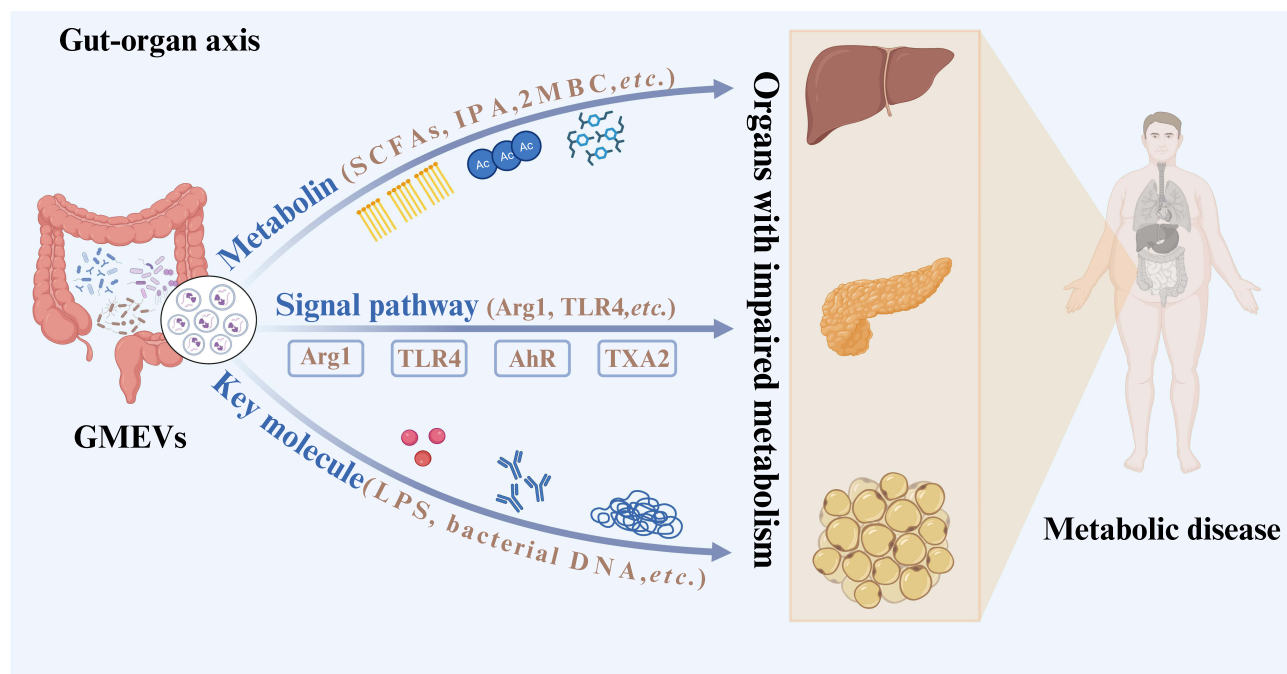


Figure 1 Schematic diagram of the “gut-organ axis” in gut microbiota and metabolic diseases.

Abbreviations: GMEVs, Gut microbiota-derived extracellular vesicles; SCFAs, Short-Chain Fatty Acids; IPA, indolepropionic acid; 2MBC, 2-methylbutyrylcarnitine; Arg1, arginase 1; TLR4, toll-like receptor 4; LPS, lipopolysaccharides.

Table 1 Functional Comparison of GMEVs from Different Sources

Source	Key Functional Components	Physiological/Pathological Effects	References
Probiotics	Surface proteins, polysaccharides, miRNAs, and other antimicrobial molecules	Maintain intestinal barrier, anti-inflammatory, protect against oxidative damage	[14–24]
Pathogens	LPS, enterotoxins, hemolysins, DNA fragments	Pro-inflammatory, induce autophagy	[25–32]
Commensals	Functional proteins, immunomodulatory proteins, metabolites	Reduce necrotic cell death, anti-inflammatory, maintain intestinal immune tolerance	[33–39]

Abbreviations: miRNA, microRNA; LPS, lipopolysaccharides.

Sources and Classification of GMEVs

GMEVs are nanoscale (30–300 nm) bilayer membrane structures actively secreted or passively released by gut microorganisms, playing a crucial role in microbial communication and host-microbe interactions.^{12,13} Based on the originating microbiota, gut microbiota-derived extracellular vesicles (EVs) can be primarily categorized into three major types: probiotics-derived EVs, pathogenic bacteria-derived EVs, and symbiotic bacteria-derived EVs (Table 1 and Figure 2).

Probiotics-Derived EVs

Probiotics-derived EVs, exemplified by *Lactobacillus* and *Bifidobacterium*, exert multifaceted regulatory roles in maintaining intestinal homeostasis and host health.¹⁴ These EVs typically carry a wealth of immunomodulatory factors, including immunogenic surface proteins and anti-inflammatory polysaccharide components,^{15–17} which can enhance intestinal epithelial barrier function and inhibit the colonization of pathogenic microorganisms through various mechanisms.^{40,41} Research has shown that extracellular vesicles derived from *A. muciniphila* can improve metabolic function in diabetic mice by reducing damage to the intestinal mucosal barrier and enhancing tight junction integrity.¹⁸ Furthermore, *Bifidobacterium*-derived EVs can carry antimicrobial substances and promote the expression of adhesion proteins that facilitate the growth of beneficial bacteria, thereby creating an environment unfavorable for pathogen colonization.⁴² Based on immune regulation, probiotics-derived EVs modulate host immune responses through complex signaling networks;^{19–21} their surface molecules interact with pattern recognition receptors on immune cells, activating the secretion of cytokines such as interleukin 22 (IL-22) and interleukin 17 (IL-17), while simultaneously inhibiting the excessive activation of pro-inflammatory signaling pathways like nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), thereby establishing an anti-inflammatory microenvironment in the gut.^{19–21} Notably, certain

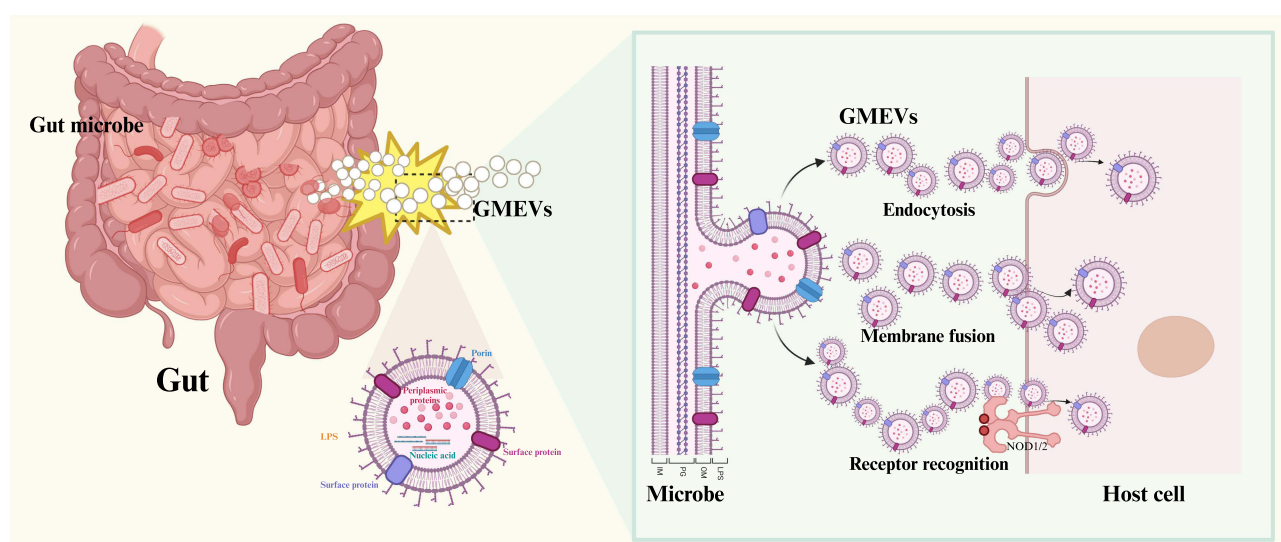


Figure 2 Schematic diagram of the molecular composition and delivery mechanism of GMEVs.

Abbreviations: GMEVs, Gut microbiota-derived extracellular vesicles; LPS, lipopolysaccharides.

Bifidobacterium-derived EVs enhance the host cell's antioxidant defense capabilities by activating the Nrf2 signaling pathway, mitigating oxidative stress-induced damage to the intestinal epithelium.^{14,22} Additionally, another class of probiotics-derived EVs from *Escherichia coli* Nissle 1917 regulate intestinal epithelial barrier function by upregulating the expression of tight junction proteins, thereby enhancing the integrity of intercellular connections to maintain the protective function of the gut barrier.²³ Recent studies have revealed that probiotics-derived EVs possess cross-species gene regulatory capabilities; the miRNA-like molecules they carry can be taken up by host cells and mimic the functions of endogenous miRNAs, finely tuning gene expression networks by targeting specific mRNAs.²⁴ This RNA-mediated gene silencing mechanism provides a novel molecular perspective for understanding microbial-host interactions.

Pathogenic Bacteria-Derived EVs

Pathogenic bacteria-derived EVs in the gut microbiota are primarily secreted by pathogenic strains such as *Escherichia coli*, *Salmonella*, *Shigella*, *Staphylococcus aureus*, and *Bacillus cereus*, acting as “molecular Trojan horses” within the intestinal microenvironment.^{43–45} These nanoscale vesicles are formed through the budding of the bacterial outer membrane, with their biogenesis strictly regulated by genetic factors, including EnvC-mediated outer membrane remodeling, Tol-Pal system-regulated membrane separation, and quorum sensing (QS) controlled programmed release.^{43,46,47} For molecular composition, these EVs represent a highly complex repository of bioactive molecules, rich in typical virulence factors such as lipopolysaccharides, enterotoxins, and hemolysins,^{25–27} while also carrying various antibiotic resistance genes and toxic DNA fragments.^{28,29} Notably, the lipopolysaccharides (LPS) on the surface of pathogenic bacteria-derived EVs exhibit immunostimulatory properties that are several times more potent than free LPS,⁴⁵ capable of activating the expression of toll-like receptor 4 (TLR4) and macrophage-related markers in the host.³⁰ Additionally, pathogenic bacteria-derived EVs can deliver a substantial amount of cytoplasmic enzymes into the host.³¹ These GMEVs not only inhibit autophagic flux by damaging autophagosome-lysosome fusion but also induce autophagy in the host; moreover, these pathogenic bacteria-derived EVs, laden with cytoplasmic enzymes, are more likely to activate non-classical inflammatory pathways, exacerbating the host's inflammatory response.^{31,48}

Symbiotic Bacteria-Derived EVs

In the gut microbiota, species such as *Bacteroides* serve as dominant symbiotic bacteria, and the EVs they secrete play complex and nuanced regulatory roles in maintaining host metabolic homeostasis and immune balance.^{48,49} These EVs are rich in unique bioactive molecules, including functional proteins, immunomodulatory proteins, and microbe-specific metabolites, which serve as important mediators of cross-talk between microorganisms and their hosts.^{33–36}

In terms of metabolic function, symbiotic bacteria-derived EVs carry metabolites such as phosphatidylcholine, which can reduce necroptotic cell death by inhibiting the receptor-interacting protein kinase 1-receptor-interacting protein kinase 3-mixed lineage kinase domain-like protein (RIPK1-RIPK3-MLKL) signaling pathway.³⁷ Regarding immune regulation, these EVs exhibit a distinctive dual regulatory characteristic: polysaccharide A (PSA) expressed on the surface of EVs derived from *Bacteroides fragilis* can mitigate inflammatory responses and potentially alter the composition of the microbiota, thereby preventing pathogen colonization.³⁸ Additionally, these symbiotic bacteria-derived EVs effectively penetrate the intestinal barrier and are enriched with ATP-binding cassette (ABC) transporters and quorum sensing proteins. These proteins stimulate the secretion of IL-10 in co-culture systems involving splenic cells and dendritic cells with CD4+ T cells, demonstrating anti-inflammatory potential and maintaining intestinal immune tolerance.^{34,39} Throughout the co-evolution of hosts and microorganisms, *Bacteroides*-derived EVs have developed sophisticated immune evasion mechanisms. For instance, certain strains possess a capsule polysaccharide variation system on their EVs surfaces that can periodically alter their antigenic epitopes, thereby avoiding excessive clearance by the host immune system while maintaining necessary immune stimulation to “train” the host's immune response capabilities.^{50,51} Disruption of this dynamic balance is associated with various diseases; for example, the proportion of immunoregulatory *Bacteroides*-derived EVs is significantly reduced in the intestines of patients with inflammatory bowel disease.³⁵

With advancements in synthetic biology, GMEVs are emerging as novel therapeutic carriers due to their nanoscale structure, ability to penetrate the blood-brain barrier, low toxicity, high biocompatibility, and ease of modification. Engineered GMEVs, such as those synthesized to carry interleukin 4 (IL-4), have shown promise in promoting the repair

of osteoporotic fractures.⁵² These studies not only deepen our understanding of the interaction mechanism between intestinal flora and host, but also provide theoretical basis and technical support for the development of precise intervention strategies based on microbial EVs.

Composition, Functional Characteristics, and Delivery Mechanisms of GMEVs

As important mediators of microbial-host interactions, GMEVs' biological functions primarily rely on the diverse signaling molecules they carry and their sophisticated molecular delivery mechanisms. These nanoscale vesicles are rich in various bioactive substances, including lipopolysaccharides,⁵³ flagellin proteins,^{54,55} nucleic acids,²⁴ metabolites,³⁷ and other protein components,^{42,56} which collectively form the functional basis of GMEVs. GMEVs interact with host cells through multiple delivery pathways, including membrane fusion, endocytosis, and receptor recognition. This precise regulatory characteristic positions them as key molecular bridges in microbial-host interactions.

LPS and Flagellin Proteins

GMEVs serve as crucial mediators in bacterial-host interactions, playing a complex and significant role in regulating host immune responses.⁵⁷ These nanoscale vesicles are rich in pathogenic components such as LPS and flagellin proteins, which can efficiently deliver bacterial virulence factors to host cells through various mechanisms, triggering a series of immune responses.⁵⁸ LPS, a major component of the outer membrane of Gram-negative bacteria, is abundantly present in GMEVs.⁵⁹ Research indicates that GMEVs act as ideal carriers for LPS, protecting it from degradation in the external environment and ensuring its intact delivery to host target organs. This delivery process is primarily achieved through two mechanisms: first, GMEVs enter host cells via endocytosis and subsequently release LPS within early endosomes, delivering it to the cytoplasm and activating caspase-11-mediated inflammatory responses.⁶⁰ Second, the LPS on the surface of GMEVs can directly bind to pattern recognition receptors on the host cell membrane, initiating a cascade of the TLR2/TLR4/NF- κ B signaling pathway, which can induce insulin resistance and chronic inflammation.^{61,62} In the context of MAFLD, the LPS carried by GMEVs interacts with TLR4 on the host cell membrane, not only disrupting intestinal barrier function but also synergistically activating hepatic stellate cells in conjunction with circulating EVs, thereby promoting the progression of liver fibrosis.^{30,63} These two mechanisms collectively regulate the host's inflammatory response and immune system function, exhibiting a dual role in maintaining intestinal homeostasis or triggering inflammatory responses. It is noteworthy that the immunomodulatory effects of GMEVs are closely related to the activity of the LPS they carry. For instance, in studies involving the pathogenic strain *Escherichia coli* Nissle 1917, it was found that GMEVs induced by glycine exhibited significantly reduced LPS activity, being 6–8 times lower than that of the non-induced group, yet still retained the ability to activate macrophage immune responses.⁶⁴ This phenomenon suggests that the immunostimulatory effects of GMEVs depend not only on the absolute quantity of LPS but also on the overall structure and delivery efficiency of the vesicle. The biological functions of GMEVs carrying LPS in inducing host responses extend beyond local immune regulation; they can also traverse critical protective structures such as the intestinal barrier and blood-brain barrier, inducing responses in distal tissues and organ.⁶⁵ Studies have shown that gut microbiota-derived GMEVs penetrate the blood-brain barrier, carrying LPS and other pro-inflammatory factors into the central nervous system, thereby activating neuroimmune cells such as microglia and triggering sustained neuroinflammatory responses, which can lead to tissue damage and organ dysfunction.⁶⁶

Flagellin proteins primarily originate from motile intestinal bacteria. These bacteria deliver flagellin proteins to the cytoplasm of host immune cells, such as macrophages, via EVs. This delivery process is endocytosis-dependent but does not rely on guanosine triphosphate (GTP)-binding proteins. Once inside the cell, flagellin can strongly activate NOD-like receptor C4 (NLRC4)-mediated caspase-1 activation and IL-1 β secretion, thereby triggering the classical activation pathway of the NLRC4 inflammasome.⁵⁴ Research indicates that pathogen-associated molecular patterns (PAMPs) such as LPS and flagellin can help train the immune system at low concentrations, but excessive amounts can lead to inflammatory responses.⁶⁷ *Salmonella*, for instance, utilizes a transport pathway regulated by its SPI-2 virulence island to deliver flagellin to the basolateral side of epithelial cells, activating the TLR5 inflammatory signaling pathway and promoting mucosal inflammation.⁶⁸ Notably, this process does not depend on the motility of the bacteria or their direct invasion.

Nucleic Acids, Metabolites, and Other Proteins

In addition to LPS and flagellin proteins, GMEVs are also rich in key signaling molecules such as nucleic acids, metabolites, and other functional proteins. Once delivered to host cells, these nucleic acid components can specifically activate nucleotide-binding oligomerization domain-containing protein 1 (NOD1), facilitating immune crosstalk with the epithelial cells on the gastrointestinal surface and regulating the activation of innate immune receptors in the gastrointestinal mucosa.⁶⁹ Recent discoveries have identified miRNA-like small RNAs, which, despite their shorter length and lack of typical hairpin structures, can exert gene-silencing effects within host cells. This phenomenon of cross-domain regulation provides new insights into the co-evolution of hosts and microorganisms. Studies have shown that analyzing the miRNA characteristics in GMEVs using machine learning-driven models can serve as effective biomarkers for disease diagnosis, prediction, and early warning.¹³

Regarding metabolites, dysbiosis in the gut microbiota can significantly alter amino acid levels and the balance of short-chain to long-chain fatty acids, contributing to disease pathogenesis. These findings greatly expand our understanding of the functional diversity of GMEVs.⁷⁰ Notably, GMEVs derived from gut microbiota can deliver bacterial effector proteins to the central nervous system via the circulatory system or neural pathways, regulating the onset and progression of neuroinflammatory diseases.⁶⁶ Additionally, GMEVs released by non-pathogenic *E. coli* Nissle 1917 can carry inner membrane and cytoplasmic proteins to host cells, modulating host immune functions.⁶⁴ Recent studies have found that the secretion of GMEVs from probiotic gut microbiota is reduced in diabetic model rats, leading to decreased levels of functional proteins or lipid components such as Amuc-1100, P9, and phosphatidylcholine in target organs. This reduction results in impaired intestinal barrier function, suppression of glucagon-like peptide-1 (GLP-1) levels, and disruption of insulin signaling pathways, ultimately triggering a series of metabolic syndrome-related issues.⁷¹ These findings highlight the synergistic advantages of GMEVs as multi-component carriers—transporting proteins, metabolites, and genetic materials—that can target and regulate gut-liver axis functions while simultaneously intervening in gut microbiota reconstruction, metabolic reprogramming, and systemic inflammation alleviation.⁷² This offers new perspectives for the prevention and treatment of metabolic diseases such as obesity, MAFLD, and diabetes.

Molecular Delivery Mechanisms and Regulatory Characteristics of GMEVs

GMEVs interact with host cells through diverse molecular delivery mechanisms, including membrane fusion, endocytosis, and receptor recognition. These precisely regulated delivery processes enable GMEVs to dynamically influence the physiological and pathological states of the host. Membrane fusion is a typical delivery method for EVs derived from Gram-positive bacteria. GMEVs preferentially fuse with the liquid-ordered regions of host cell membranes, altering the fluidity, dipole potential, and compressibility of the host membrane. The efficiency of this fusion is regulated by lipid composition (eg, phosphatidylcholine and C16 acyl chains promote fusion, while cholesterol inhibits it), thereby affecting virulence transfer and host mechanism manipulation.⁷³

In contrast, endocytosis is a more common delivery pathway. GMEVs enter host cells through clathrin-dependent endocytosis, where the DNA fragments carried by GMEVs determine the efficiency of internalization.⁷⁴ Recent studies have also identified an atypical endocytic mechanism—raft-mediated uptake—dependent on membrane cholesterol microdomains. GMEVs adhere via a pathway that does not rely on $\alpha 5 \beta 1$ integrin but rather on lipid rafts, with subsequent endocytosis relying on cholesterol and sphingolipid components, driving actin remodeling through the recruitment of Rac1 to raft regions.⁷⁵ Receptor binding is another key mechanism through which GMEVs exert their functions. GMEVs, by packaging immunostimulatory molecules such as peptidoglycan and LPS, are recognized and activated by host cell NOD-like receptors (NLRs), such as nucleotide-binding oligomerization domain containing protein 1 (NOD1), nucleotide-binding oligomerization domain containing protein 2 (NOD2), and NOD-like receptor family pyrin domain-containing 3 (NLRP3), thereby driving inflammatory responses or maintaining intestinal immune homeostasis.⁷⁶ The delivery and synergistic action of these molecules enable GMEVs to precisely regulate the physiological and pathological processes of the host: under homeostatic conditions, symbiotic bacterial EVs maintain intestinal tolerance by delivering immune regulatory molecules,³⁴ conversely, during dysbiosis, the excessive release of virulence factors from pathogenic bacterial EVs disrupts barrier functions.⁷⁷ Particularly noteworthy is the spatiotemporal specificity of GMEVs' molecular delivery. For instance, circadian rhythm disturbances alter the metabolic signaling

molecules in GMEVs, reducing insulin sensitivity in adipocytes and inducing systemic inflammation, indicating that GMEVs mediate the relationship between circadian disruption and metabolic abnormalities.⁷⁸ This precise regulatory mechanism allows GMEVs to dynamically adjust their biological effects according to the host's state.

The Impact of Metabolic Risk Factors on GMEVs

The biological characteristics of GMEVs establish their unique position in the regulation of host metabolism. For one thing, the molecules carried by GMEVs exhibit strain specificity, with significant differences in composition and function among GMEVs produced by different strains, and even among strains of the same species. For another, GMEVs demonstrate environmental responsiveness and tissue tropism, with their production and composition dynamically adjusting in response to environmental factors such as diet and medication.⁶¹ Following their generation, GMEVs can target specific organs through pathways such as the portal venous system and lymphatic circulation.¹¹ Research indicates that a high-fat diet can markedly alter the physical properties and molecular composition of GMEVs, such as increasing vesicle diameter, elevating LPS content, and reducing the levels of phospholipid fatty acids.^{79,80} These changes do not entirely align with alterations in microbial community composition, suggesting that diet may influence GMEV production by directly modulating bacterial membrane components. At the molecular level, the composition of fatty acids, particularly the ratio of saturated to unsaturated fatty acids, affects GMEV generation by regulating bacterial membrane fluidity. For instance, saturated fatty acids can dose-dependently promote the release of GMEVs from *Bacteroides fragilis*, while having no significant effect on *Bacteroides thetaiotaomicron*; unsaturated fatty acids, conversely, exhibit differential regulatory effects across various strains.⁸¹ Furthermore, disruptions in the body's biological rhythms can also impact the development of metabolic diseases through GMEVs. Studies have found that reversing light cycles can lead to insulin resistance, inflammation in adipose tissue, and a reduction in regulatory T cells, with mechanisms involving gut barrier disruption, GMEV-mediated inhibition of insulin signaling, and peripheral circadian rhythm disturbances.⁷⁸ The circadian regulatory characteristics of GMEVs provide a novel perspective on the temporal biological features of metabolic diseases. These findings underscore the pivotal role of GMEVs in the regulation of the diet-microbiome-host metabolism axis and suggest that they may serve as a crucial molecular bridge connecting biological rhythms with metabolic homeostasis.

The Regulatory Role of GMEVs in Metabolic Diseases

As key mediators of microbial-host interactions, GMEVs play a central regulatory role in the onset and progression of metabolic diseases. They deliver microbial-derived bioactive molecules to affect the host's energy metabolism, immune homeostasis and endocrine function in a multi-target and multi-level manner, thereby participating in pathological processes such as insulin resistance, chronic low-grade inflammation, and lipid metabolism disorders.^{82,83} The gut microbiota, utilizing the cross-communication capabilities of GMEVs, can simultaneously target the host's intestinal barrier function and the metabolic homeostasis of distant organs (Table 2), thereby forming a comprehensive regulatory network across spatial and temporal dimensions. This "local-distant" synergistic action enables GMEVs to integrate microbial signals with host physiological needs, offering a fresh perspective on the pathogenesis of metabolic diseases through the lens of "microbial-host dialogue". It also lays a significant theoretical foundation for the development of precision therapeutic strategies based on microbiome interventions.

Targeting the Host Intestinal Barrier

GMEVs play a pivotal regulatory role in the onset and progression of metabolic diseases, with one of their core mechanisms being the targeting of the host's intestinal barrier system to induce systemic metabolic disturbances (Figure 3). The regulation of intestinal barrier function by GMEVs manifests primarily at two levels: the physical barrier and the immune barrier. Regarding the physical barrier, GMEVs from different sources exert differential regulatory effects on the tight junction protein network. For instance, EVs derived from pathogenic bacteria encapsulate virulent toxins that can inhibit the expression of tight junction proteins such as Occludin and ZO-1, thereby compromising the intestinal epithelial barrier and activating intrinsic inflammation.⁸⁷ Concurrently, pathogenic bacterial EVs may reduce the overall concentration of short-chain fatty acids in the gut microbiota, inducing inflammatory responses that damage

Table 2 Dual Roles of GMEVs in Metabolic Diseases

Metabolic Disease	Detrimental Mechanisms	Protective Mechanisms	References
Obesity	<p>Escherichia coli-derived GMEVs: Carry LPS, disrupt Occludin and ZO-1 expression, impair intestinal barrier, and activate inflammation.</p> <p>Pathobiont GMEVs: Reduce overall SCFA production, damaging ileal mucosa.</p>	<p>Akkermansia muciniphila-EVs: Upregulate Occludin expression, enhance tight junction integrity, reduce weight gain, improve glucose tolerance, and reduce permeability in LPS-treated Caco-2 cells.</p> <p>Probiotic GMEVs: Promote M2 macrophage polarization, enhancing barrier function and reducing inflammation. Symbiont GMEVs: Penetrate the barrier, maintain immune tolerance, and indirectly strengthen tight junctions.</p>	[18,30,34,72,84–89]
Diabetes	<p>Pathobiont-derived GMEVs: Inhibit tyrosine phosphorylation of Insulin Receptor Substrates, reducing insulin sensitivity in adipocytes.</p> <p>GMEVs from dysbiotic microbiota: Increase intestinal permeability, facilitate abnormal absorption of GMEVs and their cargo, induce systemic insulin resistance and glucose intolerance by specifically blocking insulin signaling in skeletal muscle and adipose tissue.</p>	<p>Lactobacillus-derived GMEVs: Upregulate GLUT4 expression via the AMPK pathway. Faecalibacterium prausnitzii-EVs: Enhance intestinal barrier function (eg, Claudin-1, ZO-1), suppress inflammation, and improve insulin sensitivity.</p> <p>Probiotic GMEVs (general): Modulate gut microbiota balance and promote SCFA generation to improve barrier function.</p>	[30,63,72,79,86,90–93]
MAFLD	<p>Proteobacteria-derived GMEVs: Transport LPS and pro-inflammatory factors (eg, miR-155) via the gut-liver axis, activating hepatic stellate cells (HSCs), promoting collagen deposition, fibrogenesis, and disrupting intestinal barrier.</p> <p>Pathological GMEVs: Increase gut permeability, allowing more LPS into the portal circulation; directly interfere with hepatocyte lipid metabolism.</p>	<p>Bifidobacterium-derived EVs: Restore gut barrier integrity, reduce hepatic TNF-α and IL-1β levels. Prevotella-EVs: Suppress HSC activation via inhibition of the TGF-β pathway, ameliorating steatosis and liver inflammation.</p>	[11,18,30,62,63,71,72,84,91,94–96]
Metabolic Syndrome	<p>Pathobiont-derived EVs (eg, from Desulfovibrio): Increase intestinal permeability, allowing bacterial products into systemic circulation, triggering low-grade systemic inflammation and insulin resistance via NLRP3 inflammasome activation.</p> <p>Ralstonia-derived EVs: Contain low-acetylation LPS, are secreted in higher quantities, and efficiently transport LPS into the bloodstream, exacerbating chronic low-grade inflammation.</p>	<p>Roseburia intestinalis-EVs: Deliver butyrate-producing enzymes, enhancing SCFA levels, which contributes to improved blood glucose, lipids, and blood pressure.</p> <p>Bacteroidales-EVs: Modulate bile acid metabolism and GLP-1 secretion, improving glycemic and lipid control and promoting metabolic amelioration.</p>	[30,87,91,92,97,98]
Systemic Inflammation & Immunomodulation	<p>LPS-rich GMEVs (eg, from Proteobacteria in obesity): Promote adipose tissue inflammation via TLR4 signaling, characterized by increased pro-inflammatory macrophage infiltration and reduced Tregs. Recruit macrophages to the gut, polarize them to pro-inflammatory M1 phenotype by inhibiting GM-CSF/STAT3/Arg-1 pathway.</p> <p>GMEVs in Diabetic Nephropathy: Migrate from the gut to the renal tubulointerstitium, inducing renal inflammatory damage via the Caspase-11 pathway.</p>	<p>Probiotic GMEVs: Promote anti-inflammatory M2 macrophage polarization, increasing tight junction protein levels and reducing permeability.</p> <p>Immune Reprogramming: Stimulate Dendritic Cells (DCs), leading to differential miRNA packaging into DC-derived EVs, which subsequently modulates adaptive immune polarization (eg, Treg/Th1 balance).</p>	[11,30,63,89,94,97,99,100]

Abbreviations: LPS, lipopolysaccharides; GMEVs, Gut microbiota-derived extracellular vesicles; MAFLD, metabolic associated fatty liver disease.

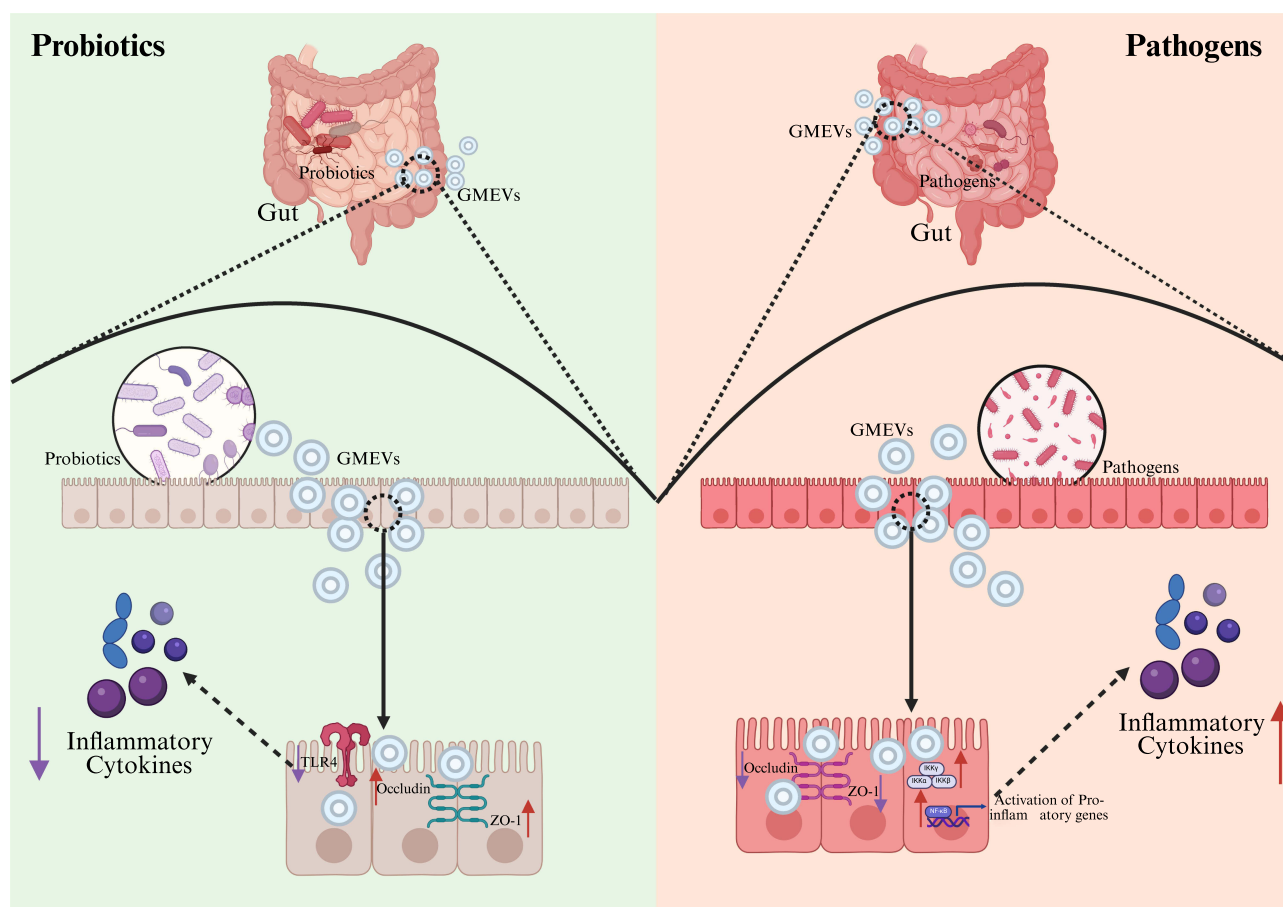


Figure 3 The mechanistic role of GMEVs in modulating metabolic diseases via intestinal barrier regulation. Purple arrows (↓) denote downregulation, while red arrows (↑) denote upregulation.

Abbreviations: GMEVs, Gut microbiota-derived extracellular vesicles; TLR4, toll-like receptor 4; ZO-1, Zona Occludens-1.

the ileal mucosa.⁸⁸ In contrast, EVs derived from probiotics or symbiotic bacteria exhibit opposing effects. The quantity of EVs originating from the probiotic *A. muciniphila* is significantly greater in fecal samples from healthy individuals compared to those from patients with type 2 diabetes.¹⁸ Furthermore, in a diabetic mouse model fed a high-fat diet, it was observed that EVs derived from *A. muciniphila* can influence intestinal permeability by modulating tight junctions.¹⁸ This enhancement of tight junction functionality not only mitigates weight gain and improves glucose tolerance but also reduces intestinal permeability in Caco-2 cells treated with LPS,¹⁸ while simultaneously upregulating the expression of Occludin to bolster intestinal barrier function.^{84,86} Similarly, EVs from symbiotic bacteria can effectively penetrate the intestinal barrier system, maintaining intestinal immune tolerance and indirectly enhancing tight junction integrity.³⁴ When the gut microbiota becomes dysregulated, an increase in pathogenic bacteria leads to the destruction of the host's intestinal barrier, resulting in the translocation of endotoxins (particularly LPS) from the gut, which contributes to metabolic endotoxemia. The circulating LPS activates inflammatory signaling in adipose tissue and the liver by binding to TLR4 receptors, serving as a significant trigger for obesity-related insulin resistance.^{101,102} Conversely, probiotic-derived EVs can help restore gut microbiota balance and promote the production of short-chain fatty acids, thereby improving intestinal barrier function.⁹⁰ In terms of immune barrier regulation, GMEVs activate the immune cell network within the intestinal lamina propria through multiple pathways. Macrophages, as the first line of defense in intestinal immunity, are precisely regulated by GMEVs. GMEVs from probiotics can promote the M2 anti-inflammatory polarization of macrophages, enhancing the levels of tight junction proteins and reducing permeability, thereby further strengthening the intestinal barrier through dual immune-barrier regulation.⁸⁹ In contrast, GMEVs from pathogenic bacteria inhibit the granulocyte-macrophage colony-stimulating factor/signal transducer and activator of transcription 5

(staT5)/Arg-1 signaling pathway, blocking the differentiation of macrophages into an anti-inflammatory phenotype and promoting their polarization towards the pro-inflammatory M1 phenotype.⁹⁹ GMEVs not only recruit macrophages to the intestine, disrupting the balance of intestinal immunity, but also enhance pro-inflammatory responses by altering their functional state. Under the influence of GMEVs, dendritic cells (DCs) become activated, and through differential regulation of miRNAs, they affect T cell responses. Following stimulation by GMEVs, DCs induce naïve CD4+ T cells to secrete effector cytokines.¹⁰⁰ Notably, the differences in Th1 and Treg-related factors are pronounced. The EVs released by DCs are enriched with co-stimulatory molecules, and the immune-related miRNAs they carry vary depending on the source of the GMEVs.¹⁰⁰ These disparities align with the phenotypes of immune responses, indicating that GMEVs regulate adaptive immune polarization by reshaping the secretion profile of DC-derived EVs.

In the clinical translation of metabolic diseases, the barrier-regulating properties of GMEVs hold dual value: for one thing, the detection of specific GMEV subpopulations in feces could serve as early biomarkers for intestinal barrier damage; for another thing, engineered probiotic GMEVs, which overexpress intestinal barrier-stimulating factors such as Occludin, hold promise as novel therapeutic agents for repairing the intestinal barrier. Recent studies suggest that targeted delivery of protective components of GMEVs to the intestine via nanocarriers can inhibit pro-inflammatory factors, repair the mucus layer and tight junction barriers, and restore gut microbiota balance while suppressing inflammation through multiple mechanisms, thereby counteracting the destructive effects of pathogenic GMEVs.¹⁰³ With the advent of single-cell sequencing and spatial transcriptomics, our understanding of the relationship among GMEVs, the intestinal barrier, and metabolic dysregulation is deepening from a tissue level to a cellular subpopulation level, providing a theoretical basis for the development of precise intervention strategies. Future research should focus on addressing the heterogeneity of GMEVs (the differences in EVs produced by the same species under varying physiological states) and establishing more humanized mouse models that closely mimic the true roles of GMEVs in human metabolic diseases.

Interactions with Distant Organs

GMEVs serve as crucial mediators of communication between gut microbiota and the host, carrying a wealth of bioactive molecules that facilitate inter-organ signaling through the circulatory system, thereby participating in the metabolic regulation of distant tissues.⁹ These vesicles, ranging from approximately 30 to 300 nm in diameter, not only mediate local immune regulation but also exert systemic effects on glucose and lipid metabolism and immune responses, providing a novel perspective for understanding the pathogenesis of metabolic diseases. The distal regulatory effects of GMEVs on lipid metabolism in metabolic diseases exhibit a complex “double-edged sword” effect. For one thing, GMEVs derived from pathogenic bacteria can inhibit the tyrosine phosphorylation of insulin receptor substrates, thereby diminishing the sensitivity of adipocytes to insulin.⁹² For another, GMEVs from probiotics demonstrate significant protective effects on lipid metabolism. Research indicates that probiotic-derived GMEVs are more effective than the bacteria themselves in ameliorating obesity, significantly reducing body weight and fat mass in mice subjected to a high-fat diet. This protective mechanism involves enhancing intestinal barrier function, reducing systemic LPS leakage, upregulating the expression of lipolysis-related genes in adipose tissue, and promoting the browning of white adipose tissue.^{30,84,94} Notably, the effects of these probiotic GMEVs surpass those of heat-inactivated bacterial cells, highlighting their therapeutic potential as “postbiotics”.^{12,86} In terms of liver metabolic regulation, GMEVs participate in the development of MAFLD through the “gut-liver axis” (Figure 4). The portal circulation positions the liver as the primary target organ for GMEV action.⁶³ Studies have shown that pathological GMEVs produced during gut microbiota dysbiosis can promote liver injury through various mechanisms:¹¹ increasing intestinal permeability to allow more LPS into the portal circulation,³⁰ directly activating hepatic stellate cells to promote collagen deposition and fibrosis,⁸⁴ and interfering with hepatocyte lipid metabolism.⁹⁶ Particularly noteworthy is the ability of some GMEVs to traverse the pores of hepatic sinusoidal endothelial cells and enter peripheral circulation, which may represent a significant mechanism for the “dissemination” of metabolic inflammation throughout the body.³⁰

As key messengers linking the gut micro-environment with systemic metabolism, GMEVs play a central regulatory role in the dysregulation of glucose metabolism in metabolic diseases through their unique compositional characteristics and inter-organ delivery capabilities. Research on obese diabetic rat models has revealed that dysbiosis in diabetic rats leads to altered proportions of gut microbiota-derived GMEVs, impaired glucose tolerance, and disrupted glucose

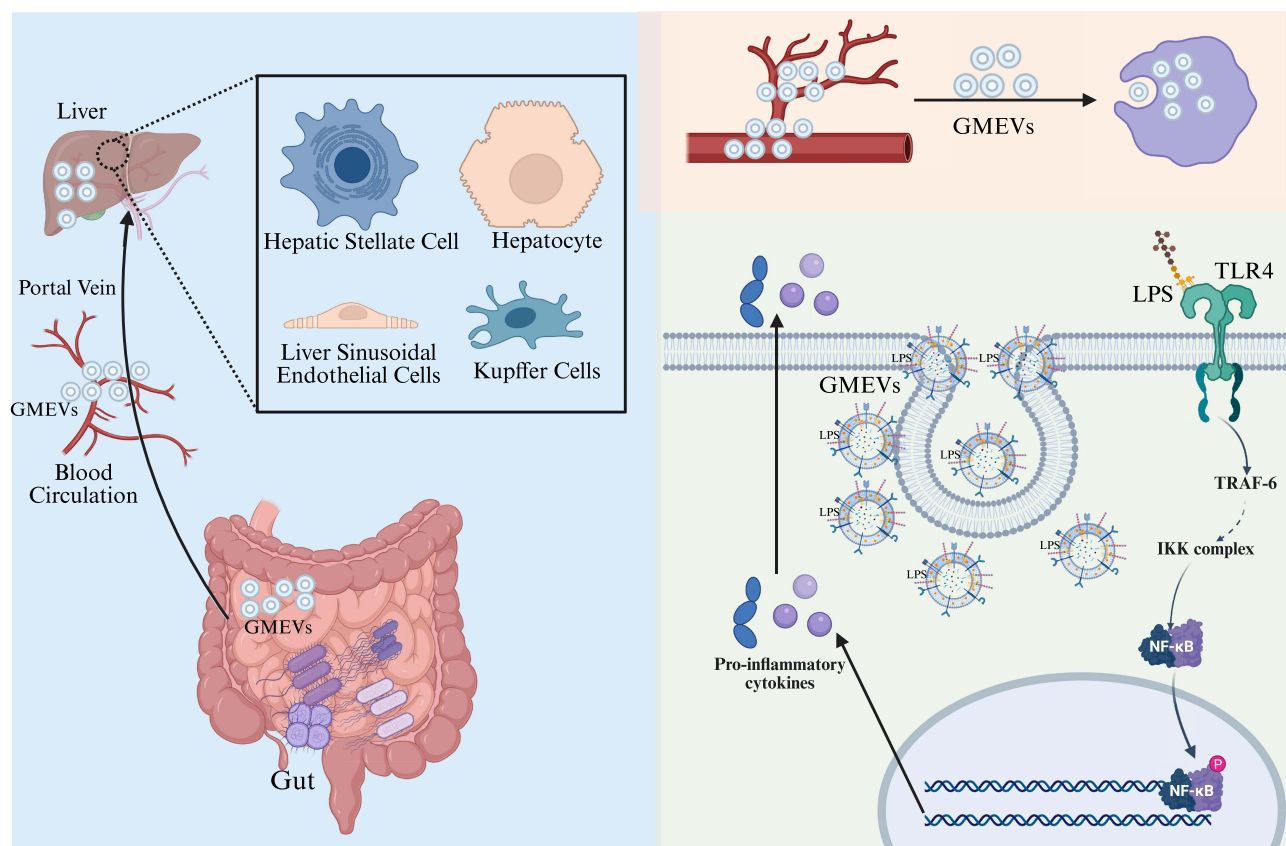


Figure 4 The “gut-liver axis” interaction network of GMEVs.

Abbreviations: GMEVs, Gut microbiota-derived extracellular vesicles; LPS, lipopolysaccharides; TLR4, toll-like receptor 4; TRAF-6, Recombinant TNF Receptor Associated Factor 6; NF-κB, nuclear factor kappa-B.

metabolism.⁹³ This indicates that GMEVs can participate in the process of glucose metabolic dysregulation by delivering bacterial active components, exerting remote effects on multiple metabolic organs. For instance, a study involving patients with type 2 diabetes found that increased intestinal permeability in these patients facilitated the abnormal absorption of GMEVs and their contents, resulting in chronic inflammation and metabolic dysregulation.⁹¹ This process promotes the translocation of GMEVs across the intestinal barrier into the circulatory system, where they induce insulin resistance and impaired glucose tolerance through the delivery of microbial components. Additionally, other studies have reported that GMEVs from mice fed a high-fat diet can induce insulin resistance and glucose intolerance, a process characterized by the specific blockade of insulin signaling in skeletal muscle and adipose tissue, leading to impaired glucose tolerance and systemic insulin resistance, thereby remotely regulating host glucose metabolism.⁷⁹ Concurrently, the virulence factors carried by GMEVs can be transferred to the liver via the circulatory system, reducing hepatic sensitivity to insulin, inhibiting glycogen synthesis, and resulting in sustained hyperglycemia, which disrupts hepatic glucose metabolic homeostasis and directly impairs insulin signaling and glycogen synthesis, thereby promoting the progression of metabolic dysregulation in diabetes.¹⁰⁴

The gut microbiota, as a complex and dynamic ecosystem, is regarded as an “essential organ” of the human body,¹⁰⁵ playing a significant regulatory role in modulating immune responses, including inflammation.¹⁰⁶ GMEVs, as messengers of the gut microbiota, also play a crucial role in maintaining inflammatory balance in metabolic diseases. Research indicates that GMEVs derived from pathogenic bacteria, such as vesicles containing high levels of LPS, can promote inflammation in adipose tissue through the TLR4 signaling pathway, characterized by an increase in pro-inflammatory macrophage infiltration and a decrease in regulatory T cells (Tregs).^{11,63} Numerous studies have shown that the biological characteristics of GMEVs undergo significant changes under metabolic dysregulation, thereby influencing the host’s inflammatory response and immune response. For instance, it has been reported that the proportion of LPS-carrying EVs in the feces of diet-induced obese mice

significantly increases, along with a higher abundance of *Proteobacteria*.³⁰ These EVs can breach the intestinal barrier and enter the liver and bloodstream, leading to upregulation of TLR4 expression and activation of inflammatory factors, thereby promoting metabolic inflammation.³⁰ The structural differences in LPS from specific gut bacteria (such as *Ralstonia*) affect their pro-inflammatory capacity; low-acylation LPS strains, although exhibiting weaker inflammatory activity, secrete more EVs, efficiently transporting LPS into the bloodstream and exacerbating chronic low-grade inflammation.⁹⁷ Recent studies have also found that specific bacterial DNA markers in serum are significantly correlated with the degree of perirenal fat inflammation, and the EPC index established based on these markers (AUC=0.81) offers a novel approach for non-invasive assessment of adipose tissue inflammation.¹⁰⁷ Furthermore, GMEVs play a critical role in the progression of diabetic nephropathy. A study investigating the regulatory role of GMEVs in the development of diabetic nephropathy showed that GMEVs from diabetic nephropathy rats can migrate from the gut to the renal interstitium, inducing renal inflammatory damage through the Caspase-11 inflammatory pathway.⁹⁴

Notably, the host organs are not passive recipients of GMEV-mediated regulation but actively modulate the generation, release, and function of GMEVs through multiple mechanisms. Studies have reported that metabolic states such as diabetes can alter the intestinal environment, thereby influencing the gut microbiota composition and their vesicle secretion behaviors. For instance, in diabetic rats treated with bariatric/metabolic surgery, glucose tolerance and microbial richness were reversed, accompanied by changes in GMEV composition.⁹³ Furthermore, the liver, as a major organ for the clearance and modification of GMEVs, actively participates in regulating their systemic distribution and biological effects.¹⁰⁸ Upon entering hepatic tissue, GMEVs are actively phagocytosed by Kupffer cells, which contributes to their removal from circulation.¹⁰⁸ Recent evidence also suggests that the host neuroendocrine system may indirectly influence the secretion profile of GMEVs via the gut-brain axis, further highlighting the complexity of the bidirectional communication network between GMEVs and the host.^{71,109}

Therapeutic Applications of GMEVs

As “microbial messengers” connecting microorganisms with the host, GMEVs exhibit unprecedented core value in the pathogenesis and intervention strategies of metabolic diseases. These nanoscale bioactive carriers, through their unique molecular composition and precise delivery mechanism, have built a “microbiome-host dialogue system” that transcends species boundaries. This provides a new perspective for understanding the microbiome basis of metabolic diseases, and also provides a new, efficient and safe microecological intervention strategy for the treatment of metabolic diseases. Research has shown that EVs derived from gut probiotics, as natural nanocarriers, can improve metabolic disorders by repairing the intestinal barrier, regulating microbial balance, and suppressing inflammatory responses.¹¹⁰ They not only enhance intestinal integrity to prevent endotoxin entry into the bloodstream but also regulate systemic glucose and lipid metabolism and neuroendocrine functions through the gut-liver/brain axis, providing new strategies for the microecological treatment of metabolic diseases such as obesity and diabetes.¹¹⁰ Moreover, GMEVs improve intestinal barrier function and regulate the gut-liver metabolic axis, ultimately achieving reductions in blood glucose levels, increased insulin sensitivity, and alleviation of obesity.⁹⁰ They intervene in the progression of metabolic diseases through mechanisms of microbial-host metabolic dialogue.⁹⁰ Additionally, GMEVs effectively ameliorate ethanol-induced liver damage by enhancing hepatic antioxidant capacity and reducing blood ethanol concentrations, thereby modulating key pathological processes such as oxidative stress.¹¹¹ EVs derived from *Akkermansia muciniphila* can significantly enhance intestinal barrier function and the integrity of the mucosal layer by delivering functional proteins and various bioactive components, while also modulating glucose and lipid metabolism. They improve symptoms of obesity and diabetes by activating GLP-1 signaling to enhance insulin sensitivity and inhibiting the NF- κ B pathway to alleviate systemic low-grade inflammation and regulate blood glucose and lipid levels. Furthermore, they influence hepatic lipid metabolism and neuroinflammation through the circulatory system, demonstrating a superior effect compared to that of the bacterial cells themselves.^{61,86,112} *Akkermansia muciniphila*-derived EVs outperform live bacteria in improving metabolic dysregulation, significantly inhibiting obesity induced by a high-fat diet, reducing weight gain, metabolic organ weight, and plasma metabolic abnormalities, whereas also alleviating inflammation in the gut, adipose tissue, and liver, and effectively restoring gut microbiota balance and increasing beneficial bacterial abundance.⁸⁴ Studies have shown that GMEVs from healthy mice conditioned with oral nano-drugs directly alleviate colonic inflammation and repair the mucosal barrier by

reshaping gut microbiota balance, whereas also regulating purine metabolism to lower uric acid levels, demonstrating significantly greater efficacy than traditional fecal microbiota transplantation.¹¹³ The cross-boundary information transmission role of GMEVs provides novel intervention strategies for metabolic diseases such as metabolic syndrome, obesity, and diabetes, with their multi-target and low-toxicity characteristics making them highly promising therapeutic carriers (Table 3).

Limitations and Future Perspectives

GMEVs, as important mediators of interactions between gut microbiota and the host, have demonstrated significant potential in the diagnosis and treatment of metabolic diseases in recent years. However, there are still several limitations in this field. For instance, the biogenesis pathways of GMEVs and their regulatory factors remain incompletely understood, particularly regarding how environmental signals (such as dietary components) are translated into molecular mechanisms that instruct vesicle loading. Additionally, the lack of standardized methods for the isolation and identification of GMEVs limits the comparability of research findings, while quality control issues in large-scale production pose major bottlenecks for clinical translation. Furthermore, the potential risks associated with long-term GMEV application (such as the induction of autoimmune responses) require more comprehensive evaluation systems. Notably, current research predominantly focuses on specific components such as LPS, while the roles of other functional molecules carried by GMEVs (eg, microbial-derived miRNAs, signaling proteins, and metabolites) in host metabolic and immune regulation remain poorly understood, thereby limiting our comprehensive understanding of the systemic functions of GMEVs. Addressing these challenges necessitates the establishment of an internationally collaborative research network, the development of next-generation analytical tools, and the formulation of unified technical standards.

Looking ahead, research on GMEVs can leverage two key advantages to develop and apply clinical diagnostic markers, providing a novel source of biomarkers for disease diagnosis (Figure 5). First, GMEVs are continuously released into the circulatory system by gut microbiota and can stably exist in clinical samples such as blood and feces. Second, they carry bioactive molecules, including proteins, nucleic acids, lipids, and metabolites from the parent bacteria, which can cross the intestinal mucosal barrier and directly or indirectly regulate the host's metabolic and immune responses. Not only does the double-membrane structure of GMEVs effectively protect their cargo from enzymatic degradation, thereby preserving the stability of bioactive molecules such as proteins, nucleic acids, and metabolites in blood, urine, and other samples over extended periods, but their surface markers also exhibit species-specificity, facilitating traceability analysis. More importantly, although the secretion profile and molecular composition of GMEVs undergo dynamic changes in response to external factors, these alterations follow predictable and identifiable patterns that reflect characteristic features of microbiota-host interactions under specific physiological or pathological

Table 3 Therapeutic Targets and Mechanisms of GMEVs in Metabolic Diseases

Therapeutic Target	Intervention Effects	Mechanisms of Action	References
Intestinal barrier repair	Amelioration of metabolic disorders (obesity, diabetes)	Enhancement of intestinal integrity to prevent endotoxin translocation; modulation of gut-liver/brain axis	[108]
Gut-liver metabolic axis modulation	Reduction of blood glucose, improved insulin sensitivity, alleviation of obesity, Improvement of liver injury	Restoration of intestinal barrier function; regulation of microbiota-host metabolic crosstalk; Enhancement of hepatic antioxidant capacity; reduction of blood ethanol levels; regulation of oxidative stress	[90,109]
GLP-1 signaling activation	Improvement of obesity and diabetes symptoms	Enhancement of insulin sensitivity; suppression of NF-κB pathway to alleviate systemic inflammation; regulation of hepatic lipid metabolism and neuroinflammation	[62,94,110]
Gut microbiota remodeling	Suppression of HFD-induced obesity; attenuation of multi-organ inflammation	Restoration of microbial balance (increased beneficial bacteria); reduction of intestinal/adipose/liver inflammation	[84]
Purine metabolism regulation	Reduction of uric acid levels; alleviation of colonic inflammation	Direct repair of mucosal barrier; remodeling of gut microbiota (superior efficacy to FMT)	[111]

Abbreviations: GLP-1, glucagon-like peptide-1; NF-κB, nuclear factor kappa-B; HFD, High-Fat Diet; FMT, fecal microbiota transplantation.

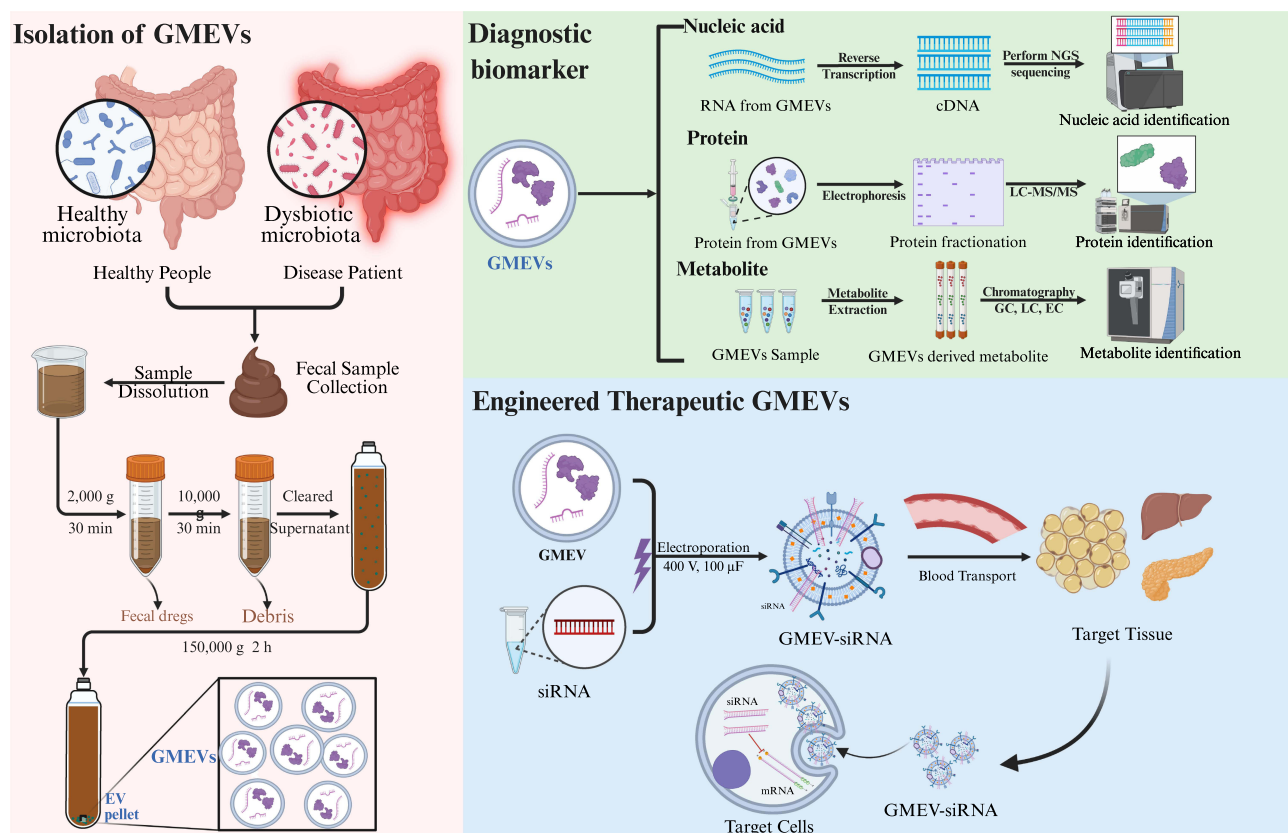


Figure 5 The Application Prospects of GMEVs as Diagnostic Markers and Therapeutic Vectors.

Abbreviations: GMEVs, Gut microbiota-derived extracellular vesicles; siRNA, Small interfering RNA.

conditions. For instance, under high-fat diet or circadian rhythm disruption, although the total quantity or specific components of GMEVs may be altered, these changes are often closely associated with metabolic abnormalities. Consequently, rather than diminishing their diagnostic value, such variations provide temporal information that can be utilized for disease staging, risk stratification, and dynamic monitoring.^{9,114,115} Population studies have shown that the characteristics of EVs in urine can predict the risk of abdominal obesity: individuals with a high abundance of *Firmicutes* and a low abundance of *Proteobacteria* have a 2.59-fold increased risk of abdominal obesity within ten years.¹¹⁶ Multi-omics analyses indicate that the microbial composition of EVs in the feces, serum, and urine of diabetic patients exhibits abnormal co-occurrence patterns, which may serve as new non-invasive biomarkers for diabetes diagnosis.⁹¹ Moreover, the composition and functional characteristics of gut microbiota undergo specific changes under different disease states, and these alterations are directly reflected in the molecular profiles of GMEVs.^{117–120} This makes it possible to achieve early disease diagnosis by detecting specific components of GMEVs in blood or feces. In metabolic diseases such as obesity, diabetes, and MAFLD, dysregulation of gut microbiota composition and function is often accompanied by changes in the secretion profiles of GMEVs.^{11,94,121} These GMEVs, derived from specific sources or containing specific components, participate in disease development by influencing insulin sensitivity, lipid metabolism, and inflammatory responses. Their unique molecular characteristics also provide new biomarkers for early diagnosis and classification of diseases. These findings suggest that the microbial source characteristics or specific molecules contained within GMEVs (such as species-specific proteins, differential miRNAs, and specific metabolites) may serve as potential diagnostic indicators for metabolic diseases.^{11,94,121} These findings suggest that by integrating multi-timepoint sampling, dynamic monitoring, and big data analytics, it is anticipated that the compositional dynamics of GMEVs can be transformed into “dynamic biomarkers” reflecting an individual’s metabolic status, thereby further enhancing their potential for application in precision diagnosis. Future research should integrate multi-omics technologies and longitudinal cohorts to further clarify the dynamic changes of GMEVs in metabolic diseases and their sensitivity and specificity as diagnostic markers.

This will promote their clinical application and achieve a qualitative leap from “understanding microorganisms” to “harnessing microbial signals”, providing new tools for the prevention and treatment of metabolic diseases.

Conclusion

In summary, as mediators of cross-communication between microorganisms and the host, GMEVs carry active molecules that mediate the regulation of the “gut-organ axis”. In metabolic diseases such as obesity and diabetes, they play dual roles: GMEVs derived from pathogenic bacteria exacerbate metabolic inflammation and insulin resistance by disrupting the intestinal barrier, activating the TLR4/NF- κ B inflammatory pathway, and inhibiting insulin signaling. In contrast, GMEVs from probiotics and commensal bacteria exert protective effects by enhancing tight junctions, regulating immune responses, and improving glucose and lipid metabolism. Metabolic risk factors can dynamically modulate the composition and function of GMEVs, and the specific molecular characteristics provide novel biomarkers for early disease diagnosis. Despite challenges such as standardization of isolation methods, GMEVs exhibit vast potential in precision therapy, such as engineered probiotic EVs for intestinal barrier repair and as drug delivery vehicles. Future research should delve deeper into the spatiotemporal interaction patterns of GMEVs and host response mechanisms, facilitating the translation of basic research into clinical diagnostics and intervention strategies, and providing a new perspective on the “microbial-host dialogue” for the prevention and treatment of metabolic diseases.

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Disclosure

The authors declare that there are no conflicts of interest.

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