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REVIEW

Metabolic memory in the gut: The microbiota-epigenetic crosstalk orchestrating obesity onset and novel therapeutic landscapes

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Abstract

Metabolic memory, defined as the persistent cellular and molecular alterations induced by transient metabolic perturbations (*e.g.*, high-fat/high-fructose diets) even after metabolic normalization, has emerged as a critical driver of chronic metabolic diseases, including obesity. Recent evidence highlights the gut as a key mediator of metabolic memory, where gut microbiota dysbiosis and subsequent epigenetic modifications establish long-lasting functional changes that predispose individuals to obesity and hinder treatment responses. This review summarizes the intricate interplay between gut-related metabolic memory and obesity: Transient exposure to obesogenic diets triggers sustained shifts in gut microbiota com-

position - such as the enrichment of *Odoribacter* (a source of histone deacetylase inhibitor butyrate, whose dosage governs beneficial versus deleterious effects) - even after the restoration of a normal diet. Butyrate, as a key microbial metabolite, modulates epigenetic marks (*e.g.*, DNA methylation and histone acetylation) in intestinal epithelial cells, immune cells, and hepatocytes, perpetuating pro-inflammatory signaling, dysregulated lipid metabolism, and impaired gut barrier function. These persistent alterations, rooted in metabolic memory, promote systemic insulin resistance, adiposity accumulation, and chronic low-grade inflammation, which are hallmarks of obesity. Additionally, maternal obesogenic diets transmit metabolic memory to offspring *via* gut microbiota-epigenetic crosstalk, increasing intergenerational obesity susceptibility. For obesity treatment, targeting gut-related metabolic memory offers promising strategies: Early dietary interventions to prevent the establishment of detrimental microbiota-epigenetic signatures, microbiota modulation (*e.g.*, probiotics targeting *Odoribacter* homeostasis), and epigenetic modifiers (*e.g.*, butyrate analogs or histone deacetylase inhibitors) to reverse persistent epigenetic alterations. Understanding the gut-metabolic memory axis provides new insights into obesity pathogenesis and underscores the need for time-sensitive, microbiota-epigenetic targeted therapies to break the cycle of metabolic memory-driven obesity.

Key Words: Metabolic memory; Gut microbiota; Epigenetics; Obesity; Microbiota-epigenetic crosstalk; Intergenerational transmission; Butyrate

Core Tip: The gut serves as a critical repository for metabolic memory, where transient exposure to obesogenic diets triggers persistent microbiota-epigenetic crosstalk. Specific microbial shifts, such as the enrichment of *Odoribacter*, lead to sustained epigenetic modifications like histone hyperacetylation *via* butyrate, driving chronic inflammation and obesity even after dietary normalization. This memory can be vertically transmitted to offspring, increasing intergenerational obesity susceptibility. Breaking this cycle requires time-sensitive interventions, including microbiota modulation and epigenetic therapies to restore metabolic homeostasis.

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INTRODUCTION

The intestine serves as a critical repository for the body's metabolic memory, capable of encoding and sustaining long-term pathological programs initiated by metabolic disturbances. The concept of metabolic memory has evolved significantly over an extended period. It originally emerged from clinical studies on diabetes and its complications, where pathological changes induced by hyperglycemia were found to persist even after blood glucose levels were normalized - a phenomenon referred to narrowly as glucose toxicity metabolic memory[1-3]. As research progressed, the notion of metabolic memory has been extended to various other pathological conditions, including those induced by high-fat diet (HFD) and hyperuricemia[4-7]. Currently, the core feature of metabolic memory lies in the long-lasting persistence of detrimental effects caused by transient metabolic disturbances, which continue even after the metabolic environment has been corrected[8].

Recent studies have unveiled that the gut microbiota possesses the capacity to form and retain enduring memories of past exposure. Such microbial memory can substantially shape host physiological and cognitive functions. Excessive sugar intake during adolescence in rats alters the gut microbiota and subsequently impairs hippocampal-dependent memory function in adulthood. Moreover, transplanting these specifically altered bacterial populations into normal rats similarly damages hippocampal function[9]. Excessive consumption of a HFD containing trans fatty acids can alter serum parameters, lipid profiles in the brain and plasma, as well as the composition of the gut microbiota in male Sprague-Dawley rats[10]. Human-based research further indicates that the gut microbiota can encode memory upon exposure to nutrients such as the prebiotic inulin within a single day, and this memory persists for several days, influencing the metabolic potential of the microbial community[11]. Beyond nutrients, a similar memory mechanism exists in response to intestinal pathogens: The gut microbiota retains a memory of prior infections, leading to enhanced resistance upon re-exposure to similar pathogens[12]. Collectively, these findings establish the gut as a critical mediator of metabolic memory and underscore its high research value.

The dynamic interplay between gut microbiota and host epigenetic mechanisms constitutes the core of gut-mediated metabolic memory[8]. Brief exposure to a HFD induces persistent alterations in microbial composition and function, leading to sustained changes in the production of key metabolites[13,14]. These metabolites drive enduring epigenetic modifications such as DNA methylation and histone acetylation, thereby locking in a pro-obesity transcriptional program that persists even after the initial dietary stressor is removed[8,15]. This review will elucidate this unified microbiota-epigenetic interaction, exploring its role in establishing metabolic memory, intergenerational transmission, and the

therapeutic opportunities it presents.

METABOLIC MEMORY: BASIC CONCEPTS AND GUT-MEDIATED CHARACTERISTICS

Molecular basis of gut-mediated metabolic memory

One core mechanism underlying metabolic memory involves epigenetic modifications, including DNA methylation, histone modifications, and regulation by non-coding RNAs. A hallmark of this phenomenon is that epigenetic changes triggered during early stages are not immediately reversed even after metabolic homeostasis is restored and can be transmitted to offspring. In mammals, alterations in maternal diet and gut microbiota can influence the training status of immune cells in offspring through epigenetic mechanisms such as microRNAs (miRNAs) present in sperm or oocytes, thereby affecting their health. Studies have shown that *Escherichia coli* possesses a form of metabolic memory stored as cellular iron levels, which can be stably inherited for up to four generations and only dissipates by the seventh generation [16]. Moreover, during phase variation of pili in pathogenic *Escherichia coli*, heritable changes in gene expression occur, and these alterations are transmitted to daughter cells *via* DNA methylation pattern[17].

The gut microbiota and its metabolites influence the metabolic memory of the intestine by participating in processes such as host DNA methylation and demethylation. Butyrate, a key short-chain fatty acid (SCFA) produced by gut microbial fermentation, primarily regulates the epigenetic state of intestinal macrophages by inhibiting histone deacetylase (HDAC) activity. This enhances the antibacterial function of macrophages and suppresses the release of pro-inflammatory cytokines, thereby contributing to the maintenance of intestinal homeostasis[18,19]. The gut microbiota and its metabolites participate in host DNA methylation and demethylation processes by modulating the activity of enzymes such as DNA methyltransferases (DNMTs) and ten-eleven translocation methylcytosine dioxygenases, consequently influencing intestinal stability. For instance, variants in the DNMT 3 alpha (*DNMT3α*) gene are associated with susceptibility to inflammatory bowel disease (IBD). Loss of DNMT3α function can lead to DNA hypomethylation and mediates the impact of environmental factors such as smoking on IBD, ultimately impairing epithelial barrier function[20,21]. Furthermore, the microbiota dynamically regulates histone modifications. In IBD patients, microbiota-dependent histone H3 lysine 4 trimethylation modifications are linked to epigenetic dysregulation associated with the disease[22]. Animal studies further demonstrate that gut colonization significantly increases levels of H4 acetylation and histone H3 lysine 27 (H3K27) methylation in colon tissues[23].

Evidence for the gut as a core site of metabolic memory

The gut is a key site for material exchange and the core storage location for metabolic memory. Animal studies show that obesogenic diets induce persistent abnormalities in gut microbiota and inflammatory signals, driving metabolic disorders even after diet withdrawal. HFD activates intestinal epithelial myeloid differentiation primary response 88 (MyD88) signaling in mice, restricting endocannabinoid and antimicrobial peptide secretion and creating a pro-inflammatory environment that remains activated after short-term diet restoration[8]. Additionally, HFD-induced histone acetylation changes mediated by gut microbiota are long-lasting, with suppressed anti-inflammatory pathways and persistent metabolic phenotypes despite partial microbiota recovery[13], consistent with the persistence criterion of metabolic memory. These studies all confirm that the alterations in gut microbiota and metabolic phenotypes induced by obesogenic diets are irreversible.

Epigenetic or immune memory formed under obesogenic conditions persists after dietary improvement, affecting metabolic function. Early HFD in mice induces lasting hepatic chromatin accessibility changes and increased histone H3 lysine 9 dimethylation, promoting fatty liver and insulin resistance despite diet restoration[8]. HFD also elevates hippocampal inflammatory factors and synaptic damage proteins, with sustained inflammation and dysfunction after diet switch[24]. Human cohort studies link specific gut microbiota and epigenetic markers to obesity recurrence risk. Intestinal CD8 alpha-beta positive T cells are increased in obesity, correlating with fasting glucose and insulin resistance, serving as a recurrence biomarker[25]. In a Chinese cohort (7521 participants), elevated Peptostreptococcaceae in metabolically unhealthy normal weight individuals correlates with cognitive decline and predicts future obesity and metabolic disorders, reflecting gut microbiota's long-term regulatory role[26].

The gut amplifies metabolic memory into systemic phenotypes *via* crosstalk with liver, adipose tissue, and brain, and serves as its core storage site. HFD impairs the intestinal barrier in mice, allowing bacterial products to induce hepatocellular steatosis, and intestinal chemokine receptor 2-positive macrophages migrate to visceral adipose tissue, inhibiting browning. After diet restoration, these inflammatory signals persist, causing steatosis and impaired thermogenesis[25]. Furthermore, gut microbiota and their metabolites influence central appetite regulation and energy metabolism through the gut-brain axis, and the formed memory effect indirectly maintains obesity. Literature has shown that reduced abundance of Turicibacteraceae in the gut of ovariectomized rats is associated with spatial memory impairment, which is related to abnormal secretion of the intestinal neurotransmitter 5-hydroxytryptamine caused by decreased SCFAs (specifically isobutyric acid). After estrogen supplementation, abnormalities in gut-brain axis neural signaling persist partially, indirectly affecting appetite and energy metabolism and maintaining the obese phenotype[27], which is a manifestation of intervention resistance in metabolic memory.

GUT MICROBIOTA DYSBIOSIS AND METABOLIC MEMORY

Obesogenic diets drive persistent remodeling of the gut microbiota

The modulation of gut microbiota by a HFD/high-sugar diet is not transiently reversible; even after subsequent restoration of a normal diet, the microbiota structure still retains long-term alterations. This memory-driven remodeling represents a core manifestation of metabolic memory at the gut microecological level, which exerts a persistent impact on host metabolic health through dynamic shifts and mechanistic crosstalk among multiple microbial taxa[14]. Dietary composition exerts distinct specificity in regulating specific bacterial genera, with the abundance variation of *Odoribacter* - especially *Odoribacter splanchnicus* (*O. splanchnicus*) - being particularly typical. High-fat low-carbohydrate diets and heme components in red meat can act as growth-promoting factors for this genus[15]. Meanwhile, intestinal bile acids can also markedly facilitate its proliferation by modulating the gut microenvironment, whereas increased vegetable intake suppresses its abundance elevation *via* the provision of dietary fiber and other nutrients[28]. This genus exerts a dual role in metabolic regulation. In genetically obese rat models, resveratrol supplementation can improve host insulin sensitivity by upregulating the abundance of *Odoribacter*, which is negatively correlated with adipose mass[29], reflecting a protective effect within a healthy microecosystem. In contrast, its aberrant proliferation under dysbiotic conditions may contribute to the development of adverse metabolic outcomes. The relevance of *Odoribacter* to human metabolic health has been confirmed by recent clinical translational studies. A multi-omics study integrating human cohorts and animal models revealed that *O. splanchnicus* is significantly reduced in the elderly population, and its abundance is positively correlated with intestinal P-glycoprotein (P-gp) expression, a key factor determining drug absorption and intestinal barrier function. Mechanistic studies showed that *O. splanchnicus* activates the eukaryotic translation initiation factor 4E/c-Jun proto-oncogene signaling pathway through secretion of guanosine diphosphate-L-fucose, restoring P-gp expression and improving aging-related intestinal barrier dysfunction. Fecal microbiota transplantation (FMT) experiments further confirmed that supplementation with this single bacterial species rescues intestinal permeability defects in mice[30].

Obesogenic diets trigger dynamic restructuring of the overall gut microbiota community, with these alterations demonstrating long-term stability. The core mechanism involves specific bacterial species acquiring a selective colonization advantage, rather than a delayed restoration of the microbial community. Multiple underlying mechanisms drive this memory-driven remodeling process. The alteration of intestinal microniches constitutes one of the core mechanisms. Long-term consumption of a Western-style high-fat, low-fiber diet can reduce gut microbiota diversity to one-third of the normal level[31]. Even subsequent restoration of a high-fiber diet or FMT fails to fully reverse the original microbiota structure. The key underlying reason is that obesogenic diets have remodeled the intestinal soil: By disrupting the intermicrobial interaction network, altering intestinal pH, mucus layer thickness and metabolic substrate distribution, they create a microenvironment conducive to the colonization of obesogenic microbiota yet unfavorable for the survival of beneficial bacteria, thereby laying the foundation for microbiota memory persistence[32]. The mutual adaptation between host immune status and the microbiota further consolidates such memory. Chronic microbiota dysbiosis induces stable phenotypic changes in immune cells, which in turn suppress the proliferation of beneficial bacteria and promote the colonization of dysbiotic microbiota, forming a vicious cycle of microbiota dysbiosis-immune dysfunction that sustains the aberrant microbiota state.

More notably, microbiota remodeling displays a distinct time-dependent effect: Exposure to a HFD during adolescence, rather than adulthood, permanently alters the ecological memory of the gut microbiota. This is specifically characterized by a persistently elevated Firmicutes/Bacteroidetes (F/B) ratio, and lipopolysaccharide (LPS)-producing strains within the phylum Proteobacteria form biofilm-like structures on the intestinal mucosal layer, which are difficult to eradicate even with FMT[33]. The F/B ratio also serves as a marker of gut dysbiosis in obese patients[34]. The ratio cause of such irreversible memory lies in the profound crosstalk between the microbiota and host epigenetics. Sustained LPS exposure leads to demethylation of the Toll-like receptor 4 (TLR4) promoter region in intestinal epithelial cells, forming a self-reinforcing inflammatory positive feedback loop[35]. This embeds the aberrant microbiota state deeply into the host epigenetic landscape, further locking in metabolic memory. The aforementioned phenomena, including the elevated F/B ratio and increased abundance of LPS-producing bacteria, are all specific manifestations of this cascade of mechanisms. A long-term HFD enhances energy harvest by promoting the proliferation of Firmicutes and inhibiting the growth of Bacteroidetes[36]; notably, the aberrant F/B ratio persists for weeks to months even after dietary normalization[37]. Meanwhile, LPS triggers chronic low-grade inflammation through the impaired intestinal barrier[38].

FMT experiments have also confirmed that alterations in the gut microbiota can serve as a vector for the transmission of metabolic phenotypes. Researchers transplanted fecal microbiota from obese and non-obese twins into germ-free mice, and found that mice receiving microbiota from obese donors gained more weight and showed more pronounced fat accumulation[39]. The effect of diet on host epigenetics depends on the presence of gut microbiota. Supplementing germ-free mice with SCFAs - the primary products of bacterial fermentation - recapitulates the chromatin modifications and transcriptional responses induced by colonization. Thus, diet regulates host epigenetic programming indirectly by modulating microbiota composition[23]. This evidence demonstrates that the microbiota is not only a transmitter of metabolic phenotypes but also a driver of host epigenetic modifications. It should be noted, however, that both studies employed whole microbiota transplantation and therefore cannot distinguish which specific bacterial taxa are responsible for driving these epigenetic changes. Addressing this gap represents a key direction for future research in this field.

Collectively, these processes sustain metabolic memory. In summary, obesogenic diets achieve memory-driven remodeling of the gut microbiota not only by selectively regulating the abundance of *Odoribacter* and reshaping the phylum-level microbiota ratio, but also through multiple intertwined mechanisms including microniche alteration, immune crosstalk, time-dependent effects and epigenetic interaction. These long-term irreversible changes not only modulate metabolic phenotypes, but also provide microecological, inflammatory and epigenetic underpinnings for metabolic memory, serving as a critical link bridging dietary exposure and long-term metabolic health. Therefore,

deciphering the mechanisms underlying the memory-driven remodeling of gut microbiota induced by obesity and precisely reversing the ecological memory of the gut microbiota are expected to become core strategies for the prevention and control of obesity and related metabolic diseases. The persistent remodeling of gut microbiota induced by obesogenic diets is summarized in Table 1.

Gut microbial metabolites as mediators of metabolic memory

Intestinal metabolites form the foundation of local metabolic memory in the gut. Butyrate acts as an environment-dependent metabolic-epigenetic switch under HFD conditions. Normally, butyrate exerts anti-inflammatory and barrier-enhancing effects by HDACs. Under obesogenic conditions, however, colonic monocarboxylate transporter 1 expression is downregulated, impairing butyrate uptake and leading to systemic butyrate deficiency[40]. This state of relative deficiency, rather than accumulation, attenuates HDAC inhibition in intestinal epithelial cells, reduces the expression of tight junction proteins, and impairs barrier integrity - all of which constitute the basis of local metabolic memory in the gut. In the liver, systemic butyrate insufficiency fails to effectively suppress the activity of abnormal HDAC1/2, thereby sustaining the high expression of lipogenic genes including fatty acid synthase and stearoyl-CoA desaturase 1 *via* histone deacetylation[41]. Zheng *et al*[41] demonstrated that HDAC1 overexpression can abrogate the inhibitory effect of butyrate on lipogenesis, and this epigenetic imbalance persists following the withdrawal of the HFD. This mechanism couples gut microbiota dysbiosis with hepatic metabolic reprogramming, establishing transorgan metabolic memory. LPS synergistically consolidates this memory from the inflammatory dimension: Intestinal barrier disruption allows LPS to translocate into the circulation, which then continuously stimulates hepatic Kupffer cells *via* the portal venous circulation. Through the TLR4-MyD88-nuclear factor kappa B pathway, LPS induces the expression of epigenetic reprogramming enzymes (*e.g.*, Jumonji domain-containing protein 3), altering the H3K27 trimethylation/histone H3 lysine 4 trimethylation balance in the promoter regions of pro-inflammatory genes (*e.g.*, tumor necrosis factor-alpha)[42]. Unlike classic endotoxin tolerance, this epigenetic modification exhibits aberrant persistence under obesogenic conditions, locking Kupffer cells in a state of low-grade activation and establishing local inflammatory memory in the liver. Butyrate insufficiency impairs the negative feedback regulation of the epigenetic effects of the LPS-TLR4 signaling pathway, while LPS-induced inflammation further suppresses monocarboxylate transporter 1 expression[43], forming a metabolic-inflammatory positive feedback loop. After such dual memory is established in two local microenvironments - the gut (microbiota-barrier axis) and the liver (metabolism-immunity axis) - epigenetic imprints can be vertically transmitted through cell turnover even if the microbiota structure is partially restored subsequently, providing a molecular basis for the persistence of systemic metabolic disorders.

However, the biological effects of butyrate exhibit a pronounced biphasic nature, conferring upon this metabolite dichotomous roles under physiological and pathological conditions[44,45]. When butyrate exposure exceeds a critical threshold - characterized by excessive concentration or compartmental mislocalization - its functional balance tilts toward deleterious outcomes[44]. Under such pathological circumstances, butyrate transcends its role as a local intestinal protector and transforms into a persistently activated epigenetic modifier: Through excessive HDAC activity, it establishes aberrant and durable histone acetylation patterns in intestinal epithelial cells, immune cells, and even hepatocytes, thereby driving pro-inflammatory gene expression and disrupting lipid metabolism. Notably, these epigenetic alterations triggered by excessive butyrate possess memorative properties - the established transcriptional programs may persist even after butyrate levels return to baseline[46]. Thus, the dualistic nature of butyrate - protective at physiological concentrations yet pathogenic in excess - constitutes a core mechanism underpinning gut metabolic memory and underscores the imperative for precision in microbiota-targeted therapies.

Gut metabolite-mediated epigenetic repair represents a mechanism underlying metabolic memory. Key microbial metabolites indole-3-propionic acid (IPA) and trimethylamine N-oxide (TMAO) further expand the transmission and persistence of metabolic memory by regulating intestinal stem cell epigenetics and modifying insulin signaling proteins [47,48]. IPA is a crucial metabolite produced by the metabolism of tryptophan by intestinal commensal bacteria, and maintain genomic stability of the intestinal epithelium by binding to the aryl hydrocarbon receptor[47]. However, a HFD leads to marked depletion of IPA, attenuating the aryl hydrocarbon receptor signaling pathway. This results in DNA mismatch repair deficiency in intestinal stem cells, and errors in *de novo* DNA methylation are vertically transmitted to daughter cells during cell proliferation and differentiation. Consequently, intestinal barrier function remains persistently impaired, enhancing ectopic translocation of microbial metabolites[49]. In contrast, TMAO, the end product of microbial choline metabolism, exerts its effects through a more covert mechanism: It promotes the activity of lysine methyltransferase SETD7, which specifically modifies lysine 492 of insulin receptor substrate 2 (IRS2) in hepatocytes. This modification disrupts the interaction between IRS2 and phosphatidylinositol 3-kinase, thereby inhibiting insulin-mediated protein kinase B phosphorylation[50]. Owing to the stability of this methylation modification against ubiquitin-proteasome degradation, the modified IRS2 persists even when TMAO levels decline, sustaining hepatic insulin resistance. In summary, IPA and TMAO consolidate the persistence and systemic nature of metabolic memory from the perspectives of intestinal epithelial homeostasis maintenance and core metabolic signal regulation, respectively. Together with butyrate and LPS, they form a multi-dimensional molecular memory bank, providing abundant potential targets for obesity treatment strategies that target gut memory.

Table 1 The persistent remodeling of gut microbiota induced by obesogenic diets

Commonality summary	Key microbial taxa/groups	Change in abundance	Key functional	Metabolic outcome	Evidence quality	Ref.
Metabolite- & epigenetics-driven "thrifty memory" (persists after HFD withdrawal; promotes lipid storage & energy conservation)	*Odoribacter* (*e.g.*, *O. splanchnicus*)	Enriched/persistent (persists after HFD withdrawal)	Major short-chain fatty acid (butyrate) producer; possesses potent HDAC inhibitor activity	Maintains hypomethylation of hepatic lipid genes (*e.g.*, *Apoa4*), facilitating lipid transport/storage upon HFD re-exposure	Review (covers *in vitro*, animal and human studies)	[8]
	Firmicutes/Bacteroidetes ratio	Elevated (residually high)	Broad indicator of energy harvest capacity	Sustained energy harvest, favoring positive energy balance despite caloric restriction	Animal study (rat model) + *in vitro* study (human microglia cells)	[105]
Impaired gut barrier & persistent low-grade inflammation (LPS/hydrogen sulfide, H_2S/mucin degradation; metabolic set-point hard to reset)	*Akkermansia muciniphila*	Persistent depletion (slow or incomplete recovery)	Mucin degrader; critical for maintaining intestinal barrier integrity (Muc2; ZO-1 expression) and stimulating GLP-1 secretion	Weakens the mucus barrier, sustaining endotoxemia and inflammation, limiting metabolic reset	Animal study (rat model)	[106]
	Desulfovibrio	Persistent enrichment	SRB; produces H_2S and highly endotoxic LPS	H_2S/LPS impairs colonocyte oxidation and increases CD36-dependent lipid uptake, promoting weight regain	Review (covers animal and human studies)	[107]
	Ruminococcus gnavus	Enriched/persistent	Mucin-degrading specialist; produces inflammatory polysaccharides	Correlates with visceral adiposity and metabolic-syndrome traits despite intervention	Animal study (mouse model)	[108]
Gut-brain axis & behavior-related changes (appetite/mood/feeding behavior; harder weight maintenance)	*Oscillibacter*	Persistent enrichment	Strictly anaerobic; associated with HFD; produces specific metabolites (*e.g.*, valeric acid) linked to barrier dysfunction	Linked to obesity susceptibility and weight-loss resistance *via* barrier dysfunction and hyperphagia	Animal study (mouse model)	[109]
	Lachnospiraceae (specific clades *e.g.*, Muribaculaceae bacterium NK4A136, NK4A136)	Altered/variable (often depleted or slow to restore)	Major butyrate producers; pivotal in carbohydrate fermentation and glucose metabolism	Associated with impaired glucose tolerance, reduced metabolic flexibility, and addictive-like feeding, undermining maintenance	Review (covers human metagenomic studies, *in vitro* and animal studies)	[110]

HFD: High-fat diet; HDAC: Histone deacetylase; Apoa4: Apolipoprotein A-IV; LPS: Lipopolysaccharide; Muc2: Mucin 2; ZO-1: Zonula occludens-1; GLP-1: Glucagon-like peptide-1; SRB: Sulfate-reducing bacterium; CD36: Cluster of differentiation 36.

MICROBIOTA-EPIGENETIC CROSSTALK IN GUT METABOLIC MEMORY

Regulatory mechanisms of core epigenetic modifications

The microbiota constructs the core epigenetic regulatory system of intestinal metabolic memory mainly through DNA methylation, histone modification and their synergistic cascade reactions. At the level of DNA methylation, microbial metabolites can target and regulate the methylation status of key genes involved in lipid metabolism and inflammatory pathways. For example, homogentisic acid, an intestinal microbial metabolite induced by a HFD, can increase the N6-methyladenosine methylation level of euchromatic histone lysine methyltransferase 2 mRNA in white adipose tissue, thereby reducing the expression of euchromatic histone lysine methyltransferase 2 protein and triggering metabolic disorders[51]. LPS stimulation can alter the N6-methyladenosine methylation level in the liver and activate the nucleotide-binding oligomerization domain-containing protein 1/nuclear factor-kappa B pathway, mediating hepatic inflammation and injury[52]. At the level of histone modification, butyrate among SCFAs is a HDAC inhibitor, which can regulate the expression of relevant downstream genes by altering the histone acetylation status[53,54]. In addition to HDAC inhibition, the microbiota can regulate host epigenetics through other pathways. At the miRNA level, Dalmasso *et*

al[55] found significant differences in miRNA expression profiles in intestinal epithelial cells between germ-free and colonized mice, suggesting that the microbiota can indirectly regulate post-transcriptional modifications of host genes by influencing the expression of specific miRNAs. At the DNA methylation level, the gut microbiota participates in the synthesis or modification of methyl donors such as folate and vitamin B12, thereby altering the methylation status of host gene promoter regions through effects on methyl metabolic flux[56]. These mechanisms do not operate in isolation from HDAC inhibition; rather, they are interwoven into a multi-layered regulatory network that collectively shapes the host's adaptation to and memory of the metabolic environment. The synergistic effects and cascade reactions of epigenetic modifications further amplify the regulatory role. In mouse embryonic stem cells, simultaneous targeting of H3K27 trimethylation and monoubiquitination of histone H2A at lysine 119 can significantly enhance the penetrance of gene silencing, with an effect far exceeding that of a single modification[57].

Epigenetic regulatory effects in different cell types

Microbiota-epigenetic crosstalk exerts cell-type-specific regulatory effects in various intestinal cell types, which collaboratively maintains intestinal metabolic homeostasis or induces metabolic disorders. In intestinal epithelial cells, microbial metabolites drive the epigenetic reprogramming of barrier function-related genes. For example, during the progression of IBD, acyl coenzyme A synthetase short-chain family member 2 upregulates the transcription of claudin-7 by promoting the crotonylation modification of histone H4 at lysine 12, thereby enhancing the intestinal epithelial barrier function[58]. In addition, microbiota-derived inositol trisphosphate (IP3) can repair the barrier function by activating epithelial HDAC3[59]. In intestinal immune cells, epigenetic modifications mediate a persistent shift in the pro-inflammatory/anti-inflammatory balance; this shifted state can be partially reversed by microbiota intervention, yet epigenetic alterations induced by long-term dysregulation tend to form a persistent memory effect. Macrophages can polarize into pro-inflammatory M1 or anti-inflammatory M2 phenotypes in response to microenvironmental stimuli, and this M2-to-M1 polarization switch is recognized as one of the key drivers of persistent intestinal inflammation[60]. Hepatocytes and adipocytes can remotely regulate the epigenetic modifications of lipid metabolism genes and genes associated with insulin sensitivity. In obesity-related non-alcoholic fatty liver disease models, abnormally elevated levels of the hepatic transcription factor Slug exacerbate hepatic steatosis and insulin resistance[61]. Mice with adipocyte-specific knockout of the E3 ubiquitin ligase RING finger 20 exhibit reduced insulin sensitivity, which suppresses glucose transporter type 4 expression and leads to adipocyte-specific insulin resistance[62]. A mechanistic model illustrating the role of gut metabolic memory in obesity is proposed in Figure 1.

INTERGENERATIONAL TRANSMISSION OF GUT-MEDIATED METABOLIC MEMORY

Intergenerational impact pathways of maternal obesogenic diets

The vertical transmission of maternal gut microbiota is a core pathway for the intergenerational impacts of obesogenic diets. Prolonged maternal high-fat, high-sugar intake reduces microbiota diversity, elevates the F/B ratio, increases harmful bacteria (*e.g.*, *Desulfovibrio*), and diminishes beneficial taxa (*e.g.*, *Bifidobacterium*)[63]. During birth, offspring acquire initial colonization from maternal vaginal microbiota; thus, maternal microbiota dysbiosis predisposes offspring to abnormal colonization patterns, characterized by delayed early-life microbiota maturation and metabolic dysfunction [64]. Similar conclusions have also been reached in human studies: Maternal HFD during pregnancy can directly influence the neonatal microbiome, and this effect persists over time. Adopting healthy dietary habits in accordance with standard nutritional guidelines may confer long-term metabolic benefits for both mother and child[65].

In mouse offspring exposed to maternal HFD, gut abundance of butyrate-producing bacteria remains significantly lower, directly correlating with increased adult obesity risk[63]. Maternal microbiota imbalance also alters breast milk composition. Beneficial milk bacteria such as *Bifidobacterium* and *Lactobacillus* promote offspring intestinal barrier development, whereas obesogenic maternal diets reduce these bacteria, exacerbating offspring microbiota disorder[66]. This vertically transmitted microbiota dysbiosis reflects the heritability criterion of metabolic memory, providing key evidence for the transgenerational continuity of metabolic memory and establishes a foundational microecological basis for intergenerational metabolic transmission.

The intrauterine microenvironment and lactational nutrition amplify intergenerational effects by regulating offspring epigenetic programming. Maternal obesogenic diets induce chronic intrauterine inflammation and elevate proinflammatory cytokines (*e.g.*, tumor necrosis factor-alpha and interleukin-6), which cross the placenta to induce abnormal epigenetic modifications (*e.g.*, DNA methylation and histone acetylation) in offspring tissues[67]. For example, maternal HFD increases methylation in the promoter of the tight junction protein occludin gene in offspring intestinal epithelium, impairing barrier function[68]. During lactation, breast milk components directly regulate offspring epigenetic programming. Maternal HFD reduces beneficial milk components (*e.g.*, unsaturated fatty acids) while increasing saturated fatty acids, inducing abnormal histone acetylation of offspring hepatic lipid metabolism genes (*e.g.*, fatty acid synthase) and promoting lipid accumulation[69]. This epigenetic programming predisposes offspring to early metabolic phenotypes, with stability closely linked to subsequent obesity susceptibility.

Human studies, though primarily observational, provide essential real-world evidence for understanding intergenerational transmission. Cohort studies from the Dutch famine[70,71] revealed that individuals exposed to famine *in utero* have a significantly higher risk of obesity and metabolic diseases in adulthood, an effect associated with DNA methylation changes at specific genes, with some epigenetic marks persisting for up to six decades. In recent years, multiple birth cohort studies[72] have further demonstrated associations between maternal obesity and infant gut microbiota composition - such as reduced *Bacteroides* abundance and increased *Staphylococcus* abundance - and these microbial

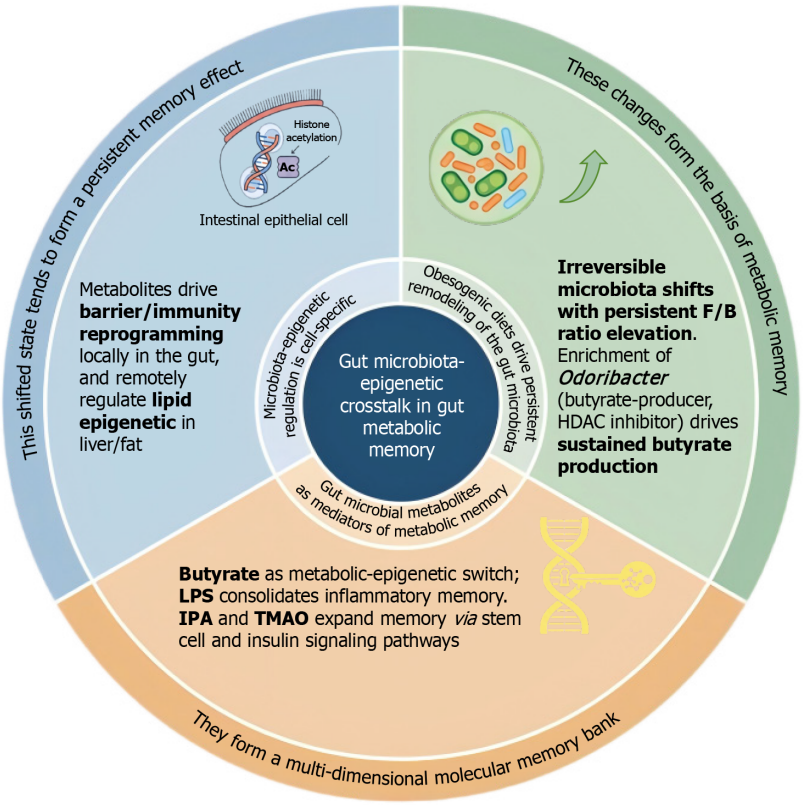

Figure 1 A mechanistic model of gut metabolic memory and its role in obesity. This schematic illustrates the integrated mechanisms of gut metabolic memory that drive obesity pathogenesis. The model is constructed as three concentric circles representing mechanistic hierarchy. The central core states the overarching concept, surrounded by three 120° sectors detailing: (1) Persistent remodeling of the gut microbiota, driven by obesogenic diets, which induces irreversible shifts characterized by an elevated Firmicutes/Bacteroidetes ratio and enrichment of specific taxa such as *Odoribacter* (a butyrate-producer with histone deacetylase inhibitor activity), establishing a dysbiotic foundation; (2) Gut microbial metabolites as key mediators, where butyrate acts as a metabolic-epigenetic switch, lipopolysaccharide consolidates inflammatory memory, and indole-3-propionic acid and trimethylamine N-oxide expand memory persistence by regulating stem cell epigenetics and insulin signaling, respectively, forming a multi-dimensional molecular memory bank; and (3) Cell-type-specific epigenetic regulation, wherein microbial metabolites locally drive barrier reprogramming and inflammatory shifts in intestinal epithelial and immune cells, and remotely regulate lipid metabolism gene epigenetics in hepatocytes and adipocytes. These spatially defined, persistent epigenetic alterations collectively sustain the metabolic memory state. Created in BioRender (Supplementary material). F/B: Firmicutes/Bacteroidetes; LPS: Lipopolysaccharide; IPA: Indole-3-propionic acid; TMAO: Trimethylamine N-oxide.

features are in turn linked to childhood obesity risk. It must be emphasized, however, that such studies cannot fully exclude confounding by genetic factors or postnatal environmental exposures, and therefore cannot directly establish causality.

Translating animal findings to humans faces multiple barriers. First, developmental windows differ considerably between species; human gestation and infancy span months to years, making it more difficult to identify sensitive periods. Second, safety considerations limit many experimental manipulations in humans, such as extreme dietary interventions or the use of epigenetic drugs during pregnancy. Third, the human gut microbiota is more diverse and environmentally influenced, making it challenging to pinpoint the causal role of any single microbial taxon. Fourth, ethical constraints preclude the application of interventions such as FMT or epigenetic editing in pregnant women or healthy infants. Thus, while animal models provide rich mechanistic insights, human translation will require large-scale longitudinal cohorts, rigorous control of confounding factors, and the development of safe, targeted interventions. Addressing these challenges represents a key direction for future research in this field.

Molecular basis of offspring susceptibility to obesity

Epigenetic defects in intestinal barrier function and immune development are key mechanisms for offspring obesity susceptibility, originating from early programming abnormalities induced by maternal obesogenic diets. Intestinal barrier integrity, which prevents microbial metabolite translocation, depends on normal tight junction protein expression (*e.g.*, occludin; zonula occludens-1). Maternal diet-induced aberrant DNA methylation persistently represses these proteins, increasing intestinal permeability[68]. Studies show that adult rat offspring exposed to maternal HFD exhibit significantly higher intestinal permeability and increased mucosal inflammatory cell infiltration[67], closely associated with enhanced inflammatory responses from demethylation in the *TLR4* gene promoter[64]. Meanwhile, epigenetic defects in offspring immune development exacerbate metabolic disorders. Maternal diets can modulate histone modifications in offspring intestinal innate immune cells (*e.g.*, macrophages, dendritic cells), leading to aberrant phenotypes with elevated pro-inflammatory and reduced anti-inflammatory cytokine secretion[73]. This vicious cycle of barrier defect and immune dysfunction continuously amplifies metabolic disturbances, and the sustained effect of metabolic memory further consol-

idates offspring obesity susceptibility.

Metabolic memory in the offspring intestinal-systemic axis provides long-term molecular support for intergenerational transmission of obesity susceptibility, primarily through stable epigenetic imprints and cross-organ crosstalk. Maternal obesogenic diets induce gut microbiota dysbiosis and metabolite abnormalities in offspring, establishing persistent epigenetic memory in intestinal epithelial and hepatic cells that continues to regulate metabolism-related gene expression even under subsequent normal diet[74]. For example, HDAC1/2 activity caused by offspring gut butyrate deficiency maintains high expression of lipogenic genes through histone deacetylation, an effect that can persist into adulthood[75]. Meanwhile, metabolic memory mediates cross-organ communication *via* pathways such as the gut-liver and gut-brain axes. Translocation of microbial LPS across a compromised barrier induces inflammatory memory in the liver, sustaining TLR4-MyD88 signaling. Additionally, intestinal stem cell DNA repair defects caused by IPA depletion further exacerbate barrier damage, forming a cycle of cross-organ metabolic dysregulation[76]. This persistent, systemic metabolic memory is key to the irreversibility of offspring obesity susceptibility and offers direction for screening precise intervention targets.

Intervention windows and potential targets for intergenerational transmission

A critical window exists for intervening in intergenerational obesity risk, with stage-specific strategies capable of blocking distinct transmission pathways. Interventions during the pre-conception, pregnancy, and lactation periods exert the most pronounced effects. Pre-conception intervention focuses on improving maternal gut microbiota and metabolic profiles through dietary modulation (*e.g.*, increased fiber intake) and probiotic supplementation, thereby restoring maternal microbial balance and reducing vertical transmission of microbiota dysbiosis[77]. Maternal pre-conception supplementation with a triple viable probiotic containing *Bifidobacterium* increases offspring beneficial bacteria and SCFA synthesis[78]. Pregnancy, a core epigenetic programming window, allows inhibiting excessive maternal inflammation and reducing offspring epigenetic defects by controlling calorie intake and supplementing nutrients (*e.g.*, folic acid and unsaturated fatty acids)[79]. Lactation intervention optimizes breast milk; supplementing butyrate precursors promotes offspring intestinal barrier development and beneficial microbiota colonization[80]. These window-specific interventions block transmission pathways, though targeting precise molecular mechanisms remains key.

Interventions focusing on microbiota, epigenetics, and metabolism are priorities. Microbiota strategies include supplementing beneficial bacteria (*e.g.*, butyrate producers), inhibiting harmful bacteria, or using FMT. Maternal FMT reverses offspring microbiota dysbiosis and metabolic phenotypes[80]. Epigenetic interventions regulate enzymes like DNMT and HDAC; DNMT inhibitors correct intestinal barrier gene methylation, while HDAC inhibitors disrupt metabolic memory [81]. Meanwhile, interventions targeting microbial metabolites also hold promising prospects. Approaches such as supplementing IPA[47] and inhibiting the production of TMAO[82] can repair intestinal barrier function, improve insulin resistance, and block metabolic memory transmission. These targets support precise strategies, though clinical validation of safety and efficacy is needed. The intergenerational impact pathways of maternal obesogenic diets are illustrated in Figure 2.

THERAPEUTIC STRATEGIES TARGETING GUT METABOLIC MEMORY FOR OBESITY

Early dietary intervention and metabolic memory prevention

To address obesity, strategies can focus on gut metabolic memory. Early dietary interventions during different developmental stages in human life can be effective. Evidence suggests that excessive protein intake in early life alters the gut metabolic memory, increasing protein demand later in life[83]. Particularly during infancy (from birth to two years), high protein intake is associated with a higher risk of obesity[84]. Even before infancy, dietary adjustments during pregnancy can mitigate the risk of excessive weight gain in children, as maternal weight gain during pregnancy has been linked to increased overweight risk in early childhood[85]. Additionally, a cross-sectional study indicates that adolescents with a lower healthy eating index have a lower prevalence of metabolic syndrome[86]. Adherence to a Mediterranean diet in adolescents has shown significant reductions in anthropometric and obesity-related indices, especially among overweight individuals[87].

Besides dietary interventions, improving gut metabolic memory can be achieved by stabilizing the gut barrier. Probiotics, with their anti-inflammatory properties, can protect gut permeability[59]. They also show therapeutic potential by restoring microbial balance, enhancing epithelial barrier function, and modulating immune responses, thereby controlling gut microbiota dysbiosis and maintaining the stability of the gut microbiota-epigenetic axis[88].

Gut microbiota modulation strategies

Further strategies include targeting specific gut microbiota. A study using IVW method for MR analysis found eight gut microbiota with causal relationships to metabolic syndrome, including *Odoribacter* genus[89]. *Odoribacter* genus plays a crucial role in maintaining gut ecological balance and is a strong candidate for next-generation probiotics[28]. Screening probiotics targeting *Odoribacter* stability, such as *Lactobacillus reuteri* ATCC PTA 6475, has shown to improve gut microbiota by increasing the relative abundance of *Odoribacter*[90]. Additionally, *O. splanchnicus* produces guanosine diphosphate-L-fucose, which aids in repairing gut barrier damage and dysfunction of drug transporters (P-gp) caused by aging [30]. FMT can also alter the composition of the recipient's gut microbiota, showing potential in reversing microbial memory[91]. However, FMT has limitations in terms of colonization efficiency, persistence, and the range of successfully transplanted species[92]. To overcome these limitations, the development of highly specific microbial regulators, such as endolysins, is encouraged for precise interventions[93]. For instance, incorporating BC99, which can reversibly alter

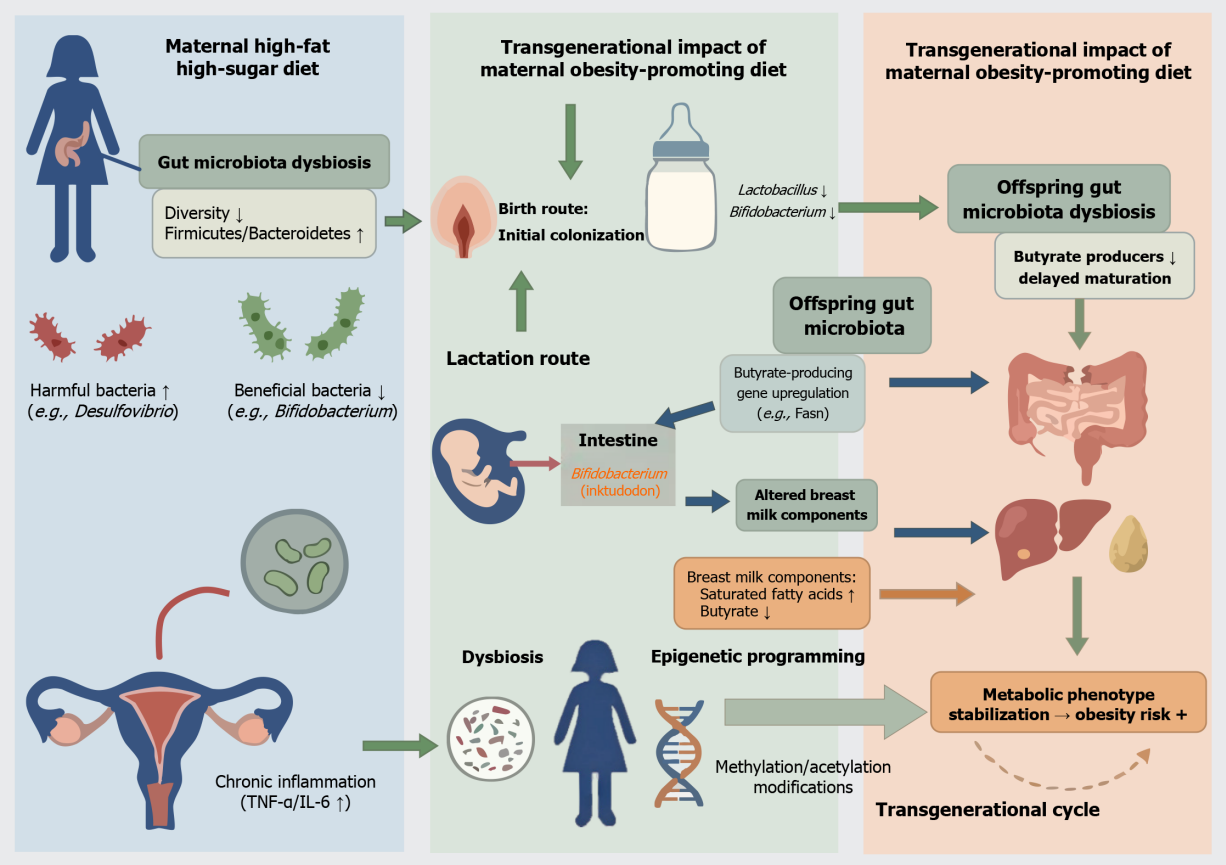

Figure 2 Intergenerational impact pathways of maternal obesogenic diets. This schematic illustrates the key mechanisms through which maternal high-fat high-sugar diets exert intergenerational effects on offspring metabolic health. Maternal diet-induced gut microbiota dysbiosis, characterized by reduced microbial diversity, elevated Firmicutes/Bacteroidetes ratio, and decreased beneficial taxa such as *Bifidobacterium* and *Lactobacillus*, is vertically transmitted to offspring *via* birth and breastfeeding. Altered breast milk composition, including increased saturated fatty acids and reduced butyrate, further disrupts offspring gut microbiota maturation and function. Concurrently, maternal chronic inflammation and epigenetic modifications (*e.g.*, DNA methylation and histone acetylation) contribute to impaired intestinal barrier function and metabolic dysregulation in offspring, perpetuating a transgenerational cycle of obesity risk. Created in BioRender (Supplementary material). TNF: Tumor necrosis factor; IL: Interleukin; Fasn: Fatty acid synthase.

bacterial flora, to develop personalized treatment regimens[94]. Endolysins[95] and microbial regulators like *Bacillus coagulans* BC99[96] are in preclinical research stages for gut metabolic memory modulation, with no human clinical data available; safety risks include off-target lysis of beneficial bacteria, and translation barriers involve intestinal site-specific delivery and large-scale clinical-grade production.

Development and application of epigenetic modifiers

Furthermore, the development and application of epigenetic regulators are noteworthy. Although butyrate can maintain the balance of the gut microbiota[94], traditional butyrate compounds exhibit low bioavailability and unpleasant odors. Therefore, novel compounds such as zinc dibutyroyllysinate can be explored. Composed of zinc, lysine, and butyrate groups, zinc dibutyroyllysinate not only retains the epigenetic regulatory capacity of butyrate, such as inhibiting HDAC, but also demonstrates enhanced transcriptional bioactivity, effectively optimizing pharmacokinetics. Clinical studies have confirmed the safety of HDAC inhibitors, such as romidepsin, belinostat, and chidamide, in treating peripheral T-cell lymphoma[97]. Future approaches may include multi-target combination therapies, such as combining HDAC inhibition with phosphatidylinositol 3-kinase blockade, to better treat cancers induced by abnormal epigenetics[98].

CONTROVERSIES AND PROSPECTS: THE REVERSIBILITY BOUNDARY OF GUT METABOLIC MEMORY

There is ongoing debate regarding the reversibility of gut microbiota-epigenetic memory. Early studies have emphasized its irreversibility, but recent evidence suggests that these changes may exhibit dynamic plasticity. A 2025 review published in *Nutrients* systematically summarized therapeutic strategies targeting the obesity-epigenetics-microbiome axis, pointing out that interventions such as probiotics, prebiotics, and dietary modulation can regulate the microbiota-epigenetic axis, providing a theoretical basis for intervening in metabolic memory[99].

Gut microbial species composition and relative abundance derived from metagenomic sequencing serve as critical determinants of host metabolic phenotypes[100]. Integration of genome-scale metabolic model repositories with pan-

species network analysis enables reconstruction of personalized microbial community metabolic models[101]. Concurrently, incorporating fecal metagenomic data into dietary assessments allows reverse inference of nutrient intake, thereby mitigating recall bias and establishing a robust foundation for precision nutrition interventions[102]. For epigenetic biomarker discovery, priority should be given to dynamically quantifiable marks - including DNA methylation and miRNAs - that facilitate therapeutic monitoring and longitudinal follow-up[103]. In the realm of personalized interventions, 16S rRNA gene sequencing coupled with artificial intelligence has already been deployed to generate tailored regimens encompassing dietary modification, probiotic/prebiotic supplementation, lifestyle adjustments, and selective antimicrobial therapy, with iterative optimization guided by real-time feedback[104]. Looking ahead, the synergistic integration of multi-omics platforms and artificial intelligence-driven analytics is poised to yield personalized microbiota- and epigenome-targeted therapeutics, thereby accelerating the clinical translation of precision medicine. Future research should focus on identifying the optimal window for reversing metabolic memory through different interventions and exploring combination strategies to achieve precise memory resetting. These directions also echo the gut microbiota modulation and epigenetic modification strategies discussed earlier in this review.

CONCLUSION

In conclusion, the crosstalk between gut microbiota and host epigenetics constitutes a core mechanism underlying metabolic memory-driven obesity. Metabolic memory is characterized by persistence, resistance to intervention, and heritability, thereby positioning the gut as a critical therapeutic target. However, current understanding is constrained by limited evidence from human clinical trials, the complexity of individual heterogeneity, and the incomplete elucidation of memory reversibility. Future research must prioritize deciphering causal interactions using advanced single-cell epigenomics and developing non-invasive biomarkers based on microbial-epigenetic signatures for early diagnosis. Ultimately, accelerating the clinical translation of precision interventions - ranging from targeted microbial modulation to epigenetic modifiers such as butyrate analogs and HDAC inhibitors - will be essential to disrupt the persistent cycle of metabolic memory and improve long-term metabolic health (Figure 3).

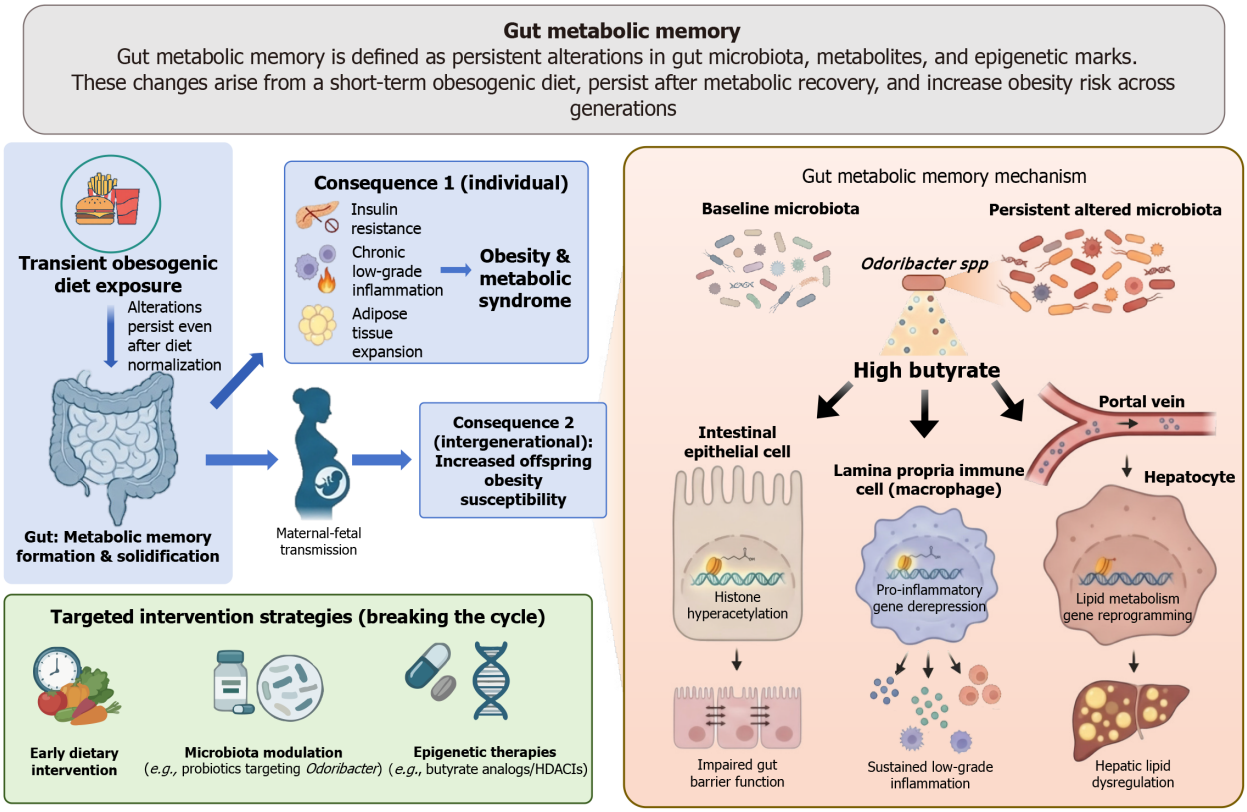

Figure 3 Gut metabolic memory. Created in BioRender (Supplementary material). HDACIs: Histone deacetylase inhibitors.

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