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Review Article

Role of gut-brain axis dysregulation in the pathogenesis of non-alcoholic fatty liver disease: mechanisms and therapeutic implications

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Abstract: Non-alcoholic fatty liver disease (NAFLD) has emerged as a global health challenge due to its rising prevalence and strong association with metabolic syndrome. Recent studies highlight the critical role of the gut-brain axis (GBA)-a bidirectional communication system between the gut, brain, and liver-in NAFLD pathogenesis. Dysregulation of this axis can worsen metabolic dysfunction, inflammation, and liver injury. This review discusses the mechanisms driving GBA dysregulation in NAFLD, including alterations in gut microbiota, increased intestinal permeability, neuroinflammation, and imbalances in the autonomic nervous system (ANS). We also explore therapeutic strategies, such as microbiota modulation, vagus nerve stimulation, and neuroprotective interventions, that may help mitigate the effects of GBA dysfunction on NAFLD progression.

Keywords: Gut-brain axis dysregulation, non-alcoholic fatty liver disease, mechanisms, therapeutic implications

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent chronic liver diseases globally, characterized by excessive fat accumulation in hepatocytes without significant alcohol consumption [1]. The disease spectrum of NAFLD ranges from simple steatosis (non-alcoholic fatty liver) to non-alcoholic steatohepatitis (NASH), which can progress to liver fibrosis, cirrhosis, or even hepatocellular carcinoma (HCC) [2, 3]. Recent epidemiological studies indicate that approximately 25% of the global population is affected by NAFLD [4], with significant regional and population-based variations. The prevalence of NAFLD has been steadily rising, posing a major global public health challenge.

The pathogenesis of NAFLD is complex and multifactorial. Traditionally, insulin resistance, dysregulated lipid metabolism, and oxidative stress have been considered the primary drivers of the disease [5-7]. However, growing evidence suggests that the gut-brain-liver axis plays a critical role in the onset and progression of NAFLD [8-11]. The gut-brain-liver axis is a bidirectional communication network between the gut, brain, and liver, involving neural, endocrine, and immune pathways. This network is essential for maintaining metabolic homeostasis [12]. The gut microbiota is a central component of the gut-brain-liver axis, influencing host metabolism through metabolites, neurotransmitters, and immune regulation. In NAFLD, dysbiosis, characterized by a reduction in beneficial bacteria and an increase in harmful bacteria, is frequently observed. This dysbiosis may impair intestinal barrier function, allowing microbial endotoxins such as lipopolysaccharides (LPS) to enter the portal circulation, triggering hepatic inflammation and steatosis [13]. Moreover, gut microbiota-derived metabolites, such as short-chain fatty acids (SCFAs) and bile

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acids, regulate liver lipid and glucose metabolism by interacting with host receptors [14-16].

The brain, as the central component of the nervous system, regulates the gut-brain-liver axis through the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal axis. In NAFLD, chronic inflammation can induce neuroinflammation in the central nervous system, disrupting appetite regulation, energy balance, and metabolic control [17]. Dysfunction of the ANS, particularly reduced vagal nerve activity, weakens its protective effects on the liver, contributing to hepatic lipid accumulation. Given the critical role of the gut-brain-liver axis in NAFLD, targeting this axis has become a promising therapeutic approach. Interventions such as probiotics, prebiotics, and fecal microbiota transplantation (FMT) have shown potential in alleviating hepatic steatosis by modulating the gut microbiota [18-20]. Moreover, neuromodulation techniques, including vagus nerve stimulation (VNS), are being explored to restore autonomic balance and reduce hepatic inflammation and steatosis [21, 22].

In summary, dysregulation of the gut-brain-liver axis is pivotal in the pathogenesis of NAFLD. A deeper understanding of the interactions within this complex network is crucial for uncovering the mechanisms underlying NAFLD and holds great promise for the development of novel diagnostic and therapeutic strategies. By exploring these mechanisms, we can pave the way for targeted interventions that may improve patient outcomes and ultimately enhance the prognosis of individuals with NAFLD. This review aims to provide insights into the intricate relationships within the gut-brain-liver axis, emphasizing their significance in NAFLD pathogenesis and the future prospects for clinical application.

The Gut-Brain Axis (GBA) in NAFLD pathogenesis

Gut microbiota and metabolic dysfunction

The gut microbiota plays a crucial role in maintaining metabolic homeostasis and serves as a key mediator of the gut-liver axis. Dysbiosis, characterized by an imbalance in the gut microbial community, has been strongly implicated in the pathogenesis of NAFLD [23]. Increasing evidence suggests that alterations in gut microbiota composition directly contribute to metabolic dysfunction by modulating host energy metabolism, insulin sensitivity, and lipid handling, thus exacerbating NAFLD progression [24].

A primary mechanism linking the gut microbiota to metabolic dysfunction is the production of microbial metabolites, including SCFAs, bile acids, and LPS. SCFAs, mainly acetate, propionate, and butyrate, are microbial fermentation products of dietary fibers [25-28]. While SCFAs generally promote metabolic health by serving as an energy source and modulating glucose and lipid metabolism, alterations in their production or absorption have been observed in NAFLD patients [29]. For example, overproduction of acetate has been shown to stimulate lipogenesis in hepatocytes via the activation of sterol regulatory element-binding protein 1c (SREBP-1c), a key transcription factor regulating de novo lipogenesis [30].

In addition to SCFAs, gut microbiota influence bile acid metabolism, another key pathway implicated in metabolic dysfunction. Bile acids act as signaling molecules that regulate glucose and lipid metabolism through activation of farnesoid X receptor (FXR) and G-protein-coupled bile acid receptor 1 [31]. Dysbiosis in NAFLD has been associated with altered bile acid profiles, including increased secondary bile acids that disrupt FXR signaling, leading to enhanced lipogenesis, insulin resistance, and hepatic inflammation [32].

Furthermore, gut-derived endotoxins such as LPS, a component of Gram-negative bacterial cell walls, are critical mediators of metabolic dysfunction in NAFLD. Dysbiosis often leads to increased intestinal permeability, referred to as a “leaky gut”. This allows the translocation of LPS and other microbial products into the portal circulation, triggering hepatic toll-like receptor 4 (TLR4)-mediated inflammation and activation of Kupffer cells, the liver’s resident macrophages [33]. Chronic low-grade inflammation induced by LPS not only promotes hepatic steatosis but also contributes to the progression from NAFLD to NASH, characterized by hepatocyte ballooning and fibrosis [34].

Emerging data also highlight the role of specific gut microbial taxa in modulating metabolic pathways relevant to NAFLD. For instance, the

Firmicutes-to-Bacteroidetes ratio, commonly used as an index of dysbiosis, is often increased in NAFLD, suggesting enhanced energy harvest from the diet [35, 36]. Additionally, species such as Escherichia coli and Enterobacteriaceae have been associated with increased endotoxemia and inflammation, while reductions in beneficial microbes like Faecalibacterium prausnitzii and Akkermansia muciniphila correlate with impaired gut barrier integrity and insulin resistance [37].

Collectively, these findings underscore the integral role of gut microbiota in orchestrating metabolic dysfunction in NAFLD. Targeting dysbiosis through interventions such as probiotics, prebiotics, FMT, and dietary modifications offers a promising therapeutic avenue [38]. Probiotic strains like Lactobacillus and Bifidobacterium have shown potential in reducing hepatic fat accumulation and inflammation, while prebiotic fibers may restore SCFA production and improve intestinal barrier function [39]. However, the heterogeneity of gut microbiota profiles in NAFLD across individuals necessitates personalized approaches for effective therapeutic strategies.

In summary, gut microbiota dysbiosis is a critical driver of metabolic dysfunction in NAFLD. Understanding the complex interplay between gut microbial composition, microbial metabolites, and host metabolic pathways will pave the way for identifying novel biomarkers and therapeutic targets to address the growing burden of NAFLD.

Intestinal permeability and endotoxemia

Intestinal permeability and subsequent endotoxemia are critical components of the gut-brain-liver axis, significantly contributing to the pathogenesis of NAFLD [40]. The intestinal epithelium acts as a selective barrier, preventing the translocation of harmful substances, such as microbial-derived endotoxins, into the systemic circulation while allowing the absorption of nutrients and metabolites. Dysfunction of this barrier, often referred to as “leaky gut”, is commonly observed in NAFLD patients and is associated with disease onset and progression [41]. The resulting endotoxemia, characterized by elevated levels of LPS and other microbial products in the bloodstream, activates pro-inflammatory pathways in the liver, promoting hepatic steatosis, inflammation, and fibrosis [42].

The integrity of the intestinal barrier is maintained by intercellular tight junctions, a complex network of proteins including claudins, occludins, and zonula occludens-1 (ZO-1) [43]. Disruption of these tight junctions is a hallmark of increased intestinal permeability in NAFLD. Several factors contribute to this dysregulation, including gut microbiota dysbiosis, dietary habits, and host immune responses. Gut microbiota dysbiosis in NAFLD is associated with an overgrowth of pathogenic bacterial species that produce metabolites such as ethanol and hydrogen sulfide, which directly damage epithelial cells and disrupt tight junction integrity [44]. For instance, studies have shown reduced expression of ZO-1 and occludin in the intestinal tissues of NAFLD patients, correlating with increased translocation of bacterial endotoxins [45].

Additionally, alterations in the gut microbial composition lead to reduced production of SCFAs, such as butyrate, a key metabolite that promotes epithelial repair and tight junction maintenance. SCFA deficiency exacerbates barrier dysfunction, further amplifying intestinal permeability. Dietary factors, particularly high-fat and high-fructose diets, have also been shown to impair intestinal barrier function [46]. Excess dietary fat alters bile acid metabolism, leading to the accumulation of toxic bile acids that damage the intestinal epithelium [47]. Similarly, fructose reduces intestinal mucin production and enhances oxidative stress in enterocytes, further compromising barrier integrity. These dietary-induced changes significantly contribute to the “leaky gut” observed in NAFLD.

Inflammation plays a central role in intestinal barrier dysfunction. Chronic low-grade inflammation, often driven by gut dysbiosis, activates immune cells and releases pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [48]. These cytokines weaken tight junctions and increase epithelial apoptosis, further compromising the intestinal barrier. Moreover, oxidative stress induced by reactive oxygen species can damage enterocytes and tight junction proteins, perpetuating intestinal permeability [49].

Increased intestinal permeability facilitates the translocation of microbial products, particularly LPS, from the gut lumen into the portal circulation. LPS is a potent activator of the innate immune system through its interaction with TLR4 on Kupffer cells, the liver's resident macrophages [50-52]. This activation triggers the release of pro-inflammatory cytokines and chemokines, leading to hepatic inflammation and recruitment of immune cells [53]. Chronic activation of TLR4 signaling also stimulates hepatic stellate cells, promoting fibrogenesis and the progression of NAFLD to NASH. Endotoxemia exacerbates hepatic steatosis by disrupting lipid metabolism. LPS-induced inflammation impairs insulin signaling, leading to hepatic insulin resistance [54]. This results in increased de novo lipogenesis and reduced β-oxidation of fatty acids, contributing to lipid accumulation in hepatocytes. Furthermore, systemic endotoxemia increases circulating free fatty acids and inflammatory markers, creating a vicious cycle of metabolic dysfunction and liver damage.

In summary, intestinal permeability and endotoxemia are central to the pathophysiology of NAFLD, acting as key drivers of hepatic inflammation, steatosis, and fibrosis. Disruption of the intestinal barrier, compounded by gut dysbiosis and dietary factors, leads to the translocation of microbial endotoxins, triggering inflammatory cascades in the liver. Therapeutic interventions targeting intestinal barrier integrity and endotoxemia hold promise for halting or reversing NAFLD progression. However, further clinical studies are necessary to optimize these strategies and evaluate their long-term efficacy in diverse patient populations.

Neuroinflammation and hypothalamic dysfunction

Neuroinflammation and hypothalamic dysfunction are increasingly recognized as critical factors in the pathogenesis of NAFLD within the framework of GBA dysregulation [55]. The hypothalamus, a key regulator of energy homeostasis, integrates peripheral metabolic signals such as leptin, insulin, and gut-derived hormones to control food intake, energy expenditure, and glucose metabolism. Chronic low-grade neuroinflammation disrupts hypothalamic function, contributing to the development and progression of metabolic disorders, including NAFLD [56, 57]. Neuroinflammation, marked by microglial and astrocytic activation, as well as elevated levels of pro-inflammatory cytokines such as IL-6 and TNF-α, impairs neuronal signaling in the hypothalamic arcuate nucleus (ARC) [58]. This disruption decreases leptin and insulin sensitivity, leading to hyperphagia, central insulin resistance, and altered lipid metabolism-critical drivers of hepatic steatosis.

The GBA plays a crucial role in initiating and maintaining hypothalamic neuroinflammation via gut microbiota-derived metabolites and systemic inflammation. Gut dysbiosis increases intestinal permeability, allowing endotoxins like LPS to enter circulation [59]. LPS activates TLR4 signaling in the hypothalamus, triggering inflammatory cascades that impair neuronal function. Moreover, changes in microbial metabolites, such as SCFAs and bile acids, affect hypothalamic inflammation and neurogenesis through the gut-brain-liver axis. Dysbiosis-related reductions in SCFA levels hinder anti-inflammatory signaling, further exacerbating hypothalamic dysfunction [60]. Emerging evidence also underscores the role of vagal nerve signaling in transmitting inflammatory signals from the gut to the brain, forming a bidirectional feedback loop that perpetuates neuroinflammation [61-64].

Therapeutic strategies targeting neuroinflammation and hypothalamic dysfunction in NAFLD are promising but still under investigation. Restoring gut microbiota composition through probiotics, prebiotics, or FMT could alleviate hypothalamic inflammation by reducing endotoxemia and promoting the production of anti-inflammatory metabolites. Pharmacological agents targeting microglial activation or inhibiting TLR4 signaling in the hypothalamus are also under study as potential therapies [65]. Furthermore, lifestyle modifications, including dietary changes and exercise, have proven effective in reducing both systemic and central inflammation, improving hypothalamic function, and enhancing metabolic outcomes. Future research should aim to clarify the molecular mechanisms linking neuroinflammation and hypothalamic dysfunction to NAFLD and evaluate the effectiveness of targeted interventions in clinical settings. Addressing neuroinflammation's central role in energy dysregulation and

liver pathology could lead to innovative therapeutic approaches to combat NAFLD.

ANS imbalance

ANS imbalance is a significant mechanism linking GBA dysregulation to the pathogenesis of NAFLD [66]. The ANS, comprising the sympathetic and parasympathetic branches, is essential for regulating metabolic processes such as glucose homeostasis, lipid metabolism, and hepatic inflammation. In NAFLD, ANS dysregulation-often characterized by heightened sympathetic tone and reduced parasympathetic activity-has been implicated in promoting insulin resistance, hepatic steatosis, and systemic inflammation [67]. This imbalance disrupts the delicate homeostatic communication between the brain and liver, aggravating metabolic dysfunction and driving disease progression.

Sympathetic overactivity is a hallmark of ANS dysregulation in NAFLD, contributing to increased hepatic lipogenesis, oxidative stress, and inflammation [68]. Elevated sympathetic tone impairs hepatic blood flow and worsens liver injury through adrenergic receptor activation on hepatocytes, stellate cells, and immune cells. Simultaneously, parasympathetic dysfunction, often mediated by vagal nerve impairment, further disrupts the gut-brain-liver axis by diminishing anti-inflammatory signaling and impairing glucose and lipid homeostasis [69]. The vagus nerve, a key component of the parasympathetic system, modulates hepatic metabolism and inflammation through interactions with gut microbiota and the enteric nervous system [70]. Disruptions in vagal signaling due to dysbiosis, compounded by increased systemic endotoxemia, exacerbate ANS imbalance and worsen NAFLD pathophysiology.

The mechanisms underlying ANS imbalance in NAFLD are multifactorial, involving gut microbiota dysbiosis, neuroinflammation, and chronic stress. Gut-derived metabolites like LPS and bile acids affect both sympathetic and parasympathetic pathways through neural and humoral mechanisms, contributing to autonomic dysregulation [71, 72]. Neuroinflammation in central autonomic control centers, such as the hypothalamus and brainstem, impairs neural regulation of the ANS, perpetuating sympathetic overactivity and vagal suppression [73]. Additionally, chronic stress, associated with hypothalamic-pituitary-adrenal axis activation, further exacerbates ANS imbalance by increasing sympathetic output and decreasing vagal tone, creating a vicious cycle of metabolic and inflammatory dysregulation [74]. Therapeutic strategies targeting ANS imbalance offer promising avenues for managing NAFLD.

Interventions aimed at enhancing vagal activity, such as VNS, have shown potential in reducing hepatic inflammation and improving metabolic parameters in preclinical models [75]. Lifestyle modifications, including regular exercise and stress reduction techniques such as mindfulness and yoga, can restore ANS balance by increasing parasympathetic activity and reducing sympathetic overdrive. Additionally, probiotic and prebiotic therapies may help mitigate ANS dysfunction by modulating gut microbiota composition and reducing endotoxemia, which influences vagal signaling. Future research should focus on elucidating the precise mechanisms of ANS involvement in NAFLD pathogenesis and evaluating the effectiveness of these interventions in clinical trials. By addressing the autonomic dysregulation underlying metabolic and inflammatory pathways, these strategies could provide novel therapeutic opportunities for the prevention and treatment of NAFLD.

Correlation between GBA dysregulation, gut microbiota, metabolic dysfunction, neuroinflammation, hypothalamic dysfunction, and NAFLD pathogenesis

The correlation between GBA dysregulation, gut microbiota, metabolic dysfunction, neuroinflammation, hypothalamic dysfunction, and the pathogenesis of NAFLD is complex, involving both upstream and downstream interactions, as well as feedback loops. The gut microbiota plays a central role in regulating the GBA. Dysbiosis, or an imbalance in the gut microbiota, can lead to increased intestinal permeability, allowing the translocation of microbial products, such as LPS into the bloodstream. These products trigger systemic inflammation, disrupting normal metabolic functions and promoting hepatic steatosis and insulin resistance-key factors in the progression of NAFLD. Simultaneously, dysregulation of the GBA impacts neuroinflammation and hypothalamic dysfunction. The hypothalamus, which regu-

lates energy homeostasis and metabolism, is particularly affected. Disruption of hypothalamic signaling leads to altered appetite regulation, insulin resistance, and ANS imbalance, all of which contribute to metabolic dysfunction and liver damage.

These components do not operate in isolation but form a dynamic, interconnected network with multiple feedback mechanisms. Metabolic dysfunction and neuroinflammation resulting from gut microbiota disturbances exacerbate each other, creating a vicious cycle. For instance, inflammation in the liver can lead to the release of pro-inflammatory cytokines, which may reach the brain, amplifying neuroinflammation and disrupting hypothalamic regulation. This, in turn, worsens metabolic abnormalities such as insulin resistance, further aggravating liver injury. Thus, these interactions can occur both in an upstream-downstream fashion and as a closed-loop system, where changes in one component perpetuate dysfunction in others. The bidirectional communication between the gut, brain, and liver emphasizes the complexity of NAFLD pathogenesis, underscoring the need for in-depth exploration of these interactions. Understanding whether these interactions are more predominantly upstream, downstream, or feedback-driven is crucial for identifying novel therapeutic strategies that target specific points within this network, ultimately breaking the cycle of NAFLD progression.

Therapeutic implications

Microbiota-targeted therapies

Microbiota-targeted therapies have emerged as a promising approach to address GBA dysregulation in the pathogenesis of NAFLD. The gut microbiota plays a pivotal role in host metabolism, immune function, and hepatic physiology, with dysbiosis strongly implicated in the development and progression of NAFLD. Therapies aimed at modulating gut microbiota composition and function-such as probiotics, prebiotics, synbiotics, and FMT-aim to restore microbial balance, enhance intestinal barrier integrity, and reduce systemic inflammation, targeting multiple pathways central to NAFLD pathogenesis [76, 77].

Probiotics, defined as live microorganisms that confer health benefits to the host, have shown promise in alleviating NAFLD-related features. Specific strains of Lactobacillus and Bifidobacterium have been shown to reduce hepatic steatosis, inflammation, and oxidative stress in both preclinical and clinical studies. These effects are mediated through mechanisms such as increased production of SCFAs, restoration of tight junction integrity, and inhibition of endotoxemia-induced TLR4 signaling [78, 79]. Clinical trials have reported improvements in liver enzymes, lipid profiles, and markers of systemic inflammation in NAFLD patients treated with probiotics, though strain-specific efficacy and optimal dosing remain areas of ongoing investigation [80].

Prebiotics, non-digestible compounds that selectively promote the growth of beneficial gut bacteria, offer another microbiota-targeted strategy [81]. Dietary fibers, such as inulin and fructooligosaccharides, enhance SCFA production, particularly butyrate, which exerts anti-inflammatory effects and strengthens the intestinal barrier [82]. By increasing the abundance of commensal bacteria, prebiotics can counteract dysbiosis, reduce LPS translocation, and alleviate hepatic inflammation. Emerging evidence suggests that prebiotic supplementation may also improve insulin sensitivity and lipid metabolism, further supporting its therapeutic potential in NAFLD.

FMT has garnered attention as an innovative approach to directly modify the gut microbiota. By transferring fecal material from healthy donors to NAFLD patients, FMT aims to restore a healthy microbial ecosystem [83]. Preclinical studies have shown that FMT can reduce hepatic steatosis, improve glucose homeostasis, and alleviate gut-liver axis dysfunction [83]. However, clinical data on FMT in NAFLD are limited, and concerns regarding donor selection, long-term safety, and regulatory oversight must be addressed before its widespread adoption. In addition to these established approaches, next-generation microbiota-based therapies are under development [84]. These include engineered microbial consortia designed to produce specific metabolites or modulate key pathways implicated in NAFLD, as well as postbiotics-microbial-derived bioactive compounds, such as SCFAs or bacterial peptides. These novel therapies have the potential to precisely modulate gut microbiota and its metabolic out-

puts, offering new avenues for targeted intervention [85].

While microbiota-targeted therapies show considerable promise, several challenges remain. The inter-individual variability in gut microbiota composition, influenced by genetics, diet, and lifestyle, necessitates personalized approaches to treatment. Furthermore, the long-term efficacy and safety of these interventions require rigorous evaluation in well-designed clinical trials. Future research should focus on identifying specific microbial taxa or metabolites as biomarkers for therapy selection and monitoring, as well as understanding the interplay between gut microbiota, host metabolism, and the brain-liver axis. Addressing these challenges will be crucial for establishing microbiota-targeted therapies as a cornerstone of precision medicine in managing NAFLD.

VNS

VNS has emerged as a promising therapeutic strategy for mitigating GBA dysregulation and its downstream effects in NAFLD [86]. The vagus nerve plays a central role in the bidirectional communication between the gut and the brain, regulating key physiological processes such as energy metabolism, inflammation, and gut barrier integrity. Dysregulation of vagal activity, characterized by reduced parasympathetic tone, has been implicated in NAFLD pathogenesis through mechanisms such as impaired anti-inflammatory signaling, increased systemic inflammation, and altered hepatic glucose and lipid metabolism [87]. By enhancing parasympathetic activity, VNS offers a novel approach to restoring homeostasis in the gut-brain-liver axis and alleviating NAFLD-related metabolic dysfunction.

One of the primary mechanisms through which VNS exerts its therapeutic effects is by attenuating systemic and hepatic inflammation. Vagal stimulation activates the cholinergic anti-inflammatory pathway, which reduces the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 by inhibiting nuclear factor-kappa B signaling in macrophages and Kupffer cells. This anti-inflammatory effect not only mitigates hepatic inflammation but also disrupts the inflammatory feedback loop contributing to insulin resistance and hepatic steatosis in NAFLD [88-91]. Additionally, VNS influences gut function and microbiota composition, both of which are critical in NAFLD pathophysiology. Stimulation of the vagus nerve enhances intestinal motility and secretion, promoting the clearance of luminal endotoxins and preventing microbial overgrowth [92]. Furthermore, VNS improves intestinal barrier integrity by upregulating tight junction proteins such as occludin and claudin-1, thereby reducing the translocation of LPS into the portal circulation. Preclinical studies have demonstrated that VNS-induced improvements in gut barrier function are associated with reduced endotoxemia, systemic inflammation, and hepatic lipid accumulation, highlighting the integral role of the gut-brain-liver axis in mediating its therapeutic effects [93].

Beyond its anti-inflammatory and gut-regulatory effects, VNS also directly impacts hepatic metabolism. Experimental models have shown that VNS improves hepatic insulin sensitivity, reduces gluconeogenesis, and enhances fatty acid β-oxidation, thereby addressing key metabolic derangements in NAFLD. These effects are mediated, in part, by the modulation of hypothalamic control centers involved in autonomic regulation and energy homeostasis, emphasizing the central role of the brain in coordinating liver metabolism. While the therapeutic potential of VNS is evident, its application in NAFLD is still in the early stages of investigation. Preclinical studies have provided robust evidence for its efficacy in reducing hepatic steatosis, inflammation, and fibrosis, but clinical studies in humans remain limited [94]. Initial pilot studies have shown that non-invasive VNS can improve metabolic markers such as glucose tolerance and inflammatory cytokine levels in patients with metabolic syndrome, a key precursor to NAFLD. However, larger randomized controlled trials are needed to establish the long-term efficacy and safety of VNS in NAFLD populations. Challenges associated with VNS include the invasiveness of traditional implantable devices, variability in patient response, and potential side effects such as bradycardia or dysphagia. Recent advancements in non-invasive VNS (nVNS) technologies, which use transcutaneous stimulation of the auricular branch of the vagus nerve, offer a less invasive and more accessible alternative, with promising results in other chronic inflammatory and metabolic diseases [95]. Future

research should focus on optimizing stimulation parameters, identifying biomarkers to predict therapeutic response, and evaluating the integration of VNS with other GBA -targeted therapies, such as microbiota modulation or dietary interventions.

VNS represents a novel and multifaceted approach to targeting GBA dysregulation in NAFLD. By restoring parasympathetic tone, reducing inflammation, improving gut barrier function, and modulating hepatic metabolism, VNS addresses several key pathways implicated in NAFLD pathogenesis. With further validation through clinical trials and technological advancements, VNS has the potential to become a cornerstone therapy for this increasingly prevalent liver disease.

Neuroprotective and anti-inflammatory therapies

Neuroprotective and anti-inflammatory therapies have gained increasing attention as potential strategies for addressing GBA dysregulation in the pathogenesis of NAFLD. Chronic low-grade inflammation and neuroinflammation are key drivers of hypothalamic dysfunction, ANS imbalance, and systemic metabolic disturbances in NAFLD. Targeting these inflammatory processes and protecting neuronal health may help restore metabolic homeostasis, reduce hepatic inflammation, and slow disease progression. Several therapeutic approaches, ranging from pharmacological agents to lifestyle modifications, have shown promise in mitigating inflammation and preserving neural function in NAFLD.

A central focus of neuroprotective therapies is the modulation of microglial activation in brain regions involved in energy regulation, particularly the hypothalamus. Excessive microglial activation in response to systemic inflammation or gut-derived endotoxins leads to the production of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α, which disrupt hypothalamic signaling and contribute to metabolic dysregulation [95]. Pharmacological agents targeting microglial activation, such as minocycline and palmitoylethanolamide (PEA), have demonstrated efficacy in reducing neuroinflammation and improving metabolic outcomes in preclinical models of NAFLD [96]. These agents hold potential for clinical application as adjunct therapies targeting central drivers of NAFLD pathology.

Anti-inflammatory therapies aimed at systemic and hepatic inflammation also play a crucial role in modulating the gut-brain-liver axis. For example, inhibitors of TLR4 signaling, such as TAK-242, have shown promise in reducing hepatic inflammation by attenuating the effects of LPS translocated from the gut [97]. Similarly, IL-1 receptor antagonists, such as anakinra, have demonstrated the ability to dampen both systemic and hepatic inflammation, indirectly improving hypothalamic function and autonomic regulation [98]. These therapies highlight the interconnected nature of systemic and neuroinflammatory pathways in NAFLD and underscore the importance of targeting both peripheral and central inflammation.

Emerging evidence suggests that neuroprotective dietary compounds, such as omega-3 polyunsaturated fatty acids (PUFAs), polyphenols, and flavonoids, may also offer significant benefits in NAFLD by reducing neuroinflammation and oxidative stress [99]. Omega-3 PUFAs, for instance, exert anti-inflammatory effects by modulating eicosanoid production and suppressing microglial activation. Polyphenols such as resveratrol and curcumin have been shown to improve hypothalamic insulin sensitivity and reduce hepatic steatosis through their antioxidant properties. These compounds may complement pharmacological therapies as part of a holistic approach to managing GBA dysregulation.

Neuroprotective and anti-inflammatory therapies represent a critical frontier in addressing GBA dysregulation in NAFLD. By targeting neuroinflammatory pathways, preserving neuronal function, and reducing systemic and hepatic inflammation, these therapies offer a multifaceted approach to mitigating NAFLD progression. Continued exploration of these interventions, alongside advances in precision medicine, has the potential to improve outcomes for patients with this complex and multifactorial disease.

Combined multimodal approaches

Given the multifaceted nature of NAFLD and its complex interplay with GBA dysregulation, combined multimodal approaches have emerged

as a promising therapeutic strategy. NAFLD involves the convergence of metabolic, inflammatory, neural, and microbial pathways, suggesting that single-target therapies are unlikely to provide optimal results. By integrating multiple interventions-such as microbiota-targeted therapies, neuroprotective agents, dietary modifications, and VNS-combined approaches aim to address the disease's systemic and interconnected drivers, offering synergistic benefits.

A key advantage of multimodal strategies is their ability to simultaneously target both upstream and downstream pathways within the gut-brain-liver axis [99]. For example, combining probiotics and prebiotics with anti-inflammatory therapies can enhance gut barrier function, reduce systemic endotoxemia, and mitigate both hepatic and neuroinflammation. Clinical evidence supports the efficacy of such combinations: trials using synbiotics (probiotics plus prebiotics) alongside dietary interventions have demonstrated significant reductions in hepatic fat content, systemic inflammation, and insulin resistance in NAFLD patients [100]. These findings underscore the importance of addressing both gut microbiota dysbiosis and dietary factors contributing to disease progression.

Another example of a multimodal approach is the integration of VNS with lifestyle interventions such as exercise and stress management. VNS enhances parasympathetic tone, reduces inflammation, and improves gut barrier integrity, while exercise and stress reduction further modulate autonomic balance and metabolic health [101, 102]. Combining these therapies may amplify their individual effects by targeting both neural and metabolic pathways, thus restoring homeostasis within the GBA. Early pilot studies in patients with metabolic syndrome and NAFLD suggest that such approaches can improve markers of liver function, glucose homeostasis, and overall quality of life.

Additionally, pharmacological interventions targeting bile acid signaling or TLR4 pathways may be combined with microbiota-based therapies to achieve comprehensive modulation of gut-liver communication [103]. For instance, bile acid-based agents like obeticholic acid not only reduce hepatic inflammation but also influence gut microbiota composition and intestinal permeability. When paired with probiotics or FMT, these agents may yield enhanced benefits by addressing dysbiosis and its downstream metabolic effects.

Despite the promise of multimodal approaches, several challenges must be addressed to facilitate their clinical implementation [104]. Coordinating and standardizing combinations of therapies, evaluating their cost-effectiveness, and assessing long-term safety and efficacy are critical areas for future research. Moreover, large-scale, randomized controlled trials are needed to validate the synergistic effects of these combined interventions and establish evidence-based guidelines for their use.

Combined multimodal approaches represent a novel and promising strategy for addressing the systemic and interconnected mechanisms underlying NAFLD. By leveraging the synergistic potential of microbiota-targeted therapies, neural interventions, dietary modifications, and precision pharmacology, these strategies offer the potential for improved therapeutic outcomes. Continued research and clinical innovation will be essential to realize their full potential and transform the management of this complex disease.

Challenges and future directions

Despite considerable progress in understanding the role of GBA dysregulation in NAFLD, significant challenges remain in translating this knowledge into clinical applications. A key obstacle is the mechanistic complexity of the gut-brain-liver axis, which involves intricate bidirectional communication between the gut microbiota, neural circuits, and hepatic metabolism. Deciphering this interplay is further complicated by inter-individual variability in microbiota composition, dietary patterns, and genetic predispositions, all of which contribute to the heterogeneous clinical presentation of NAFLD. Furthermore, methodological inconsistencies, such as non-standardized approaches to assessing gut microbiota, intestinal permeability, and neural signaling, impede reproducibility and hinder the identification of reliable biomarkers.

Looking forward, integrative multi-omics approaches, encompassing metagenomics, meta-

bolomics, and transcriptomics, will be essential for uncovering specific microbial metabolites and signaling pathways that mediate GBA dysfunction. Personalized medicine approaches, leveraging machine learning and artificial intelligence, can stratify patients based on microbiota profiles, genetic risk factors, and disease phenotypes, enabling tailored therapeutic interventions. The targets of NAFLD involved in the GBA are summarized in **Table 1**. Additionally, further exploration of emerging therapies, such as engineered probiotics, FMT, and neuroprotective agents, holds promise for addressing both microbial and neurobehavioral dimensions of GBA dysregulation. Ultimately, large-scale, longitudinal clinical trials with standardized methodologies will be critical to validate these findings and advance innovative, multi-targeted therapeutic strategies for the effective management of NAFLD.

Therapeutic implications

The therapeutic implications for current and potential clinical applications in NAFLD, especially those targeting the GBA, are becoming increasingly important due to the complex pathophysiology of the disease. As a multifactorial condition, NAFLD is closely associated with disruptions in metabolic, immune, and neural regulation. The GBA, a key mediator of these interactions, plays a pivotal role in the progression of NAFLD, making it an important target for therapeutic intervention. However, a critical question arises: is it more effective to intervene directly with NAFLD, treat the cerebro-intestinal axis, or target both? A comparison of the advantages and disadvantages of each approach is essential for guiding therapeutic strategies.

Direct interventions targeting NAFLD focus on liver-specific pathways, such as regulating lipid metabolism, reducing hepatic inflammation, and improving insulin sensitivity. The main advantage of this approach is that it directly targets the liver, where the primary pathology occurs, leading to potentially more immediate effects on liver function and metabolic parameters. However, it may not fully address the systemic and neuroinflammatory aspects that contribute to disease progression. Moreover, liver-focused therapies alone may be less effective for modulating the gut-brain-liver communication, which plays a crucial role in the disease's progression.

In contrast, treatments targeting the GBA aim to address the gut-brain-liver communication and neuroinflammation, both central to NAFLD pathogenesis. These approaches may offer the advantage of targeting multiple facets of the disease, including both the liver and neural regulation. For example, microbiota-targeted therapies, such as probiotics, prebiotics, synbiotics, and FMT, have shown promise in reducing hepatic steatosis, inflammation, and improving metabolic outcomes by producing SCFAs that regulate gut barrier integrity and reduce endotoxemia. Similarly, VNS enhances parasympathetic activity to regulate inflammation, metabolism, and gut barrier function, with preclinical studies suggesting it can reduce hepatic inflammation, improve glucose metabolism, and restore gut motility. The advantage of these approaches is their ability to target systemic pathways, offering a more holistic treatment for NAFLD. However, the downside is that they may not directly address liver-specific mechanisms of disease progression.

A combined approach-directly targeting the liver while also modulating the GBA-could offer synergistic benefits by simultaneously addressing both metabolic and neuroinflammatory pathways. For example, combining microbiota-targeted therapies with VNS could potentially provide a more comprehensive treatment by targeting multiple levels of disease. The integration of neuroprotective and anti-inflammatory therapies, which target neuroinflammation through modulation of microglial activation or cytokine signaling, could also complement microbiota-targeted treatments or VNS. These therapies may help restore hypothalamic function and improve autonomic regulation, which are often disrupted in NAFLD. The combined approach could lead to more comprehensive management, but challenges remain in determining the optimal therapeutic combination.

Emerging treatments also include the use of neuroprotective dietary compounds, such as omega-3 fatty acids and polyphenols, which have been shown to reduce neuroinflammation and oxidative stress, improving both hepatic and neural outcomes. While these therapies show great promise, the integration of multimodal approaches is likely to represent the

Table 1. The targets of NAFLD involved in the brain-gut axis

Therapeutic Strategy	Mechanism of Action	Potential Benefits in NAFLD	Current Status
Microbiota-Targeted Therapies	Modulate gut microbiota composition and function through probiotics, prebiotics, synbiotics, and FMT	Restores microbial balance, improves intestinal barrier integrity, reduces systemic inflammation	Clinical trials and preclinical studies
Probiotics	Administer beneficial live microorganisms (e.g., Lactobacillus, Bifidobacterium) to regulate gut microbiota	Reduces hepatic steatosis, inflammation, oxidative stress, and endotoxemia	Clinical studies show promising results, but strain-specific efficacy varies
Prebiotics	Non-digestible compounds (e.g., inulin, FOS) that promote growth of beneficial gut bacteria	Enhances SCFA production, reduces LPS translocation, improves insulin sensitivity	Preclinical and early clinical studies support benefits
FMT)	Transfers fecal material from healthy donors to NAFLD patients to restore microbial ecosystem	Reduces hepatic steatosis, improves glucose metabolism and gut-liver axis function	Limited clinical data; safety and donor selection challenges
VNS	Enhances parasympathetic tone to regulate inflammation, gut microbiota, and hepatic metabolism	Reduces hepatic inflammation, improves gut barrier function, and enhances metabolic homeostasis	Preclinical studies; early pilot trials in metabolic syndrome
Neuroprotective and Anti-Inflammatory Therapies	Target microglial activation and inflammatory signaling pathways (e.g., TLR4 inhibitors, IL-1 antagonists)	Reduces neuroinflammation, improves metabolic control, and restores hypothalamic function	Preclinical studies; some clinical trials ongoing
Dietary Neuroprotective Compounds	Omega-3 fatty acids, polyphenols, flavonoids with anti-inflammatory and antioxidant properties	Reduces neuroinflammation, improves hypothalamic insulin sensitivity, decreases hepatic steatosis	Clinical trials and dietary intervention studies
Combined Multimodal Approaches	Integrating microbiota-targeted therapies, neuroprotective agents, dietary modifications, and VNS	Addresses multiple pathways within the gut-brain-liver axis for synergistic benefits	Emerging therapeutic approach, requiring further clinical validation
Challenges and Future Directions	Inter-individual variability, methodological inconsistencies, need for standardized clinical trials	Personalized medicine approaches, integrative multi-omics strategies, biomarker discovery	Ongoing research and need for large-scale longitudinal studies

NAFLD: Non-Alcoholic Fatty Liver Disease; SCFA: Short-Chain Fatty Acid; FMT: Fecal Microbiota Transplantation; VNS: Vagus Nerve Stimulation; TLR4: Toll-Like Receptor 4; FOS: fructooligosaccharides.

future of NAFLD treatment. Combining microbiota-targeted therapies with VNS, anti-inflammatory agents, and neuroprotective compounds could address multiple pathways within the brain-gut-liver axis simultaneously, potentially leading to more effective management of NAFLD than single-therapy interventions.

The clinical application of these therapies faces several challenges. Personalized medicine approaches will be crucial, given the variability in gut microbiota composition, genetic predispositions, and lifestyle factors. Furthermore, the safety and efficacy of these treatments must be rigorously evaluated in large-scale, randomized controlled trials to determine the most effective combination of therapies and identify biomarkers that can predict treatment response.

Key mechanistic molecules in the GBA associated with NAFLD

The GBA is a complex communication network between the gut, central nervous system, and peripheral systems, playing a crucial role in regulating metabolism, inflammation, and energy homeostasis. Several key molecules within this axis have been implicated in NAFLD pathogenesis. For instance, glucagon-like peptide-1, a gut-derived hormone, influences insulin sensitivity and hepatic steatosis. LPS, derived from gut microbiota, can provoke systemic inflammation, contributing to insulin resistance and the development of fatty liver. Cytokines such as TNF-α, IL-6, and IL-1β are central to the inflammatory response in both the brain and liver, affecting neuroinflammation and liver function. Moreover, the vagus nerve plays a vital role in transmitting signals from the gut to the brain, influencing hypothalamic function and metabolic processes. Neuropeptides such as ghrelin and leptin are involved in appetite regulation and energy balance, and their dysregulation can exacerbate metabolic disturbances in NAFLD. Additionally, the hypothalamus, through pathways like the endocannabinoid system and the sympathetic nervous system, integrates these molecular signals to regulate food intake, fat storage, and hepatic lipid metabolism. By summarizing these molecular mechanisms, we aim to provide a clearer understanding of how these molecules interact within the GBA to influence NAFLD pathogenesis, offering potential targets for therapeutic intervention.

Conclusion

Dysregulation of the GBA plays a central role in the pathogenesis of NAFLD, influencing metabolic, inflammatory, and neural pathways. Targeting the brain-gut axis through microbiota restoration, neuroprotection, and autonomic modulation presents promising avenues for personalized NAFLD management. A deeper understanding of GBA mechanisms will pave the way for innovative therapies and improved patient outcomes in NAFLD treatment.

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Disclosure of conflict of interest

None.

Abbreviations

NAFLD, Non-Alcoholic Fatty Liver Disease; NASH, Non-Alcoholic Steatohepatitis; HCC, Hepatocellular Carcinoma; GBA, Gut-Brain Axis; LPS, Lipopolysaccharides; SCFAs, Short-Chain Fatty Acids; FMT, Fecal Microbiota Transplantation; VNS, Vagus Nerve Stimulation; HPA, Hypothalamic-Pituitary-Adrenal; ANS, Autonomic Nervous System; TLR4, Toll-Like Receptor 4; IL-1, Interleukin-1; FXR, Farnesoid X Receptor.

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References

[1] Powell EE, Wong VW and Rinella M. Non-alcoholic fatty liver disease. Lancet 2021; 397: 2212-2224.

[2] Matchett KP, Paris J, Teichmann SA and Henderson NC. Spatial genomics: mapping human steatotic liver disease. Nat Rev Gastroenterol Hepatol 2024; 21: 646-660.

[3] Adorini L and Trauner M. FXR agonists in NASH treatment. J Hepatol 2023; 79: 1317-1331.
[4] Lazarus JV, Mark HE, Anstee QM, Arab JP, Batterham RL, Castera L, Cortez-Pinto H, Crespo J, Cusi K, Dirac MA, Francque S, George J, Hagström H, Huang TT, Ismail MH, Kautz A, Sarin SK, Loomba R, Miller V, Newsome PN, Ninburg M, Ocama P, Ratziu V, Rinella M, Romero D, Romero-Gómez M, Schattenberg JM, Tsochatzis EA, Valenti L, Wong VW, Yilmaz Y, Younossi ZM and Zelber-Sagi S; NAFLD Consensus Consortium. Advancing the global public health agenda for NAFLD: a consensus statement. Nat Rev Gastroenterol Hepatol 2022; 19: 60-78.
[5] Rosso C, Kazankov K, Younes R, Esmaili S, Marietti M, Sacco M, Carli F, Gaggini M, Salomone F, Møller HJ, Abate ML, Vilstrup H, Gastaldelli A, George J, Grønbæk H and Bugianesi E. Crosstalk between adipose tissue insulin resistance and liver macrophages in non-alcoholic fatty liver disease. J Hepatol 2019; 71: 1012-1021.
[6] Sen P, Qadri S, Luukkonen PK, Ragnarsdottir O, McGlinchey A, Jäntti S, Juuti A, Arola J, Schlezinger JJ, Webster TF, Orešič M, Yki-Järvinen H and Hyötyläinen T. Exposure to environmental contaminants is associated with altered hepatic lipid metabolism in non-alcoholic fatty liver disease. J Hepatol 2022; 76: 283-293.
[7] Mitten EK and Baffy G. Mechanotransduction in the pathogenesis of non-alcoholic fatty liver disease. J Hepatol 2022; 77: 1642-1656.
[8] Chen B, Sun L, Zeng G, Shen Z, Wang K, Yin L, Xu F, Wang P, Ding Y, Nie Q, Wu Q, Zhang Z, Xia J, Lin J, Luo Y, Cai J, Krausz KW, Zheng R, Xue Y, Zheng MH, Li Y, Yu C, Gonzalez FJ and Jiang C. Gut bacteria alleviate smoking-related NASH by degrading gut nicotine. Nature 2022; 610: 562-568.
[9] Song Q, Zhang X, Liu W, Wei H, Liang W, Zhou Y, Ding Y, Ji F, Ho-Kwan Cheung A, Wong N and Yu J. Bifidobacterium pseudolongum-generated acetate suppresses non-alcoholic fatty liver disease-associated hepatocellular carcinoma. J Hepatol 2023; 79: 1352-1365.
[10] Liu C, Zhou B, Meng M, Zhao W, Wang D, Yuan Y, Zheng Y, Qiu J, Li Y, Li G, Xiong X, Bian H, Zhang H, Wang H, Ma X, Hu C, Xu L and Lu Y. FOXA3 induction under endoplasmic reticulum stress contributes to non-alcoholic fatty liver disease. J Hepatol 2021; 75: 150-162.
[11] Jiang X, Fulte S, Deng F, Chen S, Xie Y, Chao X, He XC, Zhang Y, Li T, Li F, McCoin C, Morris EM, Thyfault J, Liu W, Li L, Davidson NO, Ding WX and Ni HM. Lack of VMP1 impairs hepatic lipoprotein secretion and promotes non-alcoholic steatohepatitis. J Hepatol 2022; 77: 619-631.
[12] Forlano R, Mullish BH, Roberts LA, Thursz MR and Manousou P. The intestinal barrier and its dysfunction in patients with metabolic diseases and non-alcoholic fatty liver disease. Int J Mol Sci 2022; 23: 662.
[13] Mann ER, Lam YK and Uhlig HH. Short-chain fatty acids: linking diet, the microbiome and immunity. Nat Rev Immunol 2024; 24: 577-595.
[14] Cani PD and Van Hul M. Gut microbiota in overweight and obesity: crosstalk with adipose tissue. Nat Rev Gastroenterol Hepatol 2024; 21: 164-183.
[15] Lavelle A and Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 2020; 17: 223-237.
[16] de Vos WM, Tilg H, Van Hul M and Cani PD. Gut microbiome and health: mechanistic insights. Gut 2022; 71: 1020-1032.
[17] Drummen M, Tischmann L, Gatta-Cherifi B, Adam T and Westerterp-Plantenga M. Dietary protein and energy balance in relation to obesity and co-morbidities. Front Endocrinol (Lausanne) 2018; 9: 443.
[18] Jung JH, Kim SE, Suk KT and Kim DJ. Gut microbiota-modulating agents in alcoholic liver disease: links between host metabolism and gut microbiota. Front Med (Lausanne) 2022; 9: 913842.
[19] Yang J, Yang H and Li Y. The triple interactions between gut microbiota, mycobiota and host immunity. Crit Rev Food Sci Nutr 2023; 63: 11604-11624.
[20] Yang R, Chen Z and Cai J. Fecal microbiota transplantation: emerging applications in autoimmune diseases. J Autoimmun 2023; 141: 103038.
[21] Pahuja M, Akhtar KH, Krishan S, Nasir YM, Généreux P, Stavrakis S and Dasari TW. Neuromodulation therapies in heart failure: a state-of-the-art review. J Soc Cardiovasc Angiogr Interv 2023; 2: 101199.
[22] Fallahi MS, Azadnajafabad S, Maroufi SF, Pour-Rashidi A, Khorasanizadeh M, Sattari SA, Faramarzi S and Slavin KV. Application of vagus nerve stimulation in spinal cord injury rehabilitation. World Neurosurg. 2023; 174: 11-24.
[23] Bárcena C, Valdés-Mas R, Mayoral P, Garabaya C, Durand S, Rodríguez F, Fernández-García MT, Salazar N, Nogacka AM, Garatachea N, Bossut N, Aprahamian F, Lucia A, Kroemer G, Freije JMP, Quirós PM and López-Otín C. Healthspan and lifespan extension by fecal microbiota transplantation into progeroid mice. Nat Med 2019; 25: 1234-1242.
[24] Takeuchi T, Kubota T, Nakanishi Y, Tsugawa H, Suda W, Kwon AT, Yazaki J, Ikeda K, Nemoto S,

Mochizuki Y, Kitami T, Yugi K, Mizuno Y, Yamamichi N, Yamazaki T, Takamoto I, Kubota N, Kadowaki T, Arner E, Carninci P, Ohara O, Arita M, Hattori M, Koyasu S and Ohno H. Gut microbial carbohydrate metabolism contributes to insulin resistance. Nature 2023; 621: 389-395.

[25] Hsu CY, Khachatryan LG, Younis NK, Mustafa MA, Ahmad N, Athab ZH, Polyanskaya AV, Kasanave EV, Mirzaei R and Karampoor S. Microbiota-derived short chain fatty acids in pediatric health and diseases: from gut development to neuroprotection. Front Microbiol 2024; 15: 1456793.

[26] Abdelhalim KA. Short-chain fatty acids (SCFAs) from gastrointestinal disorders, metabolism, epigenetics, central nervous system to cancer - a mini-review. Chem Biol Interact 2024; 388: 110851.

[27] Hu J, Lin S, Zheng B and Cheung PCK. Short-chain fatty acids in control of energy metabolism. Crit Rev Food Sci Nutr 2018; 58: 1243-1249.

[28] Forte N, Marfella B, Nicois A, Palomba L, Paris D, Motta A, Pina Mollica M, Di Marzo V and Cristino L. The short-chain fatty acid acetate modulates orexin/hypocretin neurons: a novel mechanism in gut-brain axis regulation of energy homeostasis and feeding. Biochem Pharmacol 2024; 226: 116383.

[29] Hoffman S and Adeli K. Glucagon-like peptide (GLP)-1 regulation of lipid and lipoprotein metabolism. Med Rev (2021) 2024; 4: 301-311.

[30] Jia W, Xie G and Jia W. Bile acid-microbiota crosstalk in gastrointestinal inflammation and carcinogenesis. Nat Rev Gastroenterol Hepatol 2018; 15: 111-128.

[31] Chi L, YifeiYang, Bian X, Gao B, Tu P, Ru H and Lu K. Chronic sucralose consumption inhibits farnesoid X receptor signaling and perturbs lipid and cholesterol homeostasis in the mouse livers, potentially by altering gut microbiota functions. Sci Total Environ 2024; 919: 169603.

[32] Liang S, Zhong Z, Kim SY, Uchiyama R, Roh YS, Matsushita H, Gottlieb RA and Seki E. Murine macrophage autophagy protects against alcohol-induced liver injury by degrading interferon regulatory factor 1 (IRF1) and removing damaged mitochondria. J Biol Chem 2019; 294: 12359-12369.

[33] Violi F, Nocella C, Bartimoccia S, Castellani V, Carnevale R, Pignatelli P and Cammisotto V. Gut dysbiosis-derived low-grade endotoxemia: a common basis for liver and cardiovascular disease. Kardiol Pol 2023; 81: 563-571.

[34] Jiang X, Fulte S, Deng F, Chen S, Xie Y, Chao X, He XC, Zhang Y, Li T, Li F, McCoin C, Morris EM, Thyfault J, Liu W, Li L, Davidson NO, Ding WX and Ni HM. Lack of VMP1 impairs hepatic lipoprotein secretion and promotes non-alcoholic steatohepatitis. J Hepatol 2022; 77: 619-631.

[35] Zhang XL, Chen L, Yang J, Zhao SS, Jin S, Ao N, Yang J, Liu HX and Du J. Vitamin D alleviates non-alcoholic fatty liver disease via restoring gut microbiota and metabolism. Front Microbiol 2023; 14: 1117644.

[36] Chuaypen N, Asumpinawong A, Sawangsri P, Khamjerm J, Iadsee N, Jinato T, Sutheeworapong S, Udomsawaengsup S and Tangkijvanich P. Gut microbiota in patients with non-alcoholic fatty liver disease without type 2 diabetes: stratified by body mass index. Int J Mol Sci.2024; 25: 1807.

[37] Ju T, Bourrie BCT, Forgie AJ, Pepin DM, Tollenaar S, Sergi CM and Willing BP. The gut commensal escherichia coli aggravates high-fat-diet-induced obesity and insulin resistance in mice. Appl Environ Microbiol 2023; 89: e0162822.

[38] Schirmer M, Garner A, Vlamakis H and Xavier RJ. Microbial genes and pathways in inflammatory bowel disease. Nat Rev Microbiol 2019; 17: 497-511.

[39] Mijangos-Trejo A, Nuño-Lambarri N, Barbero-Becerra V, Uribe-Esquivel M, Vidal-Cevallos P and Chávez-Tapia N. Prebiotics and probiotics: therapeutic tools for nonalcoholic fatty liver disease. Int J Mol Sci 2023; 24: 14918.

[40] Pezzino S, Sofia M, Faletra G, Mazzone C, Litrico G, La Greca G and Latteri S. Gut-liver axis and non-alcoholic fatty liver disease: a vicious circle of dysfunctions orchestrated by the gut microbiome. Biology (Basel) 2022; 11: 1622.

[41] Di Vincenzo F, Del Gaudio A, Petito V, Lopetuso LR and Scaldaferri F. Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. Intern Emerg Med 2024; 19: 275-293.

[42] Ceccarelli S, Nobili V and Alisi A. Toll-like receptor-mediated signaling cascade as a regulator of the inflammation network during alcoholic liver disease. World J Gastroenterol 2014; 20: 16443-16451.

[43] Alluri H, Peddaboina CS and Tharakan B. Determination of tight junction integrity in brain endothelial cells based on tight junction protein expression. Methods Mol Biol 2024; 2711: 235-240.

[44] Zhang X, Coker OO, Chu ES, Fu K, Lau HCH, Wang YX, Chan AWH, Wei H, Yang X, Sung JJY and Yu J. Dietary cholesterol drives fatty liver-associated liver cancer by modulating gut microbiota and metabolites. Gut 2021; 70: 761-774.

[45] Rawat M, Nighot M, Al-Sadi R, Gupta Y, Viszwapriya D, Yochum G, Koltun W and Ma TY.

IL1B increases intestinal tight junction permeability by up-regulation of MIR200C-3p, which degrades occludin mRNA. Gastroenterology 2020; 159: 1375-1389.
[46] Park JE, Park HY, Kim YS and Park M. The role of diet, additives, and antibiotics in metabolic endotoxemia and chronic diseases. Metabolites 2024; 14: 704.
[47] Zheng M, Zhai Y, Yu Y, Shen J, Chu S, Focaccia E, Tian W, Wang S, Liu X, Yuan X, Wang Y, Li L, Feng B, Li Z, Guo X, Qiu J, Zhang C, Hou J, Sun Y, Yang X, Zuo X, Heikenwalder M, Li Y, Yuan D and Li S. TNF compromises intestinal bile-acid tolerance dictating colitis progression and limited infliximab response. Cell Metab 2024; 36: 2086-2103, e9.
[48] Lin S, Zhang X, Zhu X, Jiao J, Wu Y, Li Y and Zhao L. Fusobacterium nucleatum aggravates ulcerative colitis through promoting gut microbiota dysbiosis and dysmetabolism. J Periodontol 2023; 94: 405-418.
[49] Cai X, Panicker SR, Biswas I, Giri H and Rezaie AR. Protective role of activated protein C against viral mimetic poly(I:C)-induced inflammation. Thromb Haemost 2021; 121: 1448-1463.
[50] Bekeredjian-Ding I, Stein C and Uebele J. The innate immune response against staphylococcus aureus. Curr Top Microbiol Immunol 2017; 409: 385-418.
[51] Engin AB. Message transmission between adipocyte and macrophage in obesity. Adv Exp Med Biol 2024; 1460: 273-295.
[52] Vallance TM, Zeuner MT, Williams HF, Widera D and Vaiyapuri S. Toll-like receptor 4 signalling and its impact on platelet function, thrombosis, and haemostasis. Mediators Inflamm 2017; 2017: 9605894.
[53] Neurath MF. Strategies for targeting cytokines in inflammatory bowel disease. Nat Rev Immunol 2024; 24: 559-576.
[54] Groeger M, Matsuo K, Heidary Arash E, Pereira A, Le Guillou D, Pino C, Telles-Silva KA, Maher JJ, Hsiao EC and Willenbring H. Modeling and therapeutic targeting of inflammation-induced hepatic insulin resistance using human iPSC-derived hepatocytes and macrophages. Nat Commun 2023; 14: 3902.
[55] Castelnuovo G, Perez-Diaz-Del-Campo N, Guariglia M, Poggiolini I, Armandi A, Rosso C, Caviglia GP and Bugianesi E. Prebiotics targeting gut-liver axis to treat non-alcoholic fatty liver disease. Minerva Gastroenterol (Torino) 2024; 70: 446-453.
[56] Varesi A, Campagnoli LIM, Barbieri A, Rossi L, Ricevuti G, Esposito C, Chirumbolo S, Marchesi N and Pascale A. RNA binding proteins in senescence: a potential common linker for age-related diseases?. Ageing Res Rev 2023; 88: 101958.
[57] Yang AJT, Bagit A and MacPherson REK. Resveratrol, metabolic dysregulation, and Alzheimer's disease: considerations for neurogenerative disease. Int J Mol Sci 2021; 22: 4628.
[58] He Y, Ruganzu JB, Jin H, Peng X, Ji S, Ma Y, Zheng L and Yang W. LRP1 knockdown aggravates $A\beta_{1-42}$-stimulated microglial and astrocytic neuroinflammatory responses by modulating TLR4/NF-κB/MAPKs signaling pathways. Exp Cell Res 2020; 394: 112166.
[59] Chancharoenthana W, Kamolratanakul S, Schultz MJ and Leelahavanichkul A. The leaky gut and the gut microbiome in sepsis - targets in research and treatment. Clin Sci (Lond) 2023; 137: 645-662.
[60] Gupta N, El-Gawaad NSA, Mallasiy LO, Gupta H, Yadav VK, Alghamdi S and Qusty NF. Microbial dysbiosis and the aging process: a review on the potential age-deceleration role of Lactiplantibacillus plantarum. Front Microbiol 2024; 15: 1260793.
[61] Makdissi S, Parsons BD and Di Cara F. Towards early detection of neurodegenerative diseases: a gut feeling. Front Cell Dev Biol 2023; 11: 1087091.
[62] Bhuiyan P, Chen Y, Karim M, Dong H and Qian Y. Bidirectional communication between mast cells and the gut-brain axis in neurodegenerative diseases: avenues for therapeutic intervention. Brain Res Bull 2021; 172: 61-78.
[63] Kreuch D, Keating DJ, Wu T, Horowitz M, Rayner CK and Young RL. Gut mechanisms linking intestinal sweet sensing to glycemic control. Front Endocrinol (Lausanne) 2018; 9: 741.
[64] Liu T, Li T, Chen X, Li Z, Feng M, Yao W, Wan L, Zhang C and Zhang Y. EETs/sEHi alleviates nociception by blocking the crosslink between endoplasmic reticulum stress and neuroinflammation in a central poststroke pain model. J Neuroinflammation 2021; 18: 211.
[65] Chambel SS and Cruz CD. Axonal growth inhibitors and their receptors in spinal cord injury: from biology to clinical translation. Neural Regen Res. 2023; 18: 2573-2581.
[66] Tang R, Liu R, Zha H, Cheng Y, Ling Z and Li L. Gut microbiota induced epigenetic modifications in the non-alcoholic fatty liver disease pathogenesis. Eng Life Sci 2024; 24: 2300016.
[67] Vegda HS, Patel B, Girdhar GA, Pathan MSH, Ahmad R, Haque M, Sinha S and Kumar S. Role of nonalcoholic fatty liver disease in periodontitis: a bidirectional relationship. Cureus 2024; 16: e63775.
[68] Tinkov AA, Aschner M, Santamaria A, Bogdanov AR, Tizabi Y, Virgolini MB, Zhou JC and Skal-

ny AV. Dissecting the role of cadmium, lead, arsenic, and mercury in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Environ Res 2023; 238: 117134.
[69] Brüler BC, Vieira TC, Wolf M, Lucina SB, Montiani-Ferreira F and Sousa MG. Using the oculocardiac reflex to characterize autonomic imbalance in a naturally occurring canine model of valvular insufficiency. Comp Med 2018; 68: 156-162.
[70] Ma L, Wang HB and Hashimoto K. The vagus nerve: an old but new player in brain-body communication. Brain Behav Immun 2024; 124: 28-39.
[71] Yata VK. Ex vivo and miniaturized in vitro models to study microbiota-gut-brain axis. 3 Biotech 2024; 14: 280.
[72] Chen W, Zheng X, Yan F, Xu L and Ye X. Modulation of gut microbial metabolism by cyanidin-3-O-glucoside in mitigating polystyrene-induced colonic inflammation: insights from 16S rRNA sequencing and metabolomics. J Agric Food Chem 2024; 72: 7140-7154.
[73] Seoane-Collazo P, Fernø J, Gonzalez F, Diéguez C, Leis R, Nogueiras R and López M. Hypothalamic-autonomic control of energy homeostasis. Endocrine 2015; 50: 276-291.
[74] Yousefi B, Babaeizad A, Banihashemian SZ, Feyzabadi ZK, Dadashpour M, Pahlevan D, Ghaffari H and Eslami M. Gastrointestinal tract, microbiota and Multiple Sclerosis (MS) and the link between gut microbiota and CNS. Curr Microbiol 2022; 80: 38.
[75] Azabou E, Bao G, Bounab R, Heming N and Annane D. Vagus nerve stimulation: a potential adjunct therapy for COVID-19. Front Med (Lausanne) 2021; 8: 625836.
[76] Sorboni SG, Moghaddam HS, Jafarzadeh-Esfehani R and Soleimanpour S. A comprehensive review on the role of the gut microbiome in human neurological disorders. Clin Microbiol Rev 2022; 35: e0033820.
[77] Wolter M, Grant ET, Boudaud M, Steimle A, Pereira GV, Martens EC and Desai MS. Leveraging diet to engineer the gut microbiome. Nat Rev Gastroenterol Hepatol 2021; 18: 885-902.
[78] Su J, Wang Y, Yan M, He Z, Zhou Y, Xu J, Li B, Xu W, Yu J, Chen S and Lv G. The beneficial effects of Polygonatum sibiricum Red. superfine powder on metabolic hypertensive rats via gut-derived LPS/TLR4 pathway inhibition. Phytomedicine 2022; 106: 154404.
[79] Huang G, Wang Z, Wu G, Zhang R, Dong L, Huang F, Zhang M and Su D. Lychee (Litchi chinensis Sonn.) pulp phenolics activate the short-chain fatty acid-free fatty acid receptor anti-inflammatory pathway by regulating microbiota and mitigate intestinal barrier damage in dextran sulfate sodium-induced colitis in mice. J Agric Food Chem 2021; 69: 3326-3339.
[80] Pan Y, Yang Y, Wu J, Zhou H and Yang C. Efficacy of probiotics, prebiotics, and synbiotics on liver enzymes, lipid profiles, and inflammation in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. BMC Gastroenterol 2024; 24: 283.
[81] Riva A, Rasoulimehrabani H, Cruz-Rubio JM, Schnorr SL, von Baeckmann C, Inan D, Nikolov G, Herbold CW, Hausmann B, Pjevac P, Schintlmeister A, Spittler A, Palatinszky M, Kadunic A, Hieger N, Del Favero G, von Bergen M, Jehmlich N, Watzka M, Lee KS, Wiesenbauer J, Khadem S, Viernstein H, Stocker R, Wagner M, Kaiser C, Richter A, Kleitz F and Berry D. Identification of inulin-responsive bacteria in the gut microbiota via multi-modal activity-based sorting. Nat Commun 2023; 14: 8210.
[82] Fernández-Lainez C, Aan de Stegge M, Silva-Lagos LA, López-Velázquez G and de Vos P. β(2 → 1)-β(2 → 6) branched graminan-type fructans and β(2 → 1) linear fructans impact mucus-related and endoplasmic reticulum stress-related genes in goblet cells and attenuate inflammatory responses in a fructan dependent fashion. Food Funct 2023; 14: 1338-1348.
[83] Karimi M, Shirsalimi N, Hashempour Z, Salehi Omran H, Sedighi E, Beigi F and Mortezazadeh M. Safety and efficacy of fecal microbiota transplantation (FMT) as a modern adjuvant therapy in various diseases and disorders: a comprehensive literature review. Front Immunol 2024; 15: 1439176.
[84] Peuget S, Zhou X and Selivanova G. Translating p53-based therapies for cancer into the clinic. Nat Rev Cancer 2024; 24: 192-215.
[85] Zhu J, Lyu J, Zhao R Liu G and Wang S. Gut macrobiotic and its metabolic pathways modulate cardiovascular disease. Front Microbiol 2023; 14: 1272479.
[86] Feng R, Yang W, Feng W, Huang X, Cen M, Peng G, Wu W, Wang Z, Jing Y, Long T, Liu Y, Li Z, Chang G and Huang K. Time-restricted feeding ameliorates non-alcoholic fatty liver disease through modulating hepatic nicotinamide metabolism via gut microbiota remodeling. Gut Microbes 2024; 16: 2390164.
[87] Zhang S, He H, Wang Y, Wang X and Liu X. Transcutaneous auricular vagus nerve stimulation as a potential novel treatment for polycystic ovary syndrome. Sci Rep 2023; 13: 7721.
[88] Kazankov K, Jørgensen SMD, Thomsen KL, Møller HJ, Vilstrup H, George J, Schuppan D and Grønbæk H. The role of macrophages in nonalcoholic fatty liver disease and nonalco-

holic steatohepatitis. Nat Rev Gastroenterol Hepatol 2019; 16: 145-159.
[89] Shaaban HH, Alzaim I, El-Mallah A, Aly RG, El-Yazbi AF and Wahid A. Metformin, pioglitazone, dapagliflozin and their combinations ameliorate manifestations associated with NAFLD in rats via anti-inflammatory, anti-fibrotic, anti-oxidant and anti-apoptotic mechanisms. Life Sci 2022; 308: 120956.
[90] Sun B, Zhang R, Liang Z, Fan A and Kang D. Hyperoside attenuates non-alcoholic fatty liver disease through targeting Nr4A1 in macrophages. Int Immunopharmacol 2021; 94: 107438.
[91] Roglans N, Laguna JC and Alegret M. Bempedoic acid for nonalcoholic fatty liver disease: evidence and mechanisms of action. Curr Opin Lipidol 2023; 34: 141-146.
[92] Yagi M, Morishita K, Ueno A, Nakamura H, Akabori H, Senda A, Kojima M, Aiboshi J, Costantini T, Coimbra R and Otomo Y. Electrical stimulation of the vagus nerve improves intestinal blood flow after trauma and hemorrhagic shock. Surgery 2020; 167: 638-645.
[93] Gutiérrez-Miranda B, Gallardo I, Melliou E, Cabero I, Álvarez Y, Hernández M, Magiatis P, Hernández M and Nieto ML. Treatment with the olive secoiridoid oleacein protects against the intestinal alterations associated with EAE. Int J Mol Sci 2023; 24: 4977.
[94] Tilg H, Adolph TE and Tacke F. Therapeutic modulation of the liver immune microenvironment. Hepatology 2023; 78: 1581-1601.
[95] Hilz MJ. Transcutaneous vagus nerve stimulation-a brief introduction and overview. Auton Neurosci 2022; 243: 103038.
[96] Poznyak AV, Orekhov NA, Churov AV, Starodubtseva IA, Beloyartsev DF, Kovyanova TI, Sukhorukov VN and Orekhov AN. Mitochondrial dysfunction in systemic lupus erythematosus: insights and therapeutic potential. Diseases 2024; 12: 226.
[97] Ali Q, Ma S, Farooq U, Niu J, Li F, Li D, Wang Z, Sun H, Cui Y and Shi Y. Pasture intake protects against commercial diet-induced lipopolysaccharide production facilitated by gut microbiota through activating intestinal alkaline phosphatase enzyme in meat geese. Front Immunol 2022; 13: 1041070.
[98] He X and Yuan D. A review regarding the article 'targeting inflammatory signaling pathways with SGLT2 inhibitors: insights into cardiovascular health and cardiac cell improvement'. Curr Probl Cardiol 2024; 49: 102563.
[99] Andraka JM, Graham E, Szczesny D, Marchalant Y and Sharma N. Impact of krill oil supplementation on neuroinflammation and spatial memory in aged rats. FASEB J 2022; 36 Suppl 1: R3568.
[100] Rodgers A, Salam A, Schutte AE, Cushman WC, de Silva HA, Di Tanna GL, Grobbee DE, Narkiewicz K, Ojji DB, Poulter NR, Schlaich MP, Oparil S, Spiering W, Williams B, Wright JT, Lakshman P, Uluwattage W, Hay P, Pereira T, Amarasena N, Ranasinghe G, Gianacas C, Shanthakumar M, Liu X, Wang N, Gnanenthiran SR and Whelton PK; GMRx2 Investigators. Efficacy and safety of a novel low-dose triple single-pill combination of telmisartan, amlodipine and indapamide, compared with dual combinations for treatment of hypertension: a randomised, double-blind, active-controlled, international clinical trial. Lancet 2024; 404: 1536-1546.
[101] Inoue T. Neuroimmune system-mediated renal protection mechanisms. Clin Exp Nephrol 2021; 25: 915-924.
[102] Koopman FA, van Maanen MA, Vervoordeldonk MJ and Tak PP. Balancing the autonomic nervous system to reduce inflammation in rheumatoid arthritis. J Intern Med 2017; 282: 64-75.
[103] Arribillaga L, Echeverria I, Belsue V, Gomez T, Lozano T, Casares N, Villanueva L, Domingos-Pereira S, Romero PJ, Nardelli-Haefliger D, Hervás-Stubbs S, Sarobe P, Rodriguez MJ, Carrascosa JL, Zürcher T and Lasarte JJ. Bivalent therapeutic vaccine against HPV16/18 genotypes consisting of a fusion protein between the extra domain A from human fibronectin and HPV16/18 E7 viral antigens. J Immunother Cancer 2020; 8: e000704.
[104] Torous J, Bucci S, Bell IH, Kessing LV, Faurholt-Jepsen M, Whelan P, Carvalho AF, Keshavan M, Linardon J and Firth J. The growing field of digital psychiatry: current evidence and the future of apps, social media, chatbots, and virtual reality. World Psychiatry 2021; 20: 318-335.