BIBLIOGRAPHIC INFORMATION SYSTEM

Journal Full Title: Journal of Biomedical Research & Environmental Sciences

Journal NLM Abbreviation: J Biomed Res Environ Sci

Journal Website Link: https://www.jelsciences.com

Journal ISSN: 2766-2276

Category: Multidisciplinary

Subject Areas: Medicine Group, Biology Group, General, Environmental Sciences

Topics Summation: 133

Issue Regularity: Monthly

Review Process: Double Blind

Time to Publication: 21 Days

Indexing catalog: IndexCopernicus ICV 2022: 88.03 | GoogleScholar | View more

Publication fee catalog: Visit here

DOI: 10.37871 (CrossRef)

Plagiarism detection software: iThenticate

Managing entity: USA

Language: English

Research work collecting capability: Worldwide

Organized by: SciRes Literature LLC

IndexCopernicus ICV 2022: 83.03

Manuscript should be submitted in Word Document (.doc or .docx) through

Online Submission

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JOURNAL OF BIOMEDICAL RESEARCH & ENVIRONMENTAL SCIENCES
ISSN: 2766-2276
SUBJECT AREA(S): GASTROENTEROLOGY
DOI: 10.37871

REVIEW ARTICLE

Crosstalk between Inflammatory Hypoxia and Gut Microbiota in Inflammatory Bowel Disease (IBD)

Boping Jing[1] and Fei Gao[2,3]*

[1]Department of cancer system imaging, The University of Texas MD Anderson Cancer Center, Houston 77054, USA
[2]Brown Center for Immunotherapy, School of Medicine, Indiana University, Indianapolis, IN 46202, USA
[3]Experimental and Developmental Therapeutics, Melvin and Bren Simon Comprehensive Cancer Center, Indiana University, Indianapolis, IN 46202, USA

Abstract

In the healthy gut mucosa, epithelial cells lining the lumen experience low oxygen levels, typically less than 2%, referred to as physiological hypoxia or physioxia. This gradient is maintained by the diffusion of oxygen from blood vessels along the crypt-villus axis, creating varying degrees of hypoxia within the mucosal lining. Physiological hypoxia at the mucosal surface regulates innate immunity by enhancing epithelial barrier function and modulating resident immune cells. However, studies suggest that mucosal inflammatory diseases involve hypoxia, exacerbated by increased oxygen consumption due to inflammatory cell influx, termed inflammatory hypoxia. Additionally, endothelial dysfunction may induce microvascular occlusion and thrombosis, further exacerbating tissue hypoxia. The human Gastrointestinal (GI) tract harbors a diverse community of microorganisms known as gut microbiota, pivotal in intestinal immunity and metabolism. Crucially, the microbiota contributes to maintaining a physiologically low oxygen environment in the gut, crucial for mucosal defenses. Dysbiosis of gut microbiota has been implicated in the pathogenesis of various inflammatory diseases and infections. This review aims to consolidate our current knowledge of the intricate interplay between inflammatory hypoxia and gut microbiota, emphasizing the pivotal roles of gut microbiota in the pathological hypoxic conditions observed in Inflammatory Bowel Disease (IBD).

***Corresponding author(s)**

Fei Gao, Experimental and Developmental Therapeutics, Melvin and Bren Simon Comprehensive Cancer Center, Indiana University, Indianapolis, IN 46202, USA

Email: fg6@iu.edu

DOI: 10.37871/jbres1960

Submitted: 14 July 2024

Accepted: 23 July 2024

Published: 24 July 2024

Keywords

- Inflammatory hypoxia
- Microbiota
- Inflammatory bowel disease

Introduction

The GI tract operates within a unique physiological framework characterized by low partial oxygen tensions, essential for maintaining the intestinal microecosystem and functions [1,2]. In both the healthy mucosa of the small and large intestine, lumen-apposed epithelia endure low partial pressure of Oxygen (pO2) conditions of <10 mmHg, defined as physiologic hypoxia. In contrast, oxygen-rich blood vessels reside in the subepithelium, with oxygen diffusing along the crypt-villus axis to adjacent venules. Consequently, GI tissues experience varying degrees of low oxygen levels [1,3-5].

The GI mucosa sustains controlled inflammation under physiologic hypoxia, regulating innate immunity by balancing resident immune

MEDICINE GROUP
GASTROENTEROLOGY
VOLUME: 5 ISSUE: 7 - JULY, 2024

How to cite this article: Jing B, Gao F. Crosstalk between Inflammatory Hypoxia and Gut Microbiota in Inflammatory Bowel Disease (IBD). J Biomed Res Environ Sci. 2024 Jul 24; 5(7): 822-833. doi: 10.37871/jbres1960, Article ID: JBRES1960, Available at: https://www.jelsciences.com/articles/jbres1960.pdf

cells and promoting epithelial barrier function [6-8]. Mucosal inflammatory diseases, characterized by inflammatory hypoxia, result from increased inflammatory cells and oxygen demands [9-11]. Conversely, conditions primarily driven by hypoxia may manifest secondary inflammatory changes [12,13]. Furthermore, hypoxia and inflammation exhibit interdependence [14]. During intestinal inflammation, lesions are profoundly hypoxic or anoxic, penetrating deep into mucosal tissue due to factors like increased oxygen consumption, edema, thrombosis, vasoconstriction, and vasculitis [15]. IBD, characterized by chronic GI tract inflammation, is notably associated with severe mucosal hypoxia [16,17]. Hyperbaric Oxygen Therapy (HBOT), which targets both tissue hypoxia and inflammation, has been evaluated in IBD by several studies [18-25].The gut microbiota, crucial for maintaining the intestinal hypoxic environment, plays a critical role in nutrient absorption, barrier integrity, and immune response modulation [26-28]. Dysbiosis of the gut microbiota is implicated in IBD pathogenesis [29]. This paper discusses the crosstalk between inflammatory hypoxia and gut microbiota in the context of IBD pathogenesis.

Physiological Hypoxia (Physioxia) in Gut

Tissues experience their own unique 'normoxia' under physiological conditions, known as 'physioxia', which is lower than atmospheric partial Oxygen pressure (pO2) but not indicative of oxygen insufficiency [30]. Conversely, in pathological states like inflammation and cancer, tissues exhibit markedly reduced pO2 levels, termed 'hypoxia', due to increased oxygen consumption or impaired tissue oxygenation [30]. Low oxygen tension serves as a potent signaling molecule that regulates stem cell proliferation and differentiation during early developmental stages [31]. Given that the gut epithelium constitutes a continuously renewing tissue, originating from stem cells within a progenitor pool throughout an organism's lifespan, maintaining a low oxygen microenvironment in the gut is crucial physiologically [32].

The unique structural characteristics of the GI tract, including an oxygen-poor lumen juxtaposed with a highly oxygenated subepithelial mucosa, create a steep oxygen gradient across the epithelial layer [1,33]. This feature of physiologic hypoxia is essential for preserving normal gut homeostasis [34].

At the cellular level within the intestine, Hypoxia-Inducible Factor (HIF) regulates genes that facilitate adaptation to low oxygen levels [35-41], playing critical roles in immune modulation and maintaining epithelial barrier function [42,43]. Key members of the HIF family, such as HIF1 and HIF2, exhibit differential regulation of hypoxia-induced gene expression across various cell types [44]. The expression of HIF1α and HIF1α-dependent genes is pivotal for maintaining gut physioxia and gastrointestinal homeostasis [45,46].

Oxygen Dysregulation and IBD

The GI tract experiences physiological hypoxia, a state associated with persistent low-grade inflammation. Within this context, the epithelial cell layer plays crucial roles in adapting to hypoxic stress and modulating immune responses to inflammation [1]. Reduced oxygen availability in the intestine has been implicated in the pathogenesis of IBD, where hypoxic injury contributes to recurrent epithelial cell damage [47,48]. Factors such as epithelial barrier compromise, bacterial infiltration, immune cell infiltration, vascular damage, and reduced blood flow (colonic ischemia or infarction) can precipitate a decline in oxygen levels, leading to inflammatory hypoxia [49-51]. Conversely, inflammatory hypoxia in the intestine may serve as an environmental trigger for the development of IBD [52].

HIFs can adapt cells to conditions of low oxygen tension and inflammation, and both HIF1α and HIF2α expression are markedly elevated in intestinal epithelial cells of IBD patients [47,52]. Specifically, HIF1α is focal in its expression (in epithelial cells, stromal fibroblasts, and myocytes) in both active ulcerative colitis (UC) and Crohn's Disease (CD), whereas HIF2α is focal in UC and diffuse in CD, with no staining observed in normal intestinal mucosa for HIF2α [47]. HIF1α has been reported to have a protective role in colitis, reducing intestinal inflammation, whereas HIF2α exacerbates colitis and promotes massive intestinal inflammation [15,53]. However, conflicting findings suggest that HIF1α expression may augment inflammation in the proximal colon of sulindac-treated mice [54]. In a model of Dextran Sulfate Sodium (DSS)-induced colitis, HIF1a expression increases significantly in atrophic crypts during injury phase and subsequently decreases in hypertrophic crypts during the regeneration phase [55].

Interferon-γ (IFN-γ), a key cytokine in IBD pathogenesis, has been shown to increase HIF1α

expression in a time- and dose-dependent manner, while not affecting the expression of HIF1β/ARNT [56,57]. However, another study indicates that although IFN-γ moderately increases HIF1α mRNA expression in intestinal epithelial cells, it attenuates overall HIF activity, selectively repressing HIF1β in a JAK-dependent manner [58].

Hypoxia also involves nuclear factor-κB (NF-κB) as another transcription factor, and IKK/NF-κB signaling in intestinal epithelial cells is closely associated with maintaining gut epithelial integrity and immune homeostasis [59]. HIF1α has been shown to activate NF-κB, which in turn controls HIF1α transcription. IKK-β, a promoter of NF-κB, is critical for the optimal accumulation of HIF1α, but not HIF2α [60]. Additionally, the IFN-γ-induced increase in HIF1α is associated with NF-κB activation [57].

The claudin family of multigene transmembrane proteins, comprising more than 27 members, is predominantly located in intestinal epithelia and has been extensively investigated for its contributions to IBD pathogenesis [61]. Elevated expression of claudin-1 and claudin-2 is observed in active IBD and correlates positively with inflammatory activity [62,63]. Claudin-1, regulated by HIF1α, HIF2α, and HIF1β, serves as a target of HIF in the context of IBD [64].

Figure 1 illustrates the elevation of HIF1α, HIF2α, and HIF1β in IBD, with Claudin-1 identified as a prominent HIF target. The positive correlation between HIF1α and NF-κB plays a critical role in the pathogenesis of IBD, and IFN-γ activates both HIF1α and NF-κB pathways.

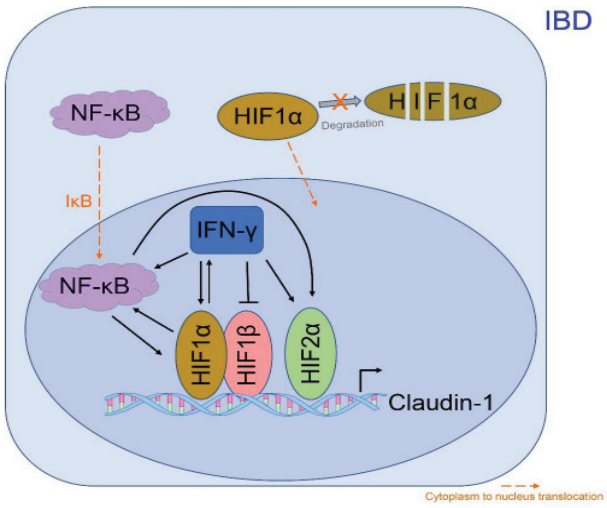

Figure 1 HIF and NF-κB signaling in IBD.

Gut Microbiota and Physioxia

The gut harbors a diverse array of microorganisms, including bacteria, yeast, viruses, and others, collectively known as gut microbiota, which serve crucial physiological roles such as regulating epithelial barrier function and immune homeostasis [65]. A healthy gut microbiota is characterized by a balanced composition of aerobic, facultative anaerobic, and obligate anaerobic bacteria. Particularly, obligate anaerobes predominate within the gut microbiota, actively reducing oxygen and nitrate levels to inhibit the proliferation of aerobic and facultative anaerobic species [66]. Both aerobic and facultative anaerobic bacteria contribute significantly to the establishment of an anaerobic environment [67]. Research on neonatal gut microbiota reveals that initial colonization by aerobic and facultative anaerobic bacteria consumes luminal oxygen, thereby facilitating the growth of obligate anaerobes [68,69]. Moreover, the microbiota in the distal gut, compared to the proximal gut, enhances microbial respiration and utilizes oxygen through processes such as lipid oxidation reactions, thereby reducing luminal oxygen availability [70].

Additionally, short-chain fatty acids, particularly butyrate, derived from microbial fermentation of dietary fibers, serve as a primary energy source for intestinal epithelial cells. During epithelial cell metabolism, butyrate enters mitochondrial fatty acid oxidation and undergoes Oxidative Phosphorylation (OXPHOS). This process consumes oxygen, leading to epithelial deoxygenation, which promotes the growth of beneficial anaerobic microbiota and reinforces epithelial barrier integrity [71-73]. Interestingly, recent studies highlight that butyrate stabilizes Hypoxia-Inducible Factor (HIF) in the anoxic gut lumen by inhibiting HIF Prolyl Hydroxylases (PHDs), enzymes responsible for HIF degradation under normoxic conditions [74-76].

Gut Microbiota and Inflammatory Hypoxia in IBD

The gut microbiota maintains a dynamic equilibrium critical for immune function, nutrient absorption, and maintaining a healthy epithelial barrier. Disruption of this balance can lead to the proliferation of opportunistic pathogens. For instance, under certain conditions, intestinal pathogens like C. rodentium can induce a glycolytic

shift in intestinal epithelial cells, promoting epithelial re-oxygenation- a microenvironment conducive to pathogen growth [73]. Conversely, severe hypoxia in the gut due to inflammatory cell infiltration and elevated pro-inflammatory factors alters the gut microbiota composition, exacerbating hypoxic injury [77].

IBD is characterized by chronic immune responses triggered by microbial antigens [17,78]. Dysbiosis, observed in both CD and UC, varies in microbial alterations influenced by factors such as diet, ethnicity, age, and disease severity indices. Generally, studies indicate significant increases in facultative anaerobic bacteria like the Fusobacteria phylum and Enterobacteria group (especially Escherichia coli) in fecal samples of CD patients [79,80]. Conversely, obligate anaerobic bacteria such as Ruminococcus torques, Roseburia inulinivorans, Blautia faecis, Clostridium lavalense, and the Clostridium leptum group, including Faecalibacterium prausnitzii, are reduced in CD, despite an increase in the obligate anaerobic Fusobacteria phylum [81-85]. In UC, which exhibits a higher rate of bacterial translocation across the intestinal epithelium, there is an increase in aerotolerant bacteria like Desulfovibrio, while anaerobic bacteria such as the Clostridium coccoides group, Faecalibacterium prausnitzii, and Akkermansia muciniphila are decreased [85,86]. Notably, Faecalibacterium prausnitzii, an important butyrate producer in the gut, shows increased levels during UC remission periods [87]. Some researchers propose that the increased presence of facultatively anaerobic species and decreased obligately anaerobic organisms in IBD could stem from heightened oxygen concentrations in the gut lumen due to increased blood flow during inflammation [17] - a hypothesis conflicting with most studies that demonstrate severe hypoxia in IBD tissues. Measurements of colon and ileum blood flow in IBD patients indicate significant elevation in severe UC cases but a marked decrease in mild colitis (by 25-30%). Conversely, CD patients exhibit near-normal ileal blood flow in early exudative stages, which sharply decreases in late fibrosing stages (by 60-70%) [88]. Similar findings are observed in an animal model of chronic intestinal inflammation initiated by naïve T-lymphocyte subsets, mimicking IBD, which shows reduced blood flow during mild inflammation [89]. Moreover, intestinal fibrosis - a common complication in chronic IBD, especially CD - is influenced by hypoxia, impacting both intestinal inflammation and fibrosis progression [90,91]. Notably, controlling inflammation alone does not prevent fibrosis progression in CD, as gut microbiota also triggers pro-fibrotic processes alongside inflammatory responses [92-95].

In summary, during early severe stages of IBD, disruptions in the intestinal wall oxygen gradient due to epithelial barrier damage and increased blood flow lead to microbiota dysbiosis, including increased facultatively anaerobic species and pathogens. Facultatively anaerobic species consume oxygen, while pathogens invade damaged intestinal walls and exacerbate oxygen depletion. Bacterial metabolites further exacerbate inflammation, leading to immune cell infiltration and increased oxygen consumption. In later stages, microvascular occlusion and thrombosis further diminish blood flow, aggravating hypoxia (Figure 2).

Interestingly, research indicates that mucosal microbiota, enriched with aerotolerant and asaccharolytic bacteria, differs significantly from fecal microbiota in healthy human intestines [28]. Mucosal microbiota dysbiosis is closely associated with IBD pathology, with mucosal-associated bacteria reflecting clinical UC outcomes to some extent, as observed in colon mucosal biopsy studies [96].

Crosstalk Between Gut Microbiota and Inflammatory Hypoxia in IBD

Microbiota and HIF crosstalk has been demonstrated to defend tissue barrier, and depletion of the microbiota using antibiotics reduces HIF expression [72]. Hypoxia and HIF-1 are recognized as key regulators in the interplay between gut microbiota and host interactions, influencing inflammation and infectious conditions in both human and murine intestinal cells [42,97]. NF-kB is a validated therapeutic target in IBD, and certain "anti-inflammatory" gut bacteria such as Faecalibacterium prausnitzii A2-165 and other Firmicutes isolates produce peptides that inhibit NF-kB signaling both in vitro and in vivo, stabilizing the IKK complex [98,99]. Given that epithelial cell hypoxic responses are dependent on microbiota metabolites, questions persist regarding the interplay between microbiota and HIF-2α in the progression of IBD [72,100].

There are three distinct types of IFNs: type I (primarily IFN-α/β), type II (IFN-γ), and type III (IFN-λs). Type II IFN/IFN-γ, a pivotal cytokine in IBD pathogenesis, plays a crucial role in combating bacterial infections, while type I and type III IFNs are associated with antiviral defenses [56,101]. In

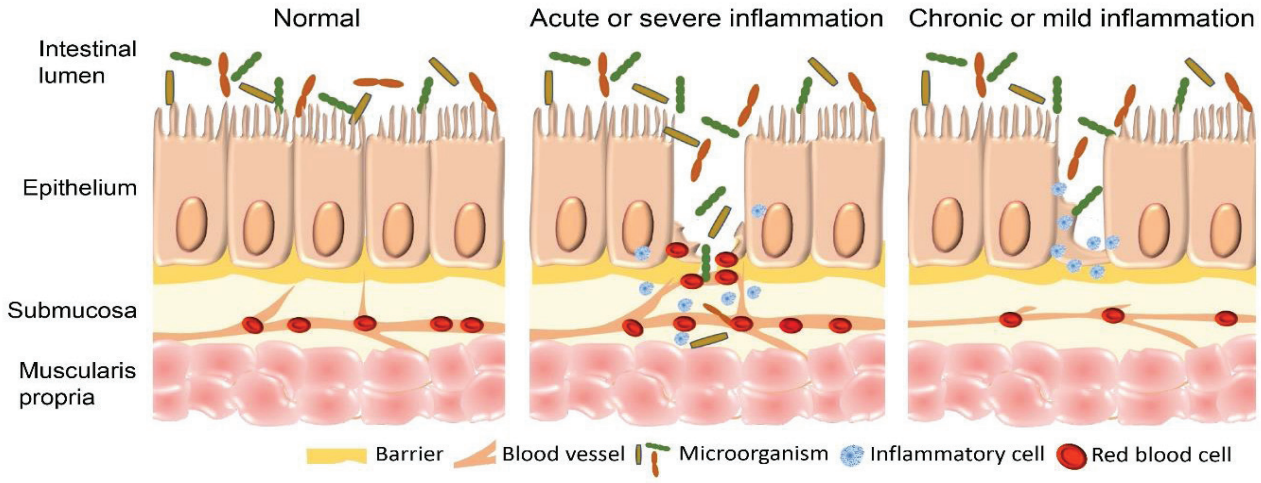

Figure 2 Gut microbiota and inflammatory hypoxia in IBD. Left panel: normal microbiota and intestinal epithelial barrier; middle panel: microbiota and inflammation in acute or severe IBD; right panel: microbiota and inflammation in chronic or mild IBD.

a DSS model of acute intestinal injury lacking both type I and III IFN receptors, mice exhibited enhanced barrier disruption, extensive loss of goblet cells, and reduced epithelial cell proliferation, highlighting the role of these IFN types in mucosal barrier homeostasis in the gastrointestinal tract [101]. Immunoregulatory therapy involving type I IFN has been shown to inhibit IFN-γ and increase interleukin-10 (IL-10) production, emphasizing its role in modulating inflammatory responses [102]. HIF1α has been reported to suppress type I IFN, however, it serves as a key mediator of IFN-γ-dependent gene expression, leading to the release of inflammatory program [103,104].

Active IBD tissues are characterized by infiltration of innate immune cells (e.g., macrophages, dendritic cells) and adaptive immune cells (T and B cells). Effector CD4+ T cells play a pivotal role in pathogen defense, while regulatory T cells (Treg) are crucial in limiting excessive immune responses and CD4+ and CD8+ T cell activities [105]. Dysregulation of these T cell subsets contributes to IBD pathogenesis [106-109]. The gut microbiota directly influences inflammation in models of T cell transfer-induced colitis [110]. γδ T cells, which express γ and δ chains in their T Cell Receptors (TCRs), act as a bridge between innate and adaptive immune responses. In chronic IBD, Vδ2 T cells exhibit a proinflammatory profile [77,111]. In a model of hypoxia-induced intestinal injury, alterations in gut microbiota exacerbated intestinal damage, which was significantly ameliorated following antibiotic-mediated microbiota depletion. Additionally, microbiota-derived metabolites exacerbate hypoxic injury via γδ T cells, highlighting the intricate interactions between microbiota, inflammatory hypoxia, and immune cells in IBD [77]. These findings underscore the complex nature of these interactions and their potential implications for understanding and treating IBD.

Conclusions and Outlook

The influence of gut microbiota on various aspects of IBD has garnered significant attention, yet the dynamic mechanisms underlying its pathogenesis remain incompletely understood. Microbiota, along with environmental factors such as oxygen levels, blood flow, and immune responses, intricately regulate intestinal epithelial barrier function. Dysregulation or imbalance among these factors can lead to epithelial damage, exacerbating or triggering IBD.

Currently, many aspects of IBD pathophysiology remain elusive or controversial. For instance, while there is consensus on the disruption of the oxygen gradient across the intestinal wall in IBD, conflicting findings exist regarding luminal oxygen levels—some studies report increased oxygen due to enhanced blood flow, whereas others observe severe hypoxia within the intestinal wall alongside reduced vascular perfusion. We hypothesize that these discrepancies stem from differences in disease progression stages and the dynamic nature of IBD. Conducting longitudinal studies to track oxygen levels at various stages of IBD would help determine how luminal oxygen and tissue hypoxia evolve as the disease progresses and identify any stage-specific patterns, using consistent methods across studies.

Pharmacological interventions targeting HIFs, such as PHD inhibitors or HIF inhibitors, have shown promise in preclinical models of IBD [53,76,100,112,113]. However, the role of HIFs in IBD is complex: while they protect the epithelial barrier under physiological conditions, they can also increase barrier permeability and promote pro-inflammatory cytokine production under pathological conditions [112,114].

Blood flow measurements in IBD patients reveal distinct patterns between UC and CD, reflecting their different clinical manifestations-CD typically involves full-thickness inflammation, while UC primarily affects mucosal and submucosal layers. We propose that inflammatory hypoxia may play distinct roles in UC and CD, warranting further investigation.

Given the reported dysbiosis of gut microbiota in IBD, it is evident that UC and CD represent distinct disease entities with unique microbial perturbations. Variations in microbiota analyses across studies underscore the challenges in utilizing microbiota-directed therapies, such as antibiotics and fecal transplantation, in clinical practice [115]. Understanding the bidirectional relationship between mucosal hypoxic responses and microbiota dynamics requires more nuanced and condition-specific investigations.

HBOT has shown variable efficacy in CD and UC, highlighting the need for tailored approaches in clinical management [18, 21,22]. Dysbiosis-induced inflammatory cell infiltration further complicates the intestinal environment by consuming oxygen and altering microbial community dynamics. Novel therapeutic avenues targeting immunological pathways in IBD have been explored, yet current pharmacological treatments often exhibit limited efficacy and significant side effects. Promising therapeutic strategies targeting T cell effector cytokines and immune-regulating pathways require further refinement and evaluation in the context of precise IBD staging, integrating factors such as oxygen dynamics and microbiota composition [116-119]. Understanding how these treatments modify the oxygen gradient can inform better management strategies for IBD.

Conclusion

In conclusion, advancing our understanding of hypoxia and HIFs in the development and progression of IBD, alongside elucidating the complex interplay with gut microbiota, holds promise for developing more effective and safer therapies. Rigorous investigation into these interconnected mechanisms will pave the way for personalized treatments that improve outcomes for patients with IBD.

Acknowledgment

F.G. received support from the National Institutes of Health (NIH) grant R01 DK126827 (Tamas Ordog), a Pilot and Feasibility award from the Mayo Clinic Center for Cell Signaling in Gastroenterology (NIH P30 DK084567; Nicholas F. LaRusso), and American Neurogastroenterology and Motility Society (ANMS) Discovery Grants (2021).

Conflicts of Interest

The authors declare no conflicts of interest.

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How to cite this article: Jing B, Gao F. Crosstalk between Inflammatory Hypoxia and Gut Microbiota in Inflammatory Bowel Disease (IBD). J Biomed Res Environ Sci. 2024 Jul 24; 5(7): 822-833. doi: 10.37871/jbres1960, Article ID: JBRES1960, Available at: https://www.jelsciences.com/articles/jbres1960.pdf