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Review article

Evidence for bidirectional gut-spleen crosstalk in rodent models: scoping review of possible mechanisms and therapeutic implications

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Abstract
Introduction: The gut-spleen axis has been proposed to link the gut environment with splenic immune regulation and systemic homeostasis. This scoping review examines this interaction in rodent models.
Methods: Following PRISMA-ScR guidelines, we analyzed literature (2015–2025) from PubMed, Scopus, and other major databases, including English-language rodent studies reporting gut and splenic outcomes.
Results: Analysis of 48 studies suggests that gut dysbiosis may alter splenic architecture and immune function mainly via microbial metabolites, particularly short-chain fatty acids. Limited evidence indicates that splenic dysfunction could impair gut barrier integrity. Systemic stressors (e.g., infection or allergy) may reinforce this bidirectional inflammatory loop. Microbiota-targeted therapies have been observed primarily through gut-initiated mechanisms. Vagus nerve-mediated signaling points to a gut-brain-spleen network, though its directional hierarchy remains unresolved.
Conclusion: Evidence supports a gut-spleen axis in rodents, with gut-derived microbial metabolites appearing to influence splenic immunity. Support for a reciprocal spleen-to-gut pathway remains limited and emergent, highlighting a research asymmetry. Together, these interactions suggest a partially bidirectional network linking the gut ecosystem to systemic immunity, with additional neural integration extending this framework toward a gut-brain-spleen axis. This integrative model proposes the gut-spleen axis as a potential therapeutic target warranting further investigation in inflammatory, metabolic, and neurological diseases.

Keywords: Gut dysbiosis; Gut-spleen axis; Microbial metabolites; Neuroimmunology; Splenic immunity

Highlights:
- Gut dysbiosis may impair the splenic structure and immune function in rodent models.
- Splenic disruption has been associated with compromised gut barrier integrity and microbiota.
- Systemic inflammation may converge on the gut-spleen immune axis.
- Microbial therapies have been shown to restore splenic health in rodent models via gut-first mechanisms.
- The gut-spleen axis represents a potential therapeutic target for further investigation in systemic diseases.

Introduction

The gut microbiota, a diverse microbial ecosystem within the gastrointestinal tract, plays a pivotal role in systemic immune homeostasis (Belkaid and Hand, 2014; Cryan et al., 2019; Scheithauer et al., 2020; Woldeamlak et al., 2019; Wu et al., 2020b). Emerging evidence positions the spleen, the body's largest secondary lymphoid organ, as a critical responder to gut-derived signals, with dysbiosis altering splenic immune cell populations (macrophages, natural killer (NK) cells, CD8$^+$ T cells) and altering its weight and structure (Fang et al., 2023; Liu et al., 2023a; Taitz et al., 2025; Tarantino and Citro, 2024; Wan et al., 2023; Wang et al., 2022). These changes correlate with elevated proinflammatory cytokines (tumor necrosis factor (TNF) α, interleukin (IL) 6) and oxidative stress, often triggered by gut barrier breach and lipopolysaccharide (LPS) translocation (Fang et al., 2023; Gomes et al., 2018; Moffa et al., 2019; Scheithauer et al., 2020; Shi et al., 2022; Tarantino and Citro, 2024; Wang et al., 2022; Wei et al., 2021; Woldeamlak et al., 2019). Conversely, splenic dysfunction (e.g., splenectomy, infection) induces gut microbial shifts, reduces diversity, increases pathogenic metabolites, and exacerbates systemic inflammation (Carsetti et al., 2020; Han et al., 2021; Wei et al.,

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2021; Wen et al., 2022). This reciprocal relationship suggests a tightly integrated gut-spleen axis, though the mechanistic underpinnings remain unresolved.

Central to this crosstalk are the gut microbes, their metabolites, immune cells, and cytokine signaling (Chen et al., 2021; Moffa et al., 2019; Wen et al., 2022; Ye et al., 2025). The gut microbes produce short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetic acid (Fusco et al., 2023; Liu et al., 2023b). The concentration of total SCFAs is approximately 1.5- to 3-fold higher in the proximal colon than in the distal colon, with molar ratio of butyrate, propionate, and acetic acid of 1:1:3 (Fu et al., 2025; Jiang et al., 2022; Liu et al., 2023b). SCFAs maintain gut barrier integrity through multiple mechanisms, including promoting the assembly of epithelial tight junction proteins [occludin, claudin, zonula occludens-1 (ZO-1)] (Fu et al., 2025; Jiang et al., 2022), stimulating the secretion of the goblet cell-specific mucin 2 (MUC2) (Jiang et al., 2022), and regulating gut immunity by modulating pro-inflammatory responses via nuclear factor-kappa B (NF-κB) signaling pathway (Liu et al., 2023b). Concurrently, splenic immune cells regulate gut microbiota composition mainly through splenic B cells, contributing to systemic IgA production via cytokine-mediated crosstalk (Carsetti et al., 2020; Lewis et al., 2019; Rosado et al., 2018; Wei et al., 2021). Therapeutic interventions, notably probiotics and fecal microbiota transplantation (FMT), demonstrate this bidirectional link by simultaneously restoring gut microbiota and splenic function in rodent models (Fang et al., 2023; Hu et al., 2023; Liu et al., 2024; Peng et al., 2014; Song et al., 2024; Tarantino and Citro, 2024; Wen et al., 2022; Ye et al., 2025; Zeng et al., 2023), yet human translation lags due to unresolved questions about tissue-specific targeting.

This scoping review aimed to assess evidence for bidirectional gut-spleen axis crosstalk in rodent models by systematically extracting gut and splenic metrics; identify plausible mechanistic pathways (immune, microbial, neural) underlying these interactions; and highlight knowledge gaps to prioritize adjuvant therapy development for other diseases where gut-spleen interactions may be pivotal but remain underexplored in human translation.

Materials and methods

Literature searches were conducted in PubMed, SCOPUS, ScienceDirect, ProQuest, Google Scholar, and Springer Nature (2015–2025) using predefined keywords, with Boolean operators (AND/OR) linking terms related to gut microbiota, spleen, and rodent models. Filters were applied to include only English-language, freely accessible full-text articles (Table 1).

Inclusion criteria comprised: primary studies in English, rodent models, and mentioned both gut and splenic outcomes. Exclusion criteria was *in vitro* studies.

Eligible articles were collected and managed in the reference management software Zotero. The screening process followed the PRISMA Scoping Review framework: the initial screening was conducted by a single reviewer, subsequently full-text review and synthesis were performed by two reviewers. Data extraction captured study design (e.g., reference, interventions) and gut/spleen metrics. Findings were thematically organized by intervention effects on gut or spleen outcomes and summarized in tables.

Results

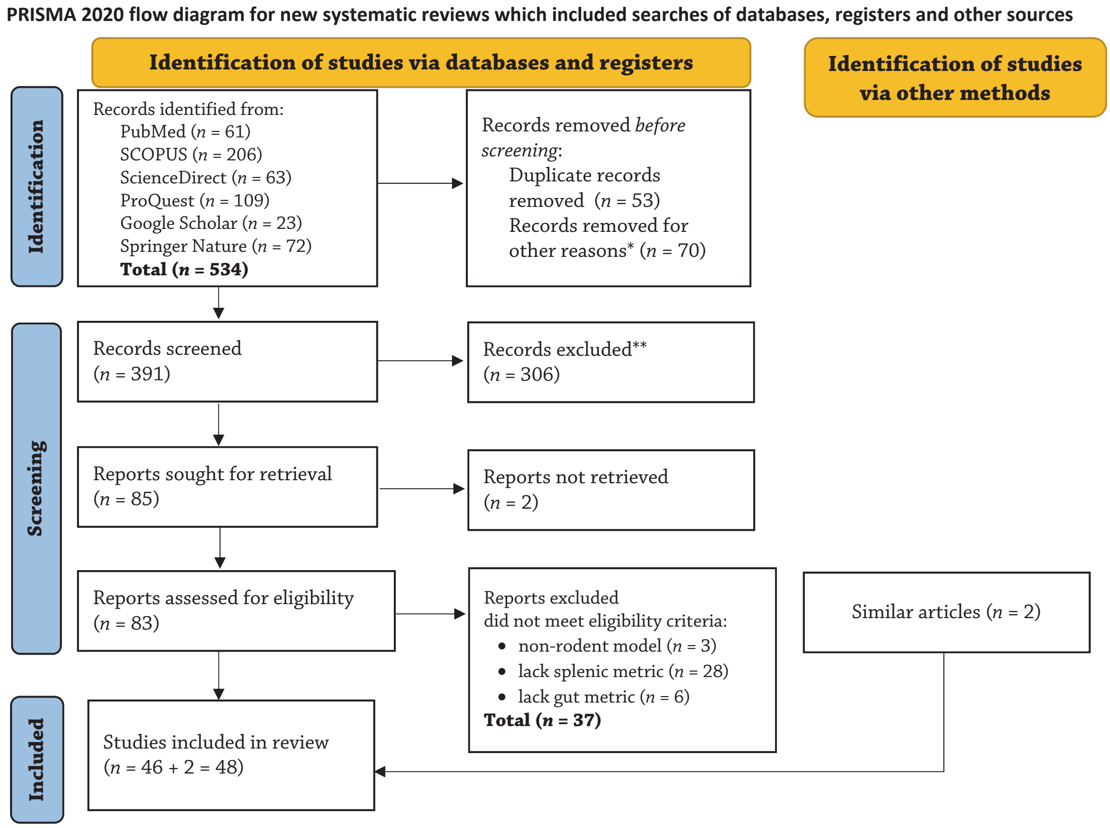
The initial database search identified a total of 534 articles: PubMed (*n* = 61), Scopus (*n* = 206), ScienceDirect (*n* = 63), ProQuest (*n* = 109), Google Scholar (*n* = 23), and Springer Nature (*n* = 72) (Table 1). After removing 53 duplicates and 90 non-primary records (e.g., reviews, conference abstracts), 391 articles underwent title/abstract screening, excluding 306 irrelevant studies. Eighty-five articles proceeded to full-text review, with 83 retrievable via Zotero.

Forty-six studies met all eligibility criteria; two additional relevant articles were manually included, yielding a final dataset of 48 studies (Fig. 1). Data extraction captured: study design (rodent species, publication year); interventions (antibiotics, toxic substances, allergen injections, splenectomy, etc.); outcomes (gut: microbial shifts, structural/immune changes,

Table 1. The database, Boolean operators and additional filters, and the number of articles found in each database

Database	Boolean operators and additional filters	Number of articles
PubMed	(“gut microbiota” OR “gut dysbiosis” OR “FMT” OR “Probiotic administration” OR “Antibiotic administration”) AND (“spleen” OR “splenectomy” OR “Spleen histology” OR “Spleen structure” OR “infection” OR “vaccination”) AND (“rat model” OR “mice model”), English, Free full text, Full text	61
SCOPUS	(“gut microbiota” OR “gut dysbiosis” OR “probiotic administration” OR “antibiotic administration”) AND (“spleen” OR “splenectomy” OR “infection” OR “vaccination”) AND (“rat model” OR “mice model”), year 2020–2025, Limited to “Medicine, Immunology, and Microbiology”; Limited to “Article”, “Final Article”, “Animal Model”, Limited to “English”, “Open Access”	206
ScienceDirect	(“gut microbiota” OR “gut dysbiosis”) AND (“spleen” OR “splenectomy”) AND (“rat model” OR “mice”), title & abstract, Research Article, Open Access & Open Archive	63
ProQuest	summary (“gut microbiota” OR “gut dysbiosis”) AND summary (“spleen” OR “splenectomy”) AND summary (“rat model” OR “mice”), English, Scholarly Journals, Article	109
Google Scholar	(“gut microbiota” OR “gut dysbiosis”) AND (“spleen” OR “splenectomy”) AND (“rat model” OR “mice”), year 2020–2025; in the title; with all the words “Spleen”, exact Phrase “Gut microbiota”, without ‘spleen deficiency’	23
Springer Nature	(“gut microbiota” OR “gut dysbiosis” OR “Probiotic administration” OR “FMT” OR “antibiotic administration”) AND (“spleen” OR “splenectomy” OR “infection” OR “vaccination”) AND (“rat model” OR “mice model”), Article, English, Open Access, Biomedicine, Microbiota, Dysbiosis, Nutrition	72

SCFAs, serum markers; spleen: structural/immune changes, cell signaling, oxidative stress markers, serum conditions); and systemic effects (where reported). Key findings were grouped by intervention theme (Table 2) and further analyzed in the discussion.



* Non-primary research articles: reviews, symposium abstracts, letters to editors, etc.

** The title and abstract were not aligned with the eligibility criteria.

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Fig. 1. Prisma-ScR flow diagram

Discussion

Gut microbiota disruption by antibiotics and toxin exposures impairs splenic structure and immune function

The gut microbiota is essential for immune development and maturation, shaping both innate and adaptive responses through its influence on secondary lymphoid organs, including the spleen (Belkaid and Hand, 2014; Hu et al., 2016; Rosado et al., 2018; Taitz et al., 2025). Disruption of microbial homeostasis by antibiotics or environmental toxins (Table 2a, b) has been reported to be associated with structural and functional alterations in the spleen in rodent models.

Early-life antibiotic exposure has been shown to markedly reduce microbial diversity (Suppl. Table S1a, b), depleting beneficial taxa such as *Lactobacillus*, and enriching potentially harmful bacteria. This imbalance compromises gut barrier integrity and has been correlated with impaired splenic development, including delayed follicular organization and reduced recruitment of follicular dendritic cells (FDCs), which may ultimately weaken immune competence (Hu et al., 2016; Luo et al., 2025; Rosado et al., 2018; Taitz et al., 2025). Antibiotic-induced dysbiosis (Suppl. Table S1c) has also been observed to reshape splenic immune populations, reducing dendritic cell subsets and spleen weight, possibly through Toll-like receptor (TLR) – mediated disruption of hematopoiesis (Taitz et al., 2025; Wan et al., 2023).

The gut-spleen axis (Fig. 2) is proposed to be largely mediated by gut microbiota and its metabolites, particularly SCFAs, based on rodent studies (Taitz et al., 2025; Wan et al., 2023; Wang et al., 2022). Gut microbiota have been reported to regulate mucosal immunity through dendritic cell (DC) antigen presentation (Moffa et al., 2019; Ye et al., 2025), modulation of the NF-κB pathway (Liu et al., 2023b), and maintenance of the Treg/Th17 balance (Koh et al., 2016; Liu et al., 2023a; Wen et al., 2022). SCFAs have been observed to enhance epithelial barrier integrity by promoting tight junction assembly (Fu et al., 2025; Fusco et al., 2023; Korsten et al., 2023), and strengthening the mucus layer via upregulation of mucin-2 expression (Fusco et al., 2023; Jiang et al., 2022; Liu et al., 2023b; Peng et al., 2009). Among them, butyrate has been shown to exert potent anti-inflammatory effects by inhibiting NF-κB activation (Fusco et al., 2023; Liu et al., 2023b), promoting Treg differentiation (Yao et al., 2022), and suppressing Th17 responses (Liu et al., 2023a; Yao et al., 2022), which may contribute to stabilizing gut-immune homeostasis.

Table 2. Summary of reported findings on the gut–spleen axis: proposed crosstalk mechanisms and disruptions in rodent models

	Disruption type	Experimental model / Agent	Reported gut alteration	Reported spleen alteration	Proposed mediating mechanism	Proposed translational relevance and limitation	Key references
Gut to spleen axis models							
a	Antibiotic exposure	Neonatal antibiotics or Broad spectrum antibiotics	↓ *Lactobacillus*, ↓ diversity, ↑ gut permeability, ↓ crypt depth	↓ FDC, ↓ follicular development, ↓ spleen weight, ↓ DC	Dysbiosis → TLR-mediated hematopoiesis disruption	Mimics early-life dysbiosis in humans; relevant to pediatric immune development. Limitation: Microbiota composition differs between species.	Hu et al., 2016; Rosado et al., 2018; Taitz et al., 2025; Wan et al., 2022
b	Toxin exposure	DSS (acute and chronic colitis), Lead, Organophosphates	Activation of NLRP3 inflammasome, ↑ gut permeability, dysbiosis, ↑ LPS (serum)	↑ spleen size, M2 macrophage skewing, ↑ Th2, ↓ Tregs, ↑ NF-κB activation	Harmful bacterial translocation + SCFAs imbalance + GSH depletion → splenic inflammation	Models gut–immune disruption due to environmental exposure.	Abou Diwan et al., 2024; Liu et al., 2020, 2021; Wu et al., 2024; Ye et al., 2025; Zhang et al., 2023a
Spleen to gut axis models							
c	Complete splenic disruption	Splenectomy, cyclophosphamide	↓ IgA, ↑ Proteobacteria, ↓ gut mucin barrier, ↑ gut permeability	↓ spleen size, ↓ immune regulation, ↑ LPS	↓ Tregs, ↓ IgA plasma cells → disrupt gut homeostasis + ↓ goblet cell + ↑ gut permeability	Relevant to asplenia or immunosuppression in cancer therapy. Limitation: Total splenectomy is rare in human cases.	Khan et al., 2022; Li et al., 2024a; Shen et al., 2025; Song et al., 2024; Wei et al., 2021; Yan et al., 2024; Zeng et al., 2023
d	Neural disruption	Splenic denervation	↑ gut permeability, ↑ Th1/Th2 ratio	↓ CAP signaling, ↑ inflammation	Sympathetic-vagal disruption	Models autonomic dysfunction relevant to stress and neuroimmune diseases. Technical challenges in replicating precise human innervation patterns.	Jiang et al., 2025
Systemic immune disruption models							
e	Systemic inflammation	LPS (serum), trauma, infection	Dysbiosis, ↑ gut permeability	↑ macrophage/ NK cells, ↑ cytokines (TNF-α, IL-6), variable spleen size	↑ pro inflammatory cytokines, Th17/Treg shift → ↑ gut permeability	Models sepsis and critical illness. LPS is a strong inflammatory trigger, but not representative of all systemic inflammation causes.	Han et al., 2021; Hu et al., 2023; Shen et al., 2022; Thim-Uam et al., 2022; Wen et al., 2022
f	Cancer / Autoimmunity	Tumor models, *Myasthenia gravis*	↓ *Lactobacillus*, ↓ SCFAs, ↓ energy-metabolizing bacteria	Tumor: Treg suppress CD8+ T cells and DC; Autoimmunity: ↑ autoantibodies, ↓ IgA	Immune exhaustion, altered metabolism → ↓ SIgA, ↓ SCFAs + impaired mucosal immunity	Reflects tumor-induced immune suppression and autoimmune mucosal dysfunction. Disease heterogeneity in humans limits direct extrapolation.	Fu et al., 2024; Li et al, 2022; Sun et al., 2023; Wang et al., 2023
g	Allergy models	Ovalbumin, β-Lg allergen	↓ SCFAs, ↓ sIgA	↑ spleen size, ↑ IgE, Th2 skewing	Th2 inflammation, impaired mucosal immunity	Represents food allergy–induced gut–immune changes. Limited to specific allergens and acute reactions	Li et al., 2024c; Liu et al., 2024; Luo et al., 2025

Table 2. ***(continued)***

	Disruption type	Experimental model / Agent	Reported gut alteration	Reported spleen alteration	Proposed mediating mechanism	Proposed translational relevance and limitation	Key references
Gut-first restorative therapy							
h	Microbial restorative therapy	Probiotics, FMT, Prebiotic, Postbiotic, Synbiotics (oral)	Restored gut permeability, restored SCFAs, restored sIgA	Correction of Th1/Th2 imbalance, restored Tregs, restored NK cells, restored DC	Gut-first repair via metabolites and immune signals	Strong translational value in inflammatory, metabolic, and infectious diseases. Strain specificity and host variability remain challenges.	Fang et al., 2023; Han et al, 2021; Li et al., 2024b; Liu et al., 2024; Ning et al., 2024; Wen et al., 2022; Song et al., 2024; Sun et al., 2023; Yan et al., 2024; Ye et al., 2025; Zeng et al., 2023

Note: Lowercase letters in the first column serve as row identifiers for cross-referencing in the text

Legend:
↑ = increased; ↓ = decreased; → = inducing
CAP = Cholinergic Anti-inflammatory Pathway
Ig = Immunoglobulin
DC = Dendritic Cells
DSS = Dextran Sodium Sulfate
FDC = Follicular Dendritic Cells
FMT = Fecal Microbiota Transplantation
GSH = Glutathione
LPS = Lipopolysaccharide
NK = Natural Killer
SCFAs = Short-Chain Fatty Acids
sIgA = secretory Immunoglobulin A
Th = T Helper Lymphocytes
TLR = Toll-Like Receptor

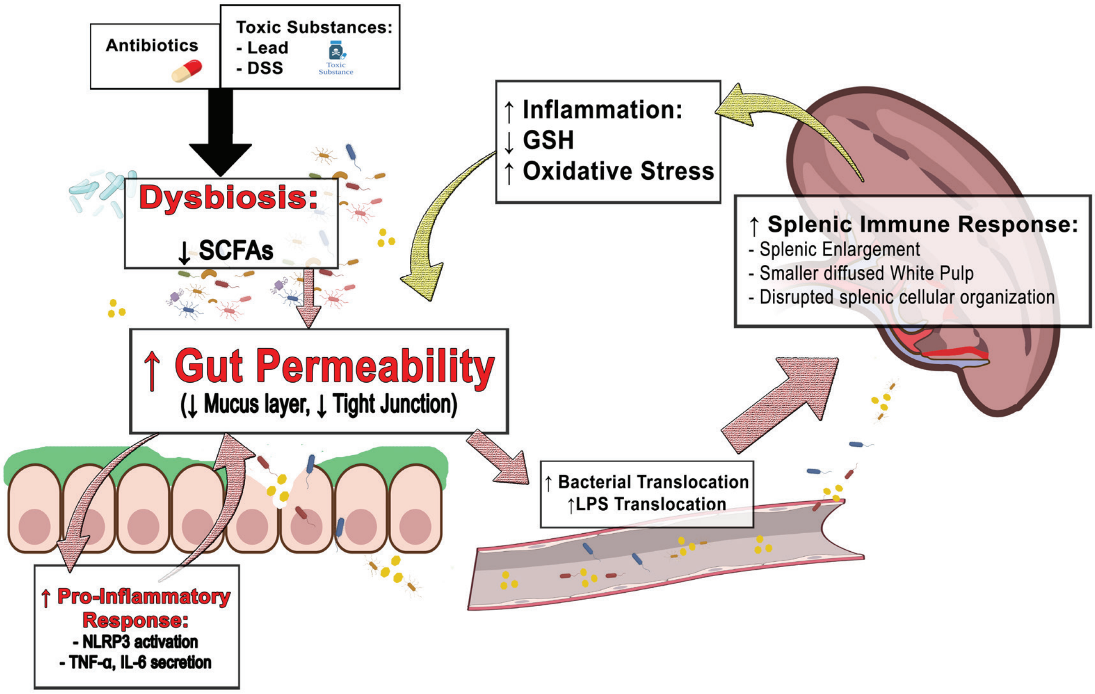

Fig. 2. Proposed mechanisms by which antibiotics and toxic substances ingestion may disrupt gut microbial ecology and barrier function in rodent models, potentially skewing local immune responses, facilitating bacterial and LPS translocation, and contributing to systemic inflammation that could influence splenic structure. Black arrow – reported causal relationship; Red textured arrow – hypothetical gut-to-spleen axis; Yellow textured arrow – hypothetical spleen-to-gut reaction. DSS – Dextran Sodium Sulfate; SCFAs – Short-Chain Fatty Acids; GSH – Glutathione; LPS – Lipopolysaccharide; TNF-α – Tumor Necrosis Factor α, IL-6 – Interleukin 6

Based on rodent studies, disruption of gut microbiota by antibiotic and toxic substances may impair the splenic structure through several possible mechanisms. Antibiotic-induced gut microbial dysbiosis (Hu et al., 2016; Liu et al., 2023a; Wan et al., 2022) has been reported to reduce SCFAs production, particularly butyrate (Liu et al., 2023a), and may impair intestinal barrier integrity through depletion of tight junction proteins (e.g., occludin, ZO-1) (Hu et al., 2016) and disruption of mucin secretion (Rosado et al., 2018). Toxic exposures, such as lead (Wu et al., 2024), organophosphates (Abou Diwan et al., 2024), and other industrial lipophilic compounds (Zhang et al., 2023a) have been observed to disrupt microbial homeostasis (Abou Diwan et al., 2024; Wu et al., 2024), damage intestinal villi (Zhang et al., 2023a), and weaken the epithelial barrier (Abou Diwan et al., 2024; Zhang et al., 2023a), which may further aggravate gut permeability (Suppl. Table S1d–g). This barrier dysfunction is suggested to facilitate the systemic dissemination of lipopolysaccharide (LPS) and bacteria to the spleen via the bloodstream (Abou Diwan et al., 2024) and may drive pathological immune polarization (Liu et al., 2023a; Taitz et al., 2025; Wan et al., 2022; Wu et al., 2024; Zhang et al., 2023a). Once in circulation, these harmful agents may reach lymphoid organs and alter immune cell function, potentially increasing pro-inflammatory cytokines such as IL-6 and TNF-α (Wu et al., 2024). Sustained tissue injury and excessive immune activation could disturb splenic architecture and may contribute to splenomegaly (Wu et al., 2024; Zhang et al., 2023a).

Similarly, dextran sodium sulfate (DSS), widely used to induce inflammatory bowel disease (IBD) in animal models, has been reported to cause gut structural alteration through several proposed mechanisms including gut dysbiosis (Liu et al., 2020, 2021; Ye et al., 2025), goblet cell-mediated mucin depletion (Chen et al., 2016; Liu et al., 2020), epithelial injury (Chen et al., 2016; Liu et al., 2020), and decreased tight junction protein (Ye et al., 2025). The resulting barrier breakdown may induce gut inflammation (Liu et al., 2020, 2021) through infiltration of luminal bacteria and antigens to the mucosa, which has been suggested to activate the NLRP3 inflammasome through Toll-like receptor (TLR) signaling (Liu et al., 2021), recruitment of neutrophils and macrophages (Liu et al., 2020), and disruption the Treg/Th17 balance (Liu et al., 2020). Persistent inflammation might further increase intestinal permeability, potentially enhances bacterial translocation to the spleen, and amplifies oxidative stress (Ye et al., 2025). This gut-spleen axis dysfunction has been reported to be linked to toxin-induced glutathione (GSH) depletion, which may intensify inflammatory processes in both organs (Ye et al., 2025).

Despite these insights, important translational gaps remain. Human microbiota diversity is shaped by genetics, diet, and xenobiotic exposures; factors that are poorly replicated in laboratory animals due to standardized housing and controlled environments (Candon et al., 2015; Woldeamlak et al., 2019). Although variability in diet, housing, and vendor-specific microbiota can influence outcomes across laboratories, animal microbiota diversity remains far more limited and cannot fully capture the complexity of the human gut ecosystem. Additional limitations include the scarcity of mechanistic studies linking gut microbial changes to splenic histopathology and the lack of longitudinal data on post-exposure recovery. Furthermore, this scoping review is constrained by its methodological parameters, including the restriction to English-language and freely accessible full-text articles, and database-specific restrictions, which may have limited the breadth of included studies and preclude strong causal claims. Given the spleen role as a systemic immune sensor, future studies should clarify how translocated harmful bacteria interact with splenocytes and immune cells, and how gut-derived signals (e.g., SCFAs, LPS) modulate splenic function in health and disease (Fukui et al., 2014; Lewis et al., 2019).

Splenic immune disruption compromises gut barrier integrity, microbial homeostasis, and eventually leads to gut dysbiosis

Although less extensively studied than the gut-to-spleen axis, emerging evidence from rodent studies suggests that splenic immune disruption may reciprocally impair gut integrity and contribute to dysbiosis. Complete splenic dysfunction, through splenectomy or immunosuppressive treatment with cyclophosphamide (Table 2c), has been reported to be associated with microbial imbalance (Khan et al., 2022; Thim-Uam et al., 2022; Wei et al., 2021; Zeng et al., 2023), decreased production of SCFAs (Wei et al., 2021), gut structural damage (Yan et al., 2024; Zeng et al., 2023), lower goblet cells numbers (Zeng et al., 2023), and decreased tight junction proteins (Song et al., 2024). A proposed mechanism (Fig. 3) is that splenectomy may weaken IgA-mediated mucosal defense (Carsetti et al., 2020; Suppl. Table S2a), potentially permitting the expansion of pathogenic Proteobacteria such as *E. coli* and reducing overall microbial diversity (Carsetti et al., 2020; Thim-Uam et al., 2022; Wei et al., 2021). Similarly, cyclophosphamide has been observed to induce splenic atrophy (Chen et al., 2021; Li et al., 2024a; Liu et al., 2023c; Yan et al., 2024; Zeng et al., 2023) and deplete immune populations essential for gut homeostasis, including Tregs and IgA$^+$ plasma cells (Khan et al., 2022; Shen et al., 2025, Suppl. Table S2d, e).

In contrast, research that created partial splenic alterations, such as splenic denervation (Jiang et al., 2025) or B cell–specific TLR9 knockout (Yang et al., 2024), has been reported to produce limited gut effects, suggesting the spleen non-redundant role in systemic immune regulation in rodent models (Suppl. Table S2b, c). Notably, the spleen-to-gut axis may involve neural mechanisms distinct from direct microbial crosstalk. The splenic nerve, a sympathetic branch from the celiac ganglia, has been suggested to regulate immune activity via noradrenergic signaling to splenic T cells, B cells, and dendritic cells (Jiang et al., 2025; Murray et al., 2017). It has been reported that disruption of this pathway impairs the vagal-cholinergic anti-inflammatory pathway (CAP), potentially increasing intestinal permeability and skewing Th1/Th2 balance; effects similarly observed after vagotomy or splenectomy (Jiang et al., 2025). These findings suggest that splenic neural signaling helps preserve gut barrier integrity by restraining systemic inflammation, although the precise interactions with gut microbiota remain to be clarified.

Collectively, these findings infer that spleen-derived immune and neural signals may cooperatively maintain microbial stability and gut barrier function, with IgA secretion and CAP pathway emerging as potential key mediators based on rodent studies. Nevertheless, important translational gaps remain. Rodent spleens differ structurally from human spleens, particularly in marginal zone B cell organization (Lewis et al., 2019), and post-splenectomy alterations in microbial metabolites, such as SCFAs, are still incompletely characterized (Wei et al., 2022). Furthermore, the methodological constraints of this scoping review mean that these findings should be interpreted as hypothesis-generating rather than definitive.

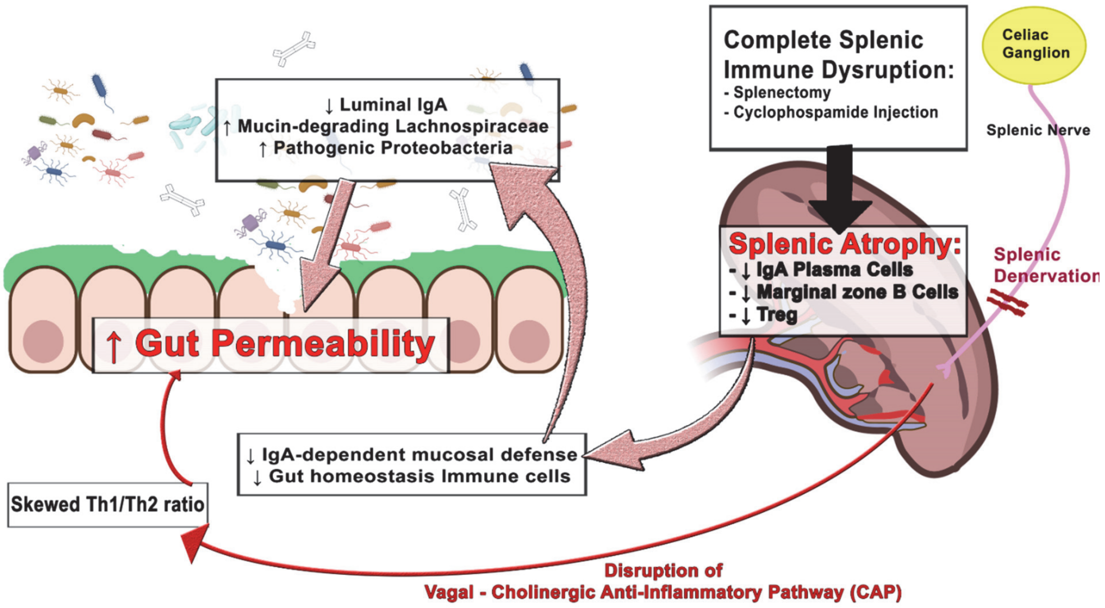

Fig. 3. Proposed mechanisms by which complete splenic immune dysfunction (e.g., via splenectomy or cyclophosphamide injection) may deplete IgA$^+$ plasma cells and marginal zone B cells in rodent models, potentially impairing gut mucosal defenses and contributing to pathogenic microbial expansion. Additionally, splenic denervation has been reported to implicate neural modulation through the vagal-cholinergic anti-inflammatory pathway (CAP), which could skew Th1/Th2 ratios and further influence gut permeability. Black arrow – reported causal relationship; Red textured arrow – hypothetical spleen-to-gut axis; IgA – Immunoglobulin A; Treg – T regulatory lymphocyte Th1 – T helper 1 lymphocyte; Th2 – T helper 2 lymphocyte

Systemic disruptions converge on immune centric gut-spleen axis dysregulation

The reviewed studies from rodent models suggest that acute systemic inflammation (Table 2e), triggered by infection (e.g., LPS, *Pseudomonas aeruginosa*; Suppl. Table S3a–f) or trauma (Suppl. Table S3j), has been consistently associated with innate immune activation in the spleen and gut (Han et al., 2021; Shen et al., 2022). LPS-induced inflammation has been reported to activate macrophages, DC, and NK cells, leading to the release of cytokines such as IFN-γ, TNF-α, IL-1β, IL-6, and IL-10 (Han et al., 2021; Shen et al., 2022; Wen et al., 2022). These cytokines may skew the Th17/Treg balance toward a pro-inflammatory phenotype, particularly in the spleen (Shen et al., 2022; Wen et al., 2022). At the same time, it has been reported that systemic inflammation may create gut dysbiosis (Han et al., 2021; Ma et al., 2022; Shen et al., 2022; Wen et al., 2022) and intestinal injury (Hu et al., 2023), and may alter SCFAs levels (Ma et al., 2022). Several studies have suggested that neural regulation may contribute to this axis, as vagus nerve dysfunction following traumatic brain injury has been observed to alter gut microbiota through disruption of the enteric neural network (Hu et al., 2023; Zhang et al., 2021).

Across models with distinct etiologies, convergent alterations in mucosal and splenic immune pathways have been observed, particularly involving dysregulated immunoglobulin responses to gut microbes and their metabolites. In cancer models (Table 2f; Suppl. Table S3g–i), the spleen paradoxically exhibits atrophy (Wang et al., 2023) despite heightened innate immune activity (Fu et al., 2024). Although splenic shrinkage may reflect cachexia, altered hematopoiesis, or metabolic stress, the reviewed studies have highlighted tumor-associated immune dysregulation, especially Treg-mediated suppression of CD8$^+$ T cells and dendritic cells (Fu et al., 2024), potentially further compounded by oxidative stress (Wang et al., 2023) and disrupted immunoglobulin secretion (Fu et al., 2024; Li et al., 2022). In contrast, autoimmune myasthenia gravis models (Suppl. Table S4e) have demonstrated antigen trafficking from the intestinal mucosa into systemic circulation, where it may stimulate splenic immune cells, particularly plasma B cells, to produce antigen-specific antibodies (Sun et al., 2023). Similar to autoimmune models, in allergic models (e.g., cow's milk β-lactoglobulin or ovalbumin; Table 2g), antigens were initially confined to the mesenteric lymph nodes and Peyer's patches (Weiberg et al., 2018). These antigens have been proposed to induce a Th1/Th2 imbalance in the gut (Liu et al., 2024) before entering the systemic circulation and potentially stimulating splenic plasma B cells, thereby contributing to increased IgE production (Li et al., 2024c; Liu et al., 2024; Weiberg et al., 2018). Sustained antibody secretion by splenic plasma cells may contribute to splenic enlargement (Liu et al., 2024) and systemic inflammation (Sun et al., 2023; Weiberg et al., 2018). This immune activation has been correlated with disruption of gut microbial composition (Li et al., 2024c; Liu et al., 2024; Sun et al., 2023), reduction of energy-metabolizing bacteria such as *Lactobacillus hominis* (Sun et al., 2023), and decreased SCFAs levels, particularly butyrate (Fu et al., 2024; Li et al., 2024c; Sun et al., 2023), which may further destabilize gut-immune homeostasis (Fu et al., 2024; Li et al., 2022; Wang et al., 2023).

From these studies it can be inferred that, during systemic disruption, three convergent mechanisms may drive immune-centric gut-spleen axis dysregulation in rodent models. First, non-specific antigens that primarily activate innate immunity, such as LPS, may stimulate splenic macrophages and promote the release of pro-inflammatory cytokines including TNF-α and IL-6 (Han et al., 2021; Shen et al., 2022; Wen et al., 2022). These mediators may impair intestinal tight junctions (Hu et al., 2023), increase gut permeability (Hu et al., 2023), and potentially facilitate bacterial translocation, thereby contributing to systemic inflammation (Han et al., 2021). Second, highly specific antigens that engage adaptive immunity, such as autoantigens or allergens, may reshape gut immunoglobulin responses (Li et al., 2024c; Liu et al., 2024; Weiberg et al., 2018) and alter SCFAs production through microbiota shifts (Huang et al., 2021; Li et al., 2024c; Liu et al., 2024; Sun et al., 2023). These adaptive immune alterations may further destabilize the gut–immune homeostasis (Fu et al., 2024; Li et al., 2022; Wang et al., 2023). Third, neural modulation via the vagus nerve may functionally link gut dysbiosis to splenic inflammation, particularly in conditions such as sepsis or trauma (Hu et al., 2023; Zhang et al., 2021). Together, this immune-centric framework (Fig. 4) highlights cytokine crosstalk and neuroimmune signaling as potential primary drivers of gut-spleen interactions, rather than direct microbial effects alone. However, important translational gaps remain. Most rodent studies rely on acute, high-dose exposures that do not accurately model chronic, low-grade inflammation in humans (Fu et al., 2024; Shen et al., 2022). In addition, vagal–splenic interactions in humans remain insufficiently characterized (Zhang et al., 2021).

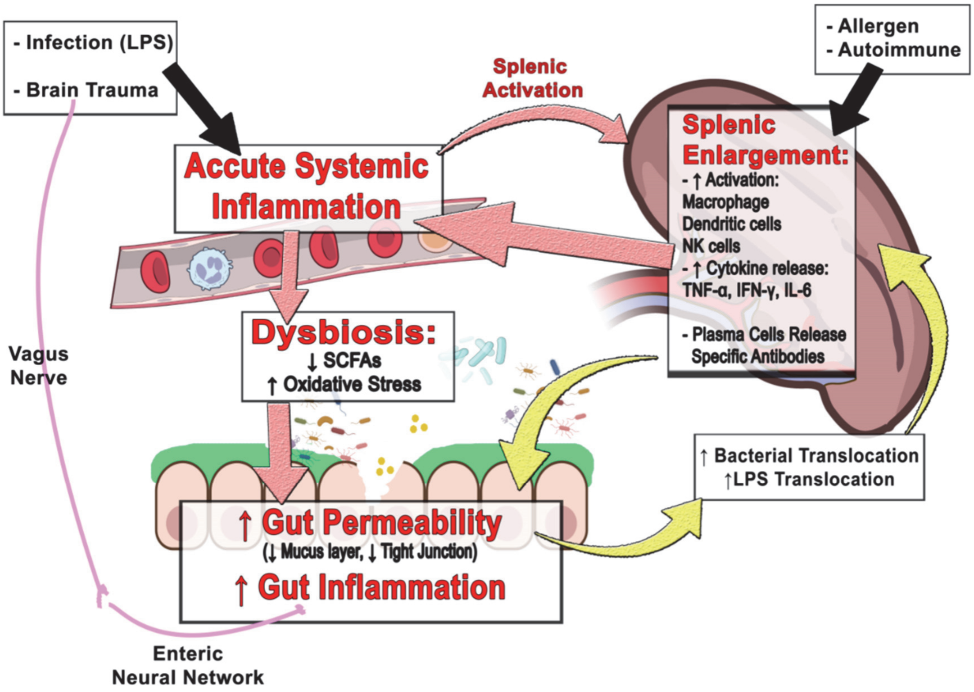

Fig. 4. Proposed mechanisms by which systemic stressors that induce acute inflammation may concurrently activate splenic immunity and gut inflammation in rodent models, potentially disrupting barrier function and contributing to dysbiosis, which could exacerbate oxidative stress and help sustain systemic inflammation. Brain trauma has been reported to imply neural involvement via vagus-enteric neural networks. Black arrow – reported causal relationship; Red textured arrow – hypothetical pathways involving non-specific antigens that primarily activate innate immunity; Yellow textured arrow – hypothetical pathways involving highly specific antigens that engage adaptive immunity; Pink line – hypothetical vagus nerve-mediated connectivity between brain, gut, and spleen. NK – Natural Killer; SCFAs – Short-Chain Fatty Acids; TNF-α – Tumor Necrosis Factor; IFN-γ – Interferon Gamma; IL6 – Interleukin 6; LPS – Lipopolysaccharide

Methodological limitations further restrict clinical interpretation. Despite the use of advanced 16S rRNA Next-Generation Sequencing (16SNGS) methods (Han et al., 2021; Li et al., 2024c; Shen et al., 2022; Wen et al., 2022), current evidence does not demonstrate that low-abundance bacteria directly exert a dominant effect on the spleen, due to the constraints of 16S amplicon profiling (e.g., sequencing depth, primer bias, chimera filtering) (Muhamad Rizal et al., 2020; Poretsky et al., 2014). However, several studies have reported that rare gut microbiota members can be highly immunogenic, potentially influencing antigen presentation pathways (e.g., MHC class II) and T-cell responses, and may exert disproportionate effects on microbial communities and host immunity (Hajishengallis et al., 2012; Han et al., 2022a). This suggests that, even numerically, minor taxa could indirectly influence splenic immune activity, though direct causal evidence remains limited. These gaps are particularly relevant given divergent outcomes across disease models. In cancer, spleen atrophy arises through multifactorial mechanisms and cannot be attributed solely to Treg-mediated CD8$^+$ T cell suppression (Fu et al., 2024). In contrast, autoimmune myasthenia gravis has been associated with splenomegaly driven by elevated autoantibody production (Sun et al., 2023). Even targeted gene knockouts (Suppl. Table S4f–h) often produce minimal microbiota alterations unless accompanied by robust neutrophil recruitment (Huang et al., 2021; Kuhbandner et al., 2019; Patel et al., 2023), suggesting the dominant role of immune activation over isolated molecular defects in shaping gut–spleen axis pathology. As noted previously, the methodological constraints of this scoping review mean that these observations should be considered hypothesis-generating and require confirmation in future studies with more comprehensive designs.

Microbial therapies restore spleen health through gut-initiated mechanisms

The therapeutic potential of microbial interventions has been documented in rodent models (Table 2h). Oral administration of probiotics (Suppl. Table S5a–f), fecal microbiota transplantation (FMT; Suppl. Table S5g–i), prebiotics (Suppl. Table S5j), postbiotics (Suppl. Table S5k–m), and synbiotics (Suppl. Table S5n) has been shown to promote restoration of gut-spleen axis dysfunction in these models.

These approaches universally follow a gut-initiated reparative sequence: probiotics like *Lactobacillus plantarum* are reported to enhance intestinal barrier function through mucus layer thickening (Maldonado Galdeano et al., 2019) and tight junction reinforcement (Maldonado Galdeano et al., 2019; Zeng et al., 2023). Meanwhile, microbial metabolites such as butyrate may contribute to inhibiting gut NLRP3 inflammasome (Liu et al., 2021), and have been associated with promoting splenic Treg differentiation and NK cell activity (Sun et al., 2023). This gut-centric focus is further evidenced by synbiotics elevating both intestinal IgA and splenic TNF-α levels when given orally, without evidence of direct splenic targeting (Ning et al., 2024).

This research infers that the mechanisms underlying these therapeutic effects may converge on three pathways. First, immunomodulation via dendritic cell maturation and TGF-β signaling, exemplified by *L. murinus* correction of Th1/Th2 imbalances in food allergy models (Liu et al., 2024). Second, metabolic reprogramming through SCFAs production, where inulin prebiotics have been observed to suppress splenic Th17 cells via microbiota-dependent pathways (Li et al., 2024a). Third, systemic metabolite signaling, evidenced by FMT-derived molecules reportedly improving splenic vascularization through indirect whole-body effects (Fang et al., 2023). Strikingly, all tested microbial origin interventions – and other interventions such as immunomodulators (Ali et al., 2024; Li et al., 2024c), nutritional herbs (Chen et al., 2021; Fu et al., 2024; Han et al., 2022b), or marine-origin proteins (Khan et al., 2022; Li et al., 2022) – rely on oral administration, suggesting a gut-first mechanism of action.

Despite promising rodent data, the consistent use of oral microbial therapies reinforces a gut-centric paradigm. It remains unknown whether splenic repair could precede gut recovery or if microbial metabolites (e.g., SCFAs) act directly on the spleen versus requiring metabolic conversion. This gap reflects our limited understanding of bidirectional gut-spleen crosstalk and underscores the need for further research focusing on spleen-first interventions. Translational challenges further arise from physiological differences in human versus murine immune-microbiome networks and methodological limitations in tracking low-abundance therapeutic taxa.

Targeting the gut-spleen axis: therapeutic opportunities and future directions

The gut-spleen axis may represent a promising therapeutic target for metabolic disorders such as diabetes and obesity, where chronic dysbiosis and splenic immune dysfunction have been associated with accelerated disease progression (Daryabor et al., 2020; Dumitrescu and Duca, 2018; Gomes et al., 2018; Peng et al., 2014; Qin et al., 2012; Scheithauer et al., 2020; Wu et al., 2020a). In diabetic models, hyperglycemia has been reported to compromise gut barrier function, potentially facilitating LPS translocation (Caricilli and Saad, 2013; Salazar et al., 2020; Vallianou et al., 2018) and splenic marginal zone B-cell activation (Ebaid et al., 2015; Wang et al., 2021). These processes have been linked to systemic inflammation and insulin resistance (Caricilli and Saad, 2013; Ebaid et al., 2015; Salazar et al., 2020; Vallianou et al., 2018; Wang et al., 2021). Parallel observations have been made in obesity, where dysbiosis-driven LPS may trigger TLR-mediated splenic cytokine production (TNF-α, IL-6) (Carvalho et al., 2012; Dumitrescu and Duca, 2018; Gomes et al., 2018), potentially contributing to metabolic dysfunction (Carvalho et al., 2012; Dumitrescu and Duca, 2018; Gomes et al., 2018; Salazar et al., 2020; Sircana et al., 2018; Zhang et al., 2023a). Rodent studies suggest that microbial therapies, including probiotics and prebiotics, can interrupt this cycle by restoring gut integrity (Ispas et al., 2023; Sircana et al., 2018) and modulating splenic Th17 responses (Zhang et al., 2023b).

Recent research points to a possible role of the brain, forming a gut-brain-spleen network (Dong and Mayer, 2024; Ullah et al., 2023; Zhang et al., 2021). Neural disturbances such as sleep deprivation have been shown to amplify systemic inflammation through vagus-mediated gut-spleen crosstalk, an effect reversible via splenic denervation (Zhang et al., 2021). Conversely, inflammation may drive neurological dysfunction, as LPS has been reported to induce depression-like phenotypes and hippocampal microglial activation through spleen-gut-microbiota interactions (Dong and Mayer, 2024; Ma et al., 2022). The subdiaphragmatic vagus nerve is thought to regulate this axis, given its role in maintaining intestinal permeability and microbial diversity (Jiang et al., 2025). In multiple animal laboratory models, microbial therapies show potential: FMT has been observed to restore neuronal integrity after traumatic brain injury (Hu et al., 2023), while SCFAs and vagal anti-inflammatory pathways may mitigate neural damage in degenerative disorders such as Alzheimer's disease (Jiang et al., 2025).

Therapeutic strategies could focus on three key pathways. First, SCFAs-producing probiotics such as *Lactobacillus* have been reported to repair gut permeability defects (Liu et al., 2024; Salazar et al., 2020; Song et al., 2024; Yan et al., 2024), reducing endotoxemia (Gomes et al., 2018) and splenic macrophage activation (Han et al., 2021; Zeng et al., 2023). Second, vagus nerve stimulation offers a potential neuroimmunological modulation of the axis, leveraging its roles in glucose homeostasis and inflammation resolution (Ma et al., 2022; Pavlov and Tracey, 2012; Ullah et al., 2023). Third, engineered synbiotics may concurrently promote beneficial taxa like *Akkermansia* and suppress pathogens such as Enterobacteriaceae, addressing both dysbiosis and immune dysregulation (Fang et al., 2023; Ning et al., 2024; Sircana et al., 2018; Yan et al., 2024). These approaches may collectively restore microbial balance, enhance barrier function, and normalize immune responses in rodent models.

However, translational challenges persist. Rodent studies consistently report splenic follicle restoration following microbial therapy (Fang et al., 2023; Rosado et al., 2018). In contrast, comparable human trials remain absent, in part because obtaining histopathological samples from the living human spleen is clinically and ethically challenging. Moreover, direct extrapolation is complicated by fundamental species differences in splenic morphology and B-cell compartment organization between rodents and humans (Lewis et al., 2019; Woldeamlak et al., 2019). Safety concerns, including probiotic risks in immunocompromised patients and lack of protocol standardization, further complicate clinical adoption (Kothari et al., 2019). Additionally, neuroendocrine pathways involving leptin and insulin signaling within the gut-brain-spleen axis remain poorly understood (Demuro and Obici, 2006; Dong and Mayer, 2024).

Despite these gaps, the gut-spleen axis offers potential for adjuvant therapies. Future research (Table 3) must bridge mechanistic insights with clinical translation, particularly in reconciling interspecies differences and elucidating neuroendocrine crosstalk. A promising research agenda for gut–spleen crosstalk should integrate multiple complementary approaches to maximize translational impact. Comparative studies across different disruption models (DSS, antibiotics, LPS) can distinguish shared mechanisms from model-specific effects, guiding appropriate model selection. Extending investigations into chronic and recovery phases may clarify whether gut and spleen immune alterations are persistent or reversible, shaping intervention timing. To enhance clinical relevance, humanized or gnotobiotic mice colonized with humans' microbiota could help bridge species gaps. Mechanistic dissection using single-cell and spatial omics may pinpoint cellular players and novel signaling pathways, while exploration of neuroimmune circuits, including vagus nerve and splenic innervation, could reveal regulatory feedback loops with potential for neuromodulatory therapies. Expanding metabolite studies beyond SCFAs to molecules like Trimethylamine N-oxide (TMAO) and tryptophan derivatives may uncover new immunomodulators and drug targets. Clinical validation in human cohorts, such as asplenic patients or those with IBD, is essential to translate preclinical findings. Finally, examining the gut–spleen axis within broader multi-organ immune networks (liver, bone marrow) may support a systems-level view of immune regulation and inform holistic therapeutic strategies.

Table 3. Suggestion for future studies

Research area	Suggestion	Benefit / Purpose
Model comparison	Conduct comparative studies across different disruption models (e.g., DSS, antibiotics, LPS).	Identify core mechanisms vs. model-specific effects; guide model selection.
Chronic and recovery phases	Investigate long-term and recovery-phase effects on gut and spleen immune function.	Understand persistence or reversibility of damage; inform timing for interventions.
Translational model systems	Use humanized or gnotobiotic mice with humans' microbiota.	Improve relevance to humans' disease; reduce translational gaps between species.
Mechanistic dissection	Apply single-cell and spatial omics tools to analyze gut-spleen cell interactions.	Identify specific immune or stromal cell targets; reveal novel signaling pathways.
Neuroimmune pathways	Explore vagus nerve, splenic innervation, and brain-gut-spleen circuits.	Reveal regulatory feedback loops; potential for neuromodulatory therapies.
Expanded microbial metabolites	Study microbial metabolites beyond SCFAs (e.g., TMAO, tryptophan catabolites).	Discover new immunomodulatory molecules and drug targets from microbiota metabolism.
Clinical validation	Conduct observational and interventional studies in humans' cohorts (e.g., asplenic patients, cancer, IBD).	Translate preclinical findings to clinical settings; assess real-world therapeutic value.
Multi-organ immune networks	Study interactions between gut–spleen axis and other organs (e.g., liver, bone marrow).	Build a systems-level understanding of immune regulation; support holistic treatment strategies.

Conclusion

Our synthesis of rodent studies offers an integrative view of the gut-spleen axis. Gut dysbiosis and microbial metabolites, particularly SCFAs, have been associated with remodeling of splenic architecture and immune cell populations, including macrophages, Tregs, and Th17 cells. Limited evidence indicates that splenic disruptions may impair gut barrier function, revealing a potential but underexplored reciprocal pathway. Systemic stressors (e.g., LPS, allergy, autoimmunity) may disturb this network and contribute to sustained inflammation, whereas microbiota-targeted interventions have been shown to restore splenic and gut homeostasis via gut-initiated mechanisms in rodent models. Emerging evidence also points to a directional gut–brain–spleen axis mediated by vagal and enteric signaling, though this remains an area requiring further investigation. This synthesis brings together diverse mechanistic observations into a preliminary coherent model, suggesting the gut–spleen axis as a potential target for therapeutic exploration. Future studies should clarify spleen-to-gut mechanisms, map neuroimmune circuits, and address translational gaps between rodent models and human physiology.

Limitation

The authors acknowledge several limitations. The inclusion criteria were limited to freely available full-text articles and English-language publications, which may have resulted in the exclusion of relevant studies. In addition, the initial screening was conducted by a single reviewer; however, the subsequent full-text review and synthesis were performed by multiple authors, thereby strengthening the reliability of the findings.

Authors' contributions

All authors contributed to the study conception and design. Finalization of conceptualization and methodology were performed by *RS*, and *DKP*. Material preparation, data curation, and analysis were performed by *TL* and *RS*. The first draft of the manuscript was written by *TL* and *RS*. All authors commented and edited on previous versions of the manuscript. All authors read and approved the final manuscript. Funding acquisition was performed by *TL*. Supervision was performed by *RS* and *DKP*.

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Supplementary data

Supplementary tables are available as separate files.

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Ethical aspects and conflict of interest

The authors have no conflict of interest to declare.

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