Journal of Clinical Gastroenterology and Hepatology
ISSN: 2575-7733

Open Access Review Article

Gut Microbiome and Immune Responses in Gastrointestinal Diseases

Byung Soo Yoo[1*], Benjamin L. Robinson[1], Ana Vilela[2], Alsiddig Elmahdi[3], Kevin Houston[3], David A. Johnson[4]

[1]*Department of Gastroenterology and Medicine, Advocate Health Wake Forest, Charlotte, North Carolina, United States of America*

[2]*Department of Medicine, Eastern Virginia Medical School, Norfolk, Virginia, United States of America*

[3]*Department of Medicine, Virginia Commonwealth University, Richmond, Virginia, United States of America*

[4]*Department of Gastroenterology and Medicine, Eastern Virginia Medical School, Norfolk, Virginia, United States of America*

ABSTRACT

Highlighting the expanding research on the Gastrointestinal (GI) microbiome, this review explores its pivotal role in disease pathogenesis, specifically, gastroesophageal reflux disease, barrett's esophagus, eosinophilic esophagitis, inflammatory bowel disease, colon cancer and hepatobiliary disease. The immune system acts as a crucial bridge, connecting the gut microbiome to these GI disorders. Studies demonstrate that microbial dysbiosis triggers immune responses, initiating a pro-inflammatory cytokine cascade. This reciprocal inflammatory interplay between the host's immune system and GI microbiome contributes to disease progression, emphasizing significant potential for diagnostic and therapeutic implications.

Keywords: Gut microbiome; Immune system; Gastrointestinal disorders; Gastroesophageal reflux disease; Barrett's esophagus; Eosinophilic esophagitis; Esophageal cancer; Inflammatory bowel disease; Colon cancer; Hepatobiliary disease

INTRODUCTION

The dynamic interplay between the Gastrointestinal (GI) microbiome and the host immune system constitutes a vibrant field of research. Delving into the intricacies of this relationship has significantly advanced our comprehension of GI diseases, shedding light on the delicate equilibrium within the immune system and its intricate interactions with the GI microbiota. The gut microbiota, composed of bacteria, viruses, fungi and archaea, inhabits various environments, including the respiratory tract, GI tract and skin [1,2]. This intricate collection of microorganisms, termed microbiota, along with its genomic components from the GI tract, referred to as the microbiome, plays a pivotal role in health and disease [3].

Studies have revealed that the human gut microbiome encompasses a diverse array of species, numbering up to 1500, with *Firmicutes* spp. and *Bacteroidetes* spp. constituting a substantial 92% of this community [4,5]. The normal composition of the microbiome is influenced by a myriad of factors, chiefly genetics and environmental cues. Maintaining a healthy equilibrium between the microbiome and the immune system is crucial for an individual's well-being. However, disruptions in this balance, leading to microbial

Received:	31-July-2024	**Manuscript No:**	IPJCGH-24-21046
Editor assigned:	05-August-2024	**PreQC No:**	IPJCGH-24-21046 (PQ)
Reviewed:	19-August-2024	**QC No:**	IPJCGH-24-21046
Revised:	26-August-2024	**Manuscript No:**	IPJCGH-24-21046 (R)
Published:	04-September-2024	**DOI:**	10.36648/2575-7733.8.4.32

Corresponding author: David A Johnson, Department of Gastroenterology and Medicine, Eastern Virginia Medical School, Norfolk, Virginia, United States of America, E-mail: dajevms@aol.com

Citation: Yoo BS, Robinson BL, Vilela A, Elmahdi A, Houston K, et al. (2024) Gut Microbiome and Immune Responses in Gastrointestinal Diseases. J Clin Gastroenterol Hepatol. 8:32.

dysbiosis, have been associated with prevalent diseases such as obesity, type 2 diabetes mellitus, hypertension and various GI disorders.

This intricate relationship extends its implications to diseases like Gastroesophageal Reflux Disease (GERD), Barrett's Esophagus (BE), Eosinophilic Esophagitis (EoE), Inflammatory Bowel Disease (IBD) and certain GI cancers. The gut microbiome's production of metabolites, its interaction with the host's immune system and the elicitation of immune responses through inflammatory signaling are central mechanisms underpinning the pathophysiology of these diseases [6]. Additionally, the diet and exogenous factors also play vital role in the composition of intestinal microbiome. The dysbiosis of intestinal microbiome was noted in high fat and high sugar diet fed murine models.

Understanding the nuanced ways in which the microbiota interacts with the host's GI tract not only enhances our comprehension of these diseases, but also opens potential avenues for diagnostic and therapeutic interventions. This review aims to provide an in-depth exploration of the intricate relationship between the gut microbiome and the host immune system, specifically in the context of GI diseases.

LITERATURE REVIEW

Gastroesophageal Reflux Disease

Gastroesophageal Reflux Disease (GERD) is one of the most widespread GI diseases with its prevalence over 25% in western countries [7]. The previously accepted etiology of GERD was an inflammatory response to gastric acid reflux from direct luminal mucosal injury. However, recent studies are investigating the propagation of the intraluminal inflammatory pathway through an immunogenic response to the Esophageal Microbiome (EM) as a possible contributor to the pathogenesis of GERD [8,9].

The normal esophageal microbiota is mainly composed of gram-positive bacteria *Firmicutes* spp., *Bacteroidetes* spp., *Proteobacteria* spp., *Fusobacteria* spp., *Actinobacteria* spp., *Saccharibacteria* spp. *Firmicutes* is the most dominant phylum and *Streptococcus* is the most prevalent genus [10]. The EM exhibits a microgeographic gradient, with gram-positive flora being more prevalent proximally and an increasingly diverse gram-negative composition distally [11]. Shifts in the esophageal continuum from gram-positive to gram-negative bacteria have been found to precede histological changes, suggesting that dysbiosis in the EM plays a role in developing pathological states of the esophagus [12]. The composition of the EM is affected by gastric refluxate and distal migration of bacteria from the oral cavity. Environmental factors like diet, age, smoking status and proton pump inhibitor use also contribute to interpersonal variability in esophageal microbiota [13].

Gram-negative bacteria contribute to the immunopathogenesis of GERD through the Lipopolysaccharide (LPS) Toll-Like-Receptor-4 (TLR4) pathway. Increased prevalence of LPS containing gram-negative spp. in the distal esophagus leads to an inflammatory cascade through the interaction of LPS with TLR-4. This sequence promotes Nuclear Factor kappa B (NF-κB) and Interferon-gamma (IFN-γ), leading to a cytokine cascade of interleukin (IL)-1B, IL-8, IL-18 and Tumor Necrosis Factor-alpha (TNF-α), ultimately resulting in transmucosal lymphocytic proliferation and resultant inflammation [14]. Moreover, this cytokine pathway leads to increased Nitric Oxide (NO) synthase activity, causing reduced gastric motility and increased relaxation of the Lower Esophageal Sphincter (LES), increasing gastric acid refluxate exposure to the distal esophagus further propagating this inflammatory pathway in a cyclical pattern [15].

Gastrointestinal microbiota produces peptides called bacteriocins whose role is to compete with pathogenic flora, improve the Gut-Blood Barrier (GBB) and modulate the immune system. The gut-blood barrier is crucial to maintaining homeostasis between the bloodstream and the gastrointestinal tract of the esophagus [16]. Studies examining the pivotal role of the GBB show that bacteriocins produced from probiotics *Streptococcus* spp., *Bi idobacterium* spp. and *Lactobacillus* spp. can reduce IL-6 and IL-17, pro-inflammatory cytokines, stimulating expression of Tight Junction (TJ) proteins, promoting gastrointestinal-blood barrier stability [17,18]. Furthermore, administration of *Lactobacillus rhamnosus* GG decreased pro-inflammatory cytokines, TNF-α and Macrophage Inflammatory Protein 2 (MIP-2) in the GI tract of murine models through increasing IL-10 receptor expression [19]. Unfavorable compositional changes to the EM and subsequent altered bacteriocin expression could lead to GBB instability and inflammatory pathways propagation, which could contribute to disease progression in GERD.

Defensins, like bacteriocins but of eukaryotic origin, are small polypeptides that contribute to innate immunity through bactericidal properties. Bacterial products, such as cytokines or LPS, induce the expression of defensins, which can disrupt bacterial cell membranes, promote pore formation in bacterial capsules and propagate the adaptive immune system [20]. The loss of defensins could result in esophageal dysbiosis from unmitigated gram-negative bacterial activity with resulting esophageal inflammation through the LPS-TLR4-NF-KB pathway, ultimately leading to the propagation of GERD [21].

Understanding the intricate interchanges between the esophageal microbiome and the immune system is crucial to treating GERD effectively. The esophageal dysbiosis with transition to gram negative bacteria and its metabolites along with resultant proinflammatory cytokines further instigates the disease in its proinflammatory state. By acknowledging the significance of therapeutic interventions that restore microbial balance and modulate immune responses, we can explore the role of the microbiome in GERD and develop targeted treatments that focus on optimizing microbial and immune system interactions. This developing narrative invites further investigation and presents an opportunity to mitigate the sequela of this disease.

DISCUSSION

Barrett's Esophagus

Barrett's Esophagus (BE) is a disease of the distal esophagus characterized by the replacement of squamous mucosa with metaplastic columnar epithelium and is associated with longstanding and uncontrolled GERD. As with GERD, the incidence of BE has increased with higher uses of antimicrobials, suggesting that esophageal dysbiosis contributes to BE's inflammatory and malignant pathogenesis [22].

Columnar metaplasia arises from the expression of specific cytokines in the distal esophagus, resulting in chronic inflammation and subsequent stimulation of gastric stem cells. As seen in GERD, a higher concentration of gram-negative bacteria in the distal esophagus results in further LPS and TLR interaction, ultimately leading to the inflammatory and metaplastic changes that characterize BE [23]. Specifically, IL-1b, a pro-inflammatory cytokine, is found to be expressed to a high degree in BE. The protease caspase-1 accomplishes proteolytic cleavage of the precursor to IL-1b [24]. Inflammasomes containing Pattern-Recognition Receptors (PRRs) interact with Pathogen-Associated Molecular Patterns (PAMPs) from microbes in the distal esophagus, leading to activation of caspase-1 and initiating inflammation [25]. Notably, the lipopolysaccharides seen in the outer membrane of gram-negative bacteria interact with NOD-like receptor protein 3 inflammasomes in Barrett's epithelial cells, resulting in apoptosis and metaplastic inflammatory changes [26]. Higher proportions of LPS containing gram-negative bacteria could lead to upregulation of cyclooxygenase (COX), isoenzymes COX-1 and -2, producing Prostaglandins (PG) and leading to delayed gastric emptying, reduction in lower esophageal sphincter tone and increased intra gastric pressure, which could promote reflux and subsequent inflammation seen in BE [27]. Similar to GERD, tight junction proteins are essential in the relationship between the innate immune response and the pathogenesis of BE. Inflammatory changes from the higher presence of gram-negative and anaerobes in the distal esophagus result in the activation of Wnt signaling that creates defects in the tight junction proteins and reduces mucin production, both of which have protective roles from carcinogenesis. [28].

The LPS-TLR4-NF-KB inflammatory pathway observed in GERD is also present in BE, but distinct dysbiosis related changes drive the metaplasia in BE. According to a study, *Neisseria* spp. *Campylobacter* spp. and *Fusobacteria* spp. are more prevalent in samples from BE than in non-BE controls [29]. Furthermore, decreased bacterial diversity and lower prevalence of *Bacteroidetes* spp. and *Prevotella* spp. are observed when analyzing the metaplastic tissue of Barrett's compared to normal esophageal tissue [30]. In GERD, an abundance of *Proteobacteria* spp. is seen with *Bacteroidetes* spp. however, a shift towards higher proportions of *Fusobacteria* spp. with less *Bacteroidetes* spp. is found in BE. As dysplastic changes progress to Esophageal Adenocarcinoma (EAC), a compositional change in the EM occurs with increased prevalence in *Firmicutes* [31]. Additionally, *Helicobacter pylori* (*H. pylori*) has been postulated to contribute to the pathogenesis of BE by expressing inflammatory NF-κB and COX-2 in distal esophageal epithelial cells [32]. It is worth noting that several factors can lead to changes in the esophageal microbiome, just like in GERD. Specifically, in the case of Barrett's esophagus, studies have shown a correlation between High-Fat Diets (HFD) and dysbiosis-related changes in the balance between *Bacteroides* spp. and *Firmicutes* spp. bacteria [33].

Similar to GERD, the observed esophageal dysbiosis and proinflammatory state in BE are crucial in understanding the disease. The complex interaction between microbial dynamics, inflammatory responses and environmental factors highlights the necessity for a comprehensive and multidimensional approach to managing and investigating Barrett's esophagus, opening the way for potential therapeutic interventions.

Eosinophilic Esophagitis

Eosinophilic Esophagitis (EoE) is a Th2 antigen-mediated, chronic inflammatory condition marked by eosinophilic inflammation in the esophagus. The complexity of the disease is closely influenced by interactions of the gut microbiome and immune responses [34]. Although the exact cause and pathophysiology remain unclear, it is currently thought to be the outcome of a confluence of genetic, environmental and immunological factors. Evidence suggests that a compromised epithelial barrier facilitates allergen contact with the esophageal mucosa, triggering alarmin release. These alarmins, acting through type 2 Innate Lymphoid Cells (ILC2s) and basophils, initiate a cytokine driven immune response, leading to eosinophilic inflammation and increased barrier disruption. Simultaneously, tissue-resident antigen-presenting cells activate CD^{4+} T helper type 2 cells, which recruit and activate eosinophils, mast cells and plasma cells, resulting in localized IgE and IgG4 production [35,36]. IgE release subsequently triggers TGF-β release from mast cells, contributing further to inflammation and fibrosis [37]. Recent research has shed light on the potential role of the innate immune system and the microbial pattern recognition receptors can play in the pathogenesis of EoE.

Studies examining the profile of esophageal microbiota of those with EoE revealed enrichment of *Neisseria* spp. and *Corynebacterium* spp. in patients with EoE compared to those without EoE. Furthermore, patients with active EoE have been found to have increased microbial load, as well as increased abundance of *Haemophilus* spp. and a decrease of specific members of the *Firmicutes phylum* [38]. Subsequently, compared to healthy individuals, an increased bacterial load was evident in patients with EoE, irrespective of their treatment status or the degree of mucosal eosinophilia, explicitly demonstrating a significant abundance of *Haemophilus* [39].

The ability of *Haemophilus* spp. to penetrate epithelial cells suggests opportunistic bacteria could take advantage of the compromised barrier in EoE, contributing to persistent

inflammation [40,41]. *Haemophilus* is linked to various Th2-mediated conditions, such as recurrent pediatric asthma, chronic obstructive pulmonary disease and rhinosinusitis, all of which suggest that these bacteria may play a role in fueling inflammation in EoE [42-44].

Investigating the role of microbiota in esophageal mucosa inflammation is essential, given its potential connection to initiating and perpetuating inflammation on mucosal surfaces. Current evidence indicates that microbiota penetration activates epithelial cells and innate and adaptive immune cells, triggering the release of cytokines and subsequent immune responses and inflammation. Toll-like receptors' involvement in EoE further underscores the potential impact of microbiota on disease progression. Evidence that compared to healthy individuals, bacterial load and specific TLRs are overexpressed in EoE patients, rectified following dietary therapy-induced remission and mucosal healing, further supports this association of microbiota and immunologic response [45]. The TLRs, as microbial pattern recognition receptors found on epithelial and lamina propria cells, play a crucial role in distinguishing between pathogens and commensal microorganisms. This implies that heightened exposure of the microbiota and microbial products to the compromised esophageal mucosal barrier could elevate the release of alarmins by esophageal epithelial cells, contributing to the progression of esophageal inflammation. This upregulation of TLRs suggests a pivotal role for microbiota in the disease's pathophysiology. The functional TLR-mediated signaling pathways in the esophageal mucosa of active EoE patients activate the innate immune system in the esophagus, contributing to cellular damage.

The relationship between eosinophilic esophagitis, the microbiome and immune responses in gastrointestinal diseases is complex and dynamic. Understanding how these interactions contribute to immune dysregulation and inflammation can help focus therapies on developing balance in the microbiome and enhancing barrier integrity. This approach would address the disease's symptomatic aspects and its underlying etiology. Further research is needed to clarify specific interactions between the esophageal microbiome and the immune system as they relate to EoE to develop more effective treatment strategies.

Esophageal Cancer

Esophageal Cancer (EC) is an aggressive malignancy, ranking as the eighth most diagnosed cancer and the sixth most common cause of cancer death in the world [46]. Although Esophageal Squamous Cell (ESCC) carcinoma is the most prevalent type worldwide, Esophageal Adenocarcinoma (EC) is increasing in prevalence in developed countries [47]. Increasing evidence suggests that achieving a thorough comprehension of the molecular composition of esophageal cancer necessitates focusing not only on tumor cells but also on the tumor microenvironment. This microenvironment comprises diverse cell populations, signaling factors and structural molecules that engage with tumor cells and play supportive roles across all stages of tumorigenesis [48]. The dynamic interplay between the host's microbiota and the immune system is emerging as a critical factor influencing the development, progression and treatment outcomes of esophageal malignancies

As in other states of esophageal disease, the microbiota in esophageal cancer is characterized by reduced microbial diversity characterized by a shift from gram-positive to gram-negative bacteria. The genera most enriched in esophageal cancer are *Fusobacterium*, *Streptococcus*, *Peptostreptococcus*, *Veilonella*, *Actinobacillus*, *Gemella*, *Rothia* and *Prevotella* [49,50]. A study done by Jing et al., studied the microbiota spectrum of ESCC patients and demonstrated a significant difference in the microbial diversity and richness between the ESCC patients; the results provided a potential association of *Streptococcus* spp., *Actinobacillus* spp., *Peptostreptococcus* spp., *Fusobacterium* spp. and *Prevotella* spp. with ESCC [51]. Reduced microbial diversity in ESCC patients could indicate a shift towards an environment conducive to chronic inflammation and tumorigenesis.

Specific bacteria, such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, have been implicated in promoting carcinogenesis in ESCC. These bacteria play a role in ESCC cell proliferation and migration through the TLR4/NF-κB and IL-6/STAT3 pathways, contributing to either disease progression or drug resistance [52]. Gao et al., identified *P. gingivalis* infects the epithelium of the esophagus of ESCC patients and established an association between infection with *P. gingivalis* and the progression of ESCC, which suggests *P. gingivalis* infection could be a biomarker for disease progression [53]. Studies indicate that *P. gingivalis* activates the NF-κB pathway in ESCC cells, promoting proliferation and motility. Animal models link *P. gingivalis* infection to advanced esophageal cancer stages and poor prognosis *via* the IL-6/STAT3 pathway, contributing to chemotherapy resistance. Clinical findings reveal elevated *P. gingivalis* in ESCC patients' saliva and tumor sites compared to controls. The presence of *P. gingivalis* infection correlates with ESCC severity and poor prognosis, indicating its role in disease progression, chemotherapy resistance and unfavorable outcomes through NF-κB and IL-6/STAT3 pathways [54].

Fusobacterium nucleatum is closely related to increased tumor staging and gene mutations such as TP53, COL22A1, TRBV10-1, CSMD3, SCN7A and PSG11 [55]. This suggests that the abundance of *Fusobacterial nucleatum* and tumor mutation burden may be combined as a potential method to predict high risk for metastasis in ESCC [56]. Additionally, more recent studies have found that *Fusobacterium nucleatum* promoted the early development of ESCC by upregulating the expression of IL-32/PRTN3 and activating the PI3K/AKT signaling pathway [57]. These findings highlight the significant roles of *Porphyromonas gingivalis* and *Fusobacterium nucleatum* in influencing the course and outcomes of esophageal squamous cell carcinoma.

Therapeutic manipulation of the microbiota, such as probiotics and prebiotics, could serve as adjuncts to modulate the tumor microenvironment and enhance the efficacy of conventionally used treatments. This multifaceted approach

emphasizes the need for a comprehensive understanding of the microbial influences in esophageal cancer biology, encouraging a broader perspective incorporating the microbiome into the traditional paradigms of oncology.

Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) refers to a category of chronic autoimmune conditions of the gastrointestinal tract. The two most recognized types are Crohn's Disease (CD) and ulcerative colitis. These conditions can be differentiated by clinical characteristics such as distribution, with UC limited to the mucosal layer of the colorectal GI tract [58]. Either condition can be characterized by relapsing symptoms of diarrhea, abdominal pain and bloody stools. While the clinical characteristics are well described, the underlying pathogenesis is complex [59].

Recent developments have demonstrated that the intestinal microbiota also plays a role in disease pathogenesis along with genetic and environmental factors [60]. IBD is characterized by intestinal epithelium damage secondary to the infiltration of lymphocytes, neutrophils and macrophages and dysregulation of the inflammatory response. The detection of intestinal flora in the GI epithelium initiates this response. As such, dysregulation of the delicate interactions between GI epithelial cells, intestinal flora and immune cells can lead to the exaggerated immune response seen in IBD [61].

The human GI tract consists of 100 trillion micro-organisms and comprises over 1,000 different bacterial species. Pattern Recognition Receptors (PRRs) are expressed throughout the cells of the intestinal tract. These PRRs influence the composition of the tract *via* the regulation of product (mucus, antimicrobial peptides and immune mediators) secretion [62].

The four major PRR classes include TLRs, NLR, C-type lectin receptors and RIG-1-like receptors. Much like in other inflammatory-mediated diseases, TLRs in the intestines recognize pathogen associated molecular patterns and activate intracellular cascades, which lead to the transcription of inflammatory cytokines. TLR-4, in particular, has significantly been implicated in this process as it binds to LPS found on gram-negative bacteria and leads to the downstream activity of prominent inflammatory cytokines such as TNF-a, IL-6, IL-1 and type-1 interferons, which all play a role in inflammatory bowel disease [63].

The TLR-4 expression is elevated in individuals with inflammatory bowel disease compared to normal individuals [64]. Nod-Like Receptors (NLR) are also thought to play a role. The Nucleotide-binding Oligomerization Domain 2 (NOD2) receptor recognizes Muramyl Dipeptide (MDP) in peptidoglycan, found in the cell walls of gram-positive and gram-negative bacteria. The downstream effect is the activation of NF-kB, which leads to the secretion of IL-12 and other pro-inflammatory cytokines. The NOD2 gene is frequently mutated in CD patients [65].

While the inflammatory cascade is a hallmark of IBD, another key characteristic is intestinal microbiota dysbiosis. Further, there is a marked reduction in the diversity of the microbiome. Specifically, reducing specific phyla such as Actinobacteria, Firmicutes and Bacteroides is associated with dysbiosis. Importantly, these organisms produce Short-Chain Fatty Acids (SCFAs), which act as anti-inflammatory products in the intestines [66]. These findings seem reversible, as long-term remission is associated with normalizing bacterial microbiota and SCFA levels in fecal specimens. It should also be noted that intestinal bacteria synthesize these fatty acids from degrading indigestible carbohydrates. The implication is that there is a complex interplay between diet, microbiome composition and degree of inflammation and these relationships should continue to be studied.

Beyond the distress from the symptoms of IBD, the disorder can also have severe complications. Patients with IBD are at increased risk of colon cancer. Having UC increases one's risk of developing colitis-associated cancer by 18%-20% and those with CD are at an 8% increase [67].

The prevailing knowledge on IBD focuses on a multi-faceted approach incorporating genetic, microbial and immune factors. The recognition of the gut microbiota's involvement in disease pathogenesis in addition to the genetics and environmental cues advances our understanding of IBD. Notably, dysbiosis of the gut microbiome marked by a reduction in diversity and specific bacterial phyla further contributes the proinflammatory state in IBD. However, emerging evidence suggests that intervention targeting microbiome restoration and dietary modifications may hold future for therapeutic intervention. The complex connections between diet, microbiome composition and degree of immune response present many opportunities for continuing research and development.

Colon Cancer

Colorectal Cancer (CRC) is the second deadliest cancer in the United States, with 52,550 deaths in 2023, including 3,750 individuals less than 50 years of age [68]. As with many other GI illnesses discussed, CRC is associated with a change in the composition of the intestinal microbiome. Compared to healthy patients, the microbiome of CRC patients has increased levels of *Fusobacterium* spp. and other gram negatives. There are also increased levels of some gram positives, such as *Enterococcus faecalis*, which has been associated with the development of adenocarcinoma in IBD patients.

Like in IBD, CRC is associated with a reduction of butyrate-producing organisms. Like other SCFAs, butyrate acts as an anti-inflammatory and an antioxidant, promoting the growth of anaerobic bacteria [69]. Activation of the previously described inflammatory also plays a role in the development of CAC. Colitis-Associated Cancer (CAC) has a poorly understood mechanism, but it appears that upregulation of TLR-4 may trigger the proliferation of intestinal epithelial cells and lead to carcinoma. Given that TLR-4 responds to LPS, an association can be made between the make-up of the intestinal microflora and the development of CAC.

Beyond their propensity to trigger inflammatory cascades through the binding of PRRs, the gut microbiota also influences the development of neoplasia by producing protein toxins, which promote proliferation and reduce apoptosis. These include Cytolethal Distending Toxins (CDT) and DNA-damaging toxins from gram-negative bacteria. Persistent exposure to these toxins can reduce their DNA-damaging effects *via* mutations and tolerance. As such, a microbiome abundant with organisms that produce these toxins can be associated with the development of CAC.

Another instance of gram-negative bacteria impacting neoplasia is the case of *Bacteroides fragilis*, which produces *Bacteroides fragilis* Toxins (BFTs). These BFRs bind to E-cadherin in the intestinal epithelial cell, releasing the protein from the tumor suppressor protein, beta catenin. Once released, E-cadherin becomes an active transcription factor that promotes cell proliferation. Furthermore, BFTs also reduce apoptosis of intestinal epithelial cells, augmenting neoplasia.

Collectively, these findings highlight the potential of targeting microbial components in CRC as an avenue for prevention or therapy. Strategies may include microbiome regulation through diet, probiotics or antimicrobials and direct targeting of notable bacterial toxins or inflammatory pathway identified in CRC.

Hepatobiliary Diseases

Hepatobiliary diseases, encompassing Hepatocellular Carcinoma (HCC), are intricately shaped by the interplay between the gut microbiome and immunotherapy. Recent research illuminates this complex relationship, with the gut microbiota composition emerging as a robust predictor of immune checkpoint therapy response in hepatobiliary diseases [70]. The comprehension of the gut-liver axis proves crucial in unraveling the mechanisms of chronic liver diseases, such as Non-Alcoholic Fatty Liver Disease (NAFLD), intricately connected to the gut microbiota [71]. Exploring interactions between gut microbes and the tumor immune microenvironment reveals promising avenues for immunotherapeutic interventions in liver cancer [72].

Numerous studies highlight the profound connection between the GI microbiome and its communication with the liver. Key players in this interaction include the portal vein and biliary system. The portal vein facilitates the direct transportation of immune cells, cytokines and gut-derived products to the liver. In contrast, the liver reciprocates by secreting bile and bioactive mediators into the intestine *via* the biliary system. The intricate structure of the gut vascular and single layer epithelial cells, bound by tight junction proteins, along with the mucus layer and microorganisms, forms a robust physical barrier. Components like antimicrobial molecules and Secreted Immunoglobulin A (SIgA) contribute to maintaining biochemical barriers. The intestinal barrier, functioning as the first line of defense in human immunity, complements the liver's role as the second line of defense against pathogenic factors escaping from the intestinal mucosal immune defense [73].

Gastrointestinal microbiome dysbiosis can compromise these barriers, heightening mucosal permeability. Dietary factors impact the composition of the intestinal microbiome and play a crucial role in preserving the integrity of the intestinal barrier. The pathological state induced by a high-fat diet results in bacterial translocation and endotoxin entry into the portal venous system, activating immune cells in the liver and triggering inflammatory responses, ultimately causing tissue damage to the intestinal mucosa, liver and systemic organs [74].

The close relationship between the gut and the liver in immune pathogenesis underscores its significance for translational therapy [75]. The hepatic immunological response triggered by gut permeability, especially the role of Kupffer cells in the initial immune response, is explored. Continuous exposure of the liver to gut microbiome components through the portal vein emerges as a critical factor influencing liver adaptation.

The intricate interplay between the gut microbiome and immunotherapy in hepatobiliary diseases such as HCC highlights the importance of understanding the gut-liver axis. Central to the relationship of gut liver axis are the portal vein and biliary system which facilitate bidirectional communication between the gut and liver. Dysbiosis of the GI microbiome can compromise the integrity of the intestinal barrier. Additionally, dietary factors play a crucial role in modulating the gut microbiome and the intestinal barrier function. As our understanding of these intricate interactions advances, translational therapies target the gut liver axis hold promise for improved management of hepatobiliary diseases.

CONCLUSION

The intricate relationship between the GI microbiome and the immune system has been revealed as a pivotal factor in the pathogenesis of various GI diseases, including GERD, BE, EoE, IBD, colon cancer and hepatobiliary disease. Through a comprehensive exploration of existing studies, it becomes evident that microbial dysbiosis eliciting an immune response has a cyclic mechanism that potentially fuels these diseases' development and/or progression. Recognizing the gut microbiome as a critical player in the pathophysiology of GI disorders provides a foundation for developing strategies to modulate the microbiome and harness its potential for clinical applications. Future research promises to unveiling novel therapeutic approaches that can address the diseases provide personalized medicine.

AUTHOR CONTRIBUTIONS

David A. Johnson MD and Byung Soo Yoo MD contributed to the construction of the project; all authors wrote and edited the manuscript.

CONFLICTS OF INTEREST

David A Johnson MD research investigator for ISOTHRIVE.

REFERENCES

1. Marchesi JR, Adams DH, Fava F, Hermes GD, Hirschfield GM, et al. (2016) The gut microbiota and host health: A new clinical frontier. Gut. 65(2):330-339.
2. Sender R, Fuchs S, Milo R (2016) Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 14(8): 533-536.
3. Shi N, Li N, Duan X (2017) Interaction between the gut microbiome and mucosal immune system. Military Med Res. 24:1-7.
4. Harmsen HJ, de Goffau MC (2016) The human gut microbiota. Adv Exp Med Biol. 902:95-108.
5. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, et al. (2005) Diversity of the human intestinal microbial flora. Science. 308(5728):1635-1638.
6. Liu J, Tan Y, Cheng H, Zhang D, Feng W, et al. (2022) Functions of gut microbiota metabolites, current status and future perspectives. Aging Dis. 13(4):1106.
7. El-Serag HB, Sweet S, Winchester CC, Dent J (2014) Update on the epidemiology of gastro-oesophageal reflux disease: A systematic review. Gut. 63(6):871-880.
8. Wang K, Wang S, Chen Y, Lu X, Wang D, et al. (2024) Causal relationship between gut microbiota and risk of gastroesophageal reflux disease: A genetic correlation and bidirectional Mendelian randomization study. Front Immunol. 15:1327503.
9. Mazgaeen L, Gurung P (2020) Recent advances in lipopolysaccharide recognition systems. Int J Mol Sci. 21(2):379.
10. Pei Z, Bini EJ, Yang L, Zhou M, Francois F, et al. (2004) Bacterial biota in the human distal esophagus. Proc Natl Acad Sci. 101(12):4250-4255.
11. Dong L, Yin J, Zhao J, Ma SR, Wang HR, et al. (2018) Microbial similarity and preference for specific sites in healthy oral cavity and esophagus. Front Microbiol. 9:1603.
12. Blackett KL, Siddhi SS, Cleary S, Steed H, Miller MH, et al. (2013) Oesophageal bacterial biofilm changes in gastro-oesophageal reflux disease, Barrett's and oesophageal carcinoma: Association or causality? Aliment Pharmacol Ther. 37(11):1084-1092.
13. D'Souza SM, Houston K, Keenan L, Yoo BS, Parekh PJ, et al. (2021) Role of microbial dysbiosis in the pathogenesis of esophageal mucosal disease: A paradigm shifts from acid to bacteria? World J Gastroenterol. 27(18):2054.
14. Zavala-Solares MR, Fonseca-Camarillo G, Valdovinos M, Granados J, Grajales-Figueroa G, et al. (2021) Gene expression profiling of inflammatory cytokines in esophageal biopsies of different phenotypes of gastroesophageal reflux disease: A cross-sectional study. BMC Gastroenterol. 21:1-9.
15. PishKenari FN, Qujeq D, Bonahi SS, Kashifard M, Hajian-Tilaki K (2022) Nitric oxide and inducible nitric oxide synthase levels in EE and NERD patients. Gastroenterol Hepatol Bed Bench. 15(1):79.
16. Dicks LM, Dreyer L, Smith C, van Staden AD (2018) A review: The fate of bacteriocins in the human gastro-intestinal tract: Do they cross the gut–blood barrier? Front Microbiol. 9:2297.
17. Wang Y, Kasper LH (2014) The role of microbiome in central nervous system disorders. Brain Behav Immun. 38:1-12.
18. Ling X, Linglong P, Weixia D, Hong W (2016) Protective effects of bifidobacterium on intestinal barrier function in LPS-induced enterocyte barrier injury of Caco monolayers and in a rat NEC model. PloS One. 11(8):e0161635.
19. Mirpuri J, Sotnikov I, Myers L, Denning TL, Yarovinsky F, et al. (2012) *Lactobacillus rhamnosus* (LGG) regulates IL-10 signaling in the developing murine colon through upregulation of the IL-10R2 receptor subunit. PLoS One. 7(12):e51955.
20. Machado LR, Ottolini B (2015) An evolutionary history of defensins: A role for copy number variation in maximizing host innate and adaptive immune responses. Front Immunol. 6:115.
21. Schroeder S, Robinson ZD, Masterson JC, Hosford L, Moore W, et al. (2013) Esophageal human β-defensin expression in eosinophilic esophagitis. Pediatr Res. 73(5): 647-654.
22. Yu G, Gail MH, Shi J, Klepac-Ceraj V, Paster BJ, et al. (2014) Association between upper digestive tract microbiota and cancer-predisposing states in the esophagus and stomach. Cancer Epidemiol Biomarkers Prev. 23(5):735-741.
23. Yang L, Lu X, Nossa CW, Francois F, Peek RM, et al. (2009) Inflammation and intestinal metaplasia of the distal esophagus are associated with alterations in the microbiome. Gastroenterology. 137(2):588-597.
24. Quante M, Bhagat G, Abrams JA, Marache F, Good P, et al. (2012). Bile acid and inflammation activate gastric cardia stem cells in a mouse model of Barrett-like metaplasia. Cancer Cell. 21(1):36-51.
25. O'Neill LA (2002) Signal transduction pathways activated by the IL-1 receptor/toll-like receptor superfamily. Curr Top Microbiol Immunol. 270:47-61.
26. Nadatani Y, Huo X, Zhang X, Yu C, Cheng E, et al. (2016) NOD-like receptor protein 3 inflammasome priming and activation in Barrett's epithelial cells. Cell Mol Gastroenterol Hepatol. 2(4):439-453.
27. Verbeek RE, Siersema PD, Ten Kate FJ, Fluiter K, Souza RF, et al. (2014) Toll-like receptor 4 activation in Barrett's esophagus results in a strong increase in COX-2 expression. J Gastroenterol. 49:1121-1134.
28. Jovov B, Shaheen NJ, Orlando GS, Djukic Z, Orlando RC (2013) Defective barrier function in neosquamous epithelium. Am J Gastroenterol T. 108(3):386-391.
29. Macfarlane S, Furrie E, Macfarlane GT, Dillon JF (2007) Microbial colonization of the upper gastrointestinal tract in patients with Barrett's esophagus. Clin Infect Dis. 45(1):29-38.

30. Lopetuso LR, Severgnini M, Pecere S, Ponziani FR, Boskoski I, et al. (2020). Esophageal microbiome signature in patients with Barrett's esophagus and esophageal adenocarcinoma. PLoS One. 15(5):e0231789.
31. Zhou J, Shrestha P, Qiu Z, Harman DG, Teoh WC, et al. (2020) Distinct microbiota dysbiosis in patients with non-erosive reflux disease and esophageal adenocarcinoma. J Clin Med. 9(7):2162.
32. Kountouras J, Zavos C, Polyzos SA, Katsinelos P (2015) Helicobacter pylori infection and gastroesophageal reflux disease-Barrett's esophagus sequence "dilemma". Ann Gastroenterol. 2015:153.
33. Sonnenburg ED, Zheng H, Joglekar P, Higginbottom SK, Firbank SJ, et al. (2010) Specificity of polysaccharide use in intestinal bacteroides species determines diet-induced microbiota alterations. Cell. 141(7):1241-1252.
34. Mennini M, Tambucci R, Riccardi C, Rea F, de Angelis P, et al. (2021) Eosinophilic esophagitis and microbiota: State of the art. Front Immunol. 12:595762.
35. Clayton F, Fang JC, Gleich GJ, Lucendo AJ, Olalla JM, et al. (2014) Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology. 147(3):602-609.
36. Mitson-Salazar A, Yin Y, Wansley DL, Young M, Bolan H, et al. (2016) Hematopoietic prostaglandin D synthase defines a proeosinophilic pathogenic effector human TH2 cell subpopulation with enhanced function. J Clin Immunol. 137(3):907-918.
37. Mishra A, Rothenberg ME (2003) Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1 and STAT6-dependent mechanism. Gastroenterology. 125(5): 1419-1427.
38. Benitez AJ, Hoffmann C, Muir AB, Dods KK, Spergel JM, et al. (2015) Inflammation associated microbiota in pediatric eosinophilic esophagitis. Microbiome. 3:1-1.
39. Harris JK, Fang R, Wagner BD, Choe HN, Kelly CJ, et al. (2015) Esophageal microbiome in eosinophilic esophagitis. PloS One. 10(5):e0128346.
40. Clementi CF, Hakansson AP, Murphy TF (2014) Internalization and trafficking of nontypeable *Haemophilus influenzae* in human respiratory epithelial cells and roles of IgA1 proteases for optimal invasion and persistence. Infect Immun. 82(1):433-444.
41. Clementi CF, Murphy TF (2011) Non-typeable *Haemophilus influenzae* invasion and persistence in the human respiratory tract. Front Cell Infect Microbiol. 1:1.
42. Hoggard M, Biswas K, Zoing M, Wagner Mackenzie B, Taylor MW, et al. (2017) Evidence of microbiota dysbiosis in chronic rhinosinusitis. Int Forum Allergy Rhinol. 7(3): 230-239.
43. Chunxi L, Haiyue L, Yanxia L, Jianbing P, Jin S (2020) The gut microbiota and respiratory diseases: New evidence. J Immunol Res. 2020(1):2340670.
44. Hufnagl K, Pali-Scholl I, Roth-Walter F, Jensen-Jarolim E (2020) Dysbiosis of the gut and lung microbiome has a role in asthma. Semin Immunopathol. 42(1): 75-93.
45. Arias A, Vicario M, Bernardo D, Olalla JM, Fortea M, et al. (2018). Toll-like receptors-mediated pathways activate inflammatory responses in the esophageal mucosa of adult eosinophilic esophagitis. Clin Transl Gastroenterol. 9(4):e147.
46. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, et al. (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin. 71(3):209-249.
47. Uhlenhopp DJ, Then EO, Sunkara T, Gaduputi V (2020) Epidemiology of esophageal cancer: Update in global trends, etiology and risk factors. Clin J Gastroenterol. 13(6):1010-1021.
48. Lin EW, Karakasheva TA, Hicks PD, Bass AJ, Rustgi AK (2016) The tumor microenvironment in esophageal cancer. Oncogene. 1:13.
49. Kovaleva O, Podlesnaya P, Rashidova M, Samoilova D, Petrenko A, et al. (2021) Prognostic significance of the microbiome and stromal cells phenotype in esophagus squamous cell carcinoma. Biomedicines. 9(7):743.
50. Yamamura K, Baba Y, Nakagawa S, Mima K, Miyake K, et al. (2016) Human microbiome *Fusobacterium nucleatum* in esophageal cancer tissue is associated with prognosis. Clin Cancer Res. 22(22):5574-5581.
51. Zou Q, Feng L, Cai X, Qian Y, Xu L (2023) Esophageal microflora in esophageal diseases. Front Cell Infect Microbiol. 13:1145791.
52. Jiang Z, Wang J, Shen Z, Zhang Z, Wang S (2021) Characterization of esophageal microbiota in patients with esophagitis and esophageal squamous cell carcinoma. Front Cell Infect Microbiol. 11:774330.
53. Gao S, Li S, Ma Z, Liang S, Shan T, et al. (2016) Presence of *Porphyromonas gingivalis* in esophagus and its association with the clinicopathological characteristics and survival in patients with esophageal cancer. Infect Agent Cancer. 11:3.
54. Chiang HC, Hughes M, Chang WL (2023) The role of microbiota in esophageal squamous cell carcinoma: A review of the literature. Thorac Cancer. 14(28): 2821-2829.
55. Li Z, Shi C, Zheng J, Guo Y, Fan T, et al. (2021) *Fusobacterium nucleatum* predicts a high risk of metastasis for esophageal squamous cell carcinoma. BMC Microbiol. 21:1-4.
56. Lei J, Xu F, Deng C, Nie X, Zhong L, et al. (2023) *Fusobacterium nucleatum* promotes the early occurrence of esophageal cancer through upregulation of IL-32/ PRTN3 expression. Cancer Sci. 114(6):2414-2428.
57. Yamamura K, Baba Y, Nakagawa S, Mima K, Miyake K, et al. (2016) Human microbiome *Fusobacterium nucleatum* in esophageal cancer tissue is associated with prognosis. Clin Cancer Res. 22(22):5574-5581.
58. Zhang M, Sun K, Wu Y, Yang Y, Tso P, et al. (2017) Interactions between intestinal microbiota and host immune response in inflammatory bowel disease. Front Immunol. 8:942.

59. Wilson JC, Furlano RI, Jick SS, Meier CR (2016) Inflammatory bowel disease and the risk of autoimmune diseases. J Crohns Colitis. 10(2):186-193.
60. Guan Q (2019) A comprehensive review and update on the pathogenesis of inflammatory bowel disease. J Immunol Res. 2019(1):7247238.
61. Abraham C, Abreu MT, Turner JR (2022) Pattern recognition receptor signaling and cytokine networks in microbial defenses and regulation of intestinal barriers: Implications for inflammatory bowel disease. Gastroenterology. 162(6):1602-1616.
62. Kuo WT, Lee TC, Yu LC (2016) Eritoran suppresses colon cancer by altering a functional balance in toll-like receptors that bind lipopolysaccharide. Cancer Res. 76(16):4684-4695.
63. Wu Y, Wu J, Chen T, Li Q, Peng W (2018) *Fusobacterium nucleatum* potentiates intestinal tumorigenesis in mice *via* a toll-like receptor 4/p21-activated kinase 1 cascade. Dig Dis Sci. 63:1210-1218.
64. Yamamoto S, Ma X (2009) Role of Nod2 in the development of Crohn's disease. Microbes Infect. 11(12): 912-918.
65. Chia LW, Mank M, Blijenberg B, Aalvink S, Bongers RS, et al. (2020) *Bacteroides thetaiotaomicron* fosters the growth of butyrate-producing *Anaerostipes caccae* in the presence of lactose and total human milk carbohydrates. Microorganisms. 8(10):1513.
66. Grivennikov SI (2013) Inflammation and colorectal cancer: Colitis-associated neoplasia. Semin Immunopathol. 35:229-244.
67. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A (2023) Colorectal cancer statistics, 2023. Cancer J Clin. 73(3): 233-254.
68. Gubatan J, Boye TL, Temby M, Sojwal RS, Holman DR, et al. (2022) Gut microbiome in inflammatory bowel disease: Role in pathogenesis, dietary modulation and colitis-associated colon cancer. Microorganisms. 10(7): 1371.
69. Mao J, Wang D, Long J, Yang X, Lin J, et al. (2021). Gut microbiome is associated with the clinical response to anti-PD-1 based immunotherapy in hepatobiliary cancers. J ImmunoTher Cancer. 9(12):e003334.
70. Tripathi A, Debelius J, Brenner DA, Karin M, Loomba R, et al. (2018) The gut–liver axis and the intersection with the microbiome. Nat Rev Gastroenterol Hepatol. 15(7): 397-411.
71. Brandl K, Kumar V, Eckmann L (2017) Gut-liver axis at the frontier of host-microbial interactions. Am J Physiol Gastrointest Liver Physiol. 312(5):413-419.
72. Taniki N, Nakamoto N, Chu PS, Mikami Y, Amiya T, et al. (2018) Intestinal barrier regulates immune responses in the liver *via* IL-10-producing macrophages. JCI Insight. 3(12):e91980.
73. He LH, Yao DH, Wang LY, Zhang L, Bai XL (2021) Gut microbiome-mediated alteration of immunity, inflammation and metabolism involved in the regulation of non-alcoholic fatty liver disease. Front Microbiol. 12:761836.
74. Bozward AG, Ronca V, Osei-Bordom D, Oo YH (2021) Gut-liver immune traffic: Deciphering immune-pathogenesis to underpin translational therapy. Frontiers Immunol. 12:711217.
75. Chopyk DM, Grakoui A (2020) Contribution of the intestinal microbiome and gut barrier to hepatic disorders. Gastroenterology. 159(3):849-863.