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Review Article

Review Article

Hypoxia, hypoxia-inducible factors and inflammatory bowel diseases

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Abstract

Adequate oxygen supply is essential for maintaining the body's normal physiological function. In chronic inflammatory conditions such as inflammatory bowel disease (IBD), insufficient oxygen reaching the intestine triggers the regulatory system in response to environmental changes. However, the pathogenesis of IBD is still under investigation. Recent research has highlighted the significant role of hypoxia in IBD, particularly the involvement of hypoxia-inducible factors (HIF) and their regulatory mechanisms, making them promising therapeutic targets for IBD. This review will delve into the role of hypoxia, HIF, and the associated hypoxia-inflammatory microenvironment in the context of IBD. Potential interventions for addressing these challenging gastrointestinal inflammatory diseases will also be discussed within this framework.

Keywords: hypoxia; hypoxia-inducible factor; inflammatory bowel disease; Crohn's disease; ulcerative colitis

Introduction

Crohn's disease (CD) is characterized by transmural inflammation and skip lesions, which are distributed from the mouth to the anus, whereas ulcerative colitis (UC) is generally a luminal inflammatory disease with continuous inflammation limited to the colon [1]. Although the etiology of inflammatory bowel disease (IBD) remains unclear, the most widely held hypothesis is that exaggerated aggressive acquired (T-cell) immune responses to a subset of commensal enteric bacteria occur in genetically susceptible hosts [2]. IBD is a complex disease characterized by persistent infection, dysbiosis (an abnormal ratio of beneficial to detrimental commensal microbial agents), defective mucosal barrier function, defective microbial clearance, and aberrant immunoregulation in the hypoxic-inflammatory gastrointestinal microenvironment. Hypoxia is a pathological process in which the supply of oxygen to tissues in various parts of the body is insufficient or not fully utilized, resulting in abnormal tissue metabolism and impaired function. Hypoxia-inducible factors (HIFs) are core regulators of the body's adaptation to a hypoxic environment and are pivotal for maintaining homeostasis in the body's internal environment [3]. Many studies have shown that hypoxia is associated with numerous diseases, such as cancer [4], chronic kidney disease [5], coronary heart disease [6], and diabetes [7]. An increasing amount of evidence suggests that hypoxia exacerbates intestinal inflammatory damage and that HIFs play an important role in this pathological process [8]. Here, we discussed the roles of hypoxia and HIFs in IBD and suggested new approaches for the treatment of IBD.

Hypoxia and IBD

Hypoxia is defined as a reduction in O_2 tension below critical values. Ischemia results from insufficient arterial perfusion of tissues, resulting in hypoxia, decreased oxidative phosphorylation, and ATP depletion. Hypoxia/ischemia is dangerous; therefore, several pathways are critical for the cell/tissue response to hypoxia/ischemia, including the generation of reactive oxygen species (ROS) [9], disruption of Ca^{2+} homeostasis [10], hypoxia-inducible factors [11], unfolded protein response following endoplasmic reticulum stress [12], and inflammation (at the organ level).

ROS are highly bioactive and participate in several biochemical processes. They act as secondary messengers in signal transduction and gene regulation [13]. When ROS levels exceed the cellular antioxidant capacity, oxidative stress is induced. ROS rapidly increases following hypoxia, mainly due to insufficient oxygen in the mitochondria to accept the available electrons [14]. ROS mediates cell damage, activates 5' adenosine monophosphate-activated protein kinase and pancreatic endoplasmic reticulum kinase-like

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endoplasmic reticulum kinase, and increases the levels of hypoxia-inducible factor (HIF)-1 and nuclear factor κB (NF-κB) [15]. Activate 5' adenosine monophosphate-activated protein kinase plays a role in glucose uptake and glycolysis and activates HIF-1; HIF-1 plays a role in transcription, translation, and stability [16]; NF-κB induces cytokines, chemokines, and HIF-1 [17]; and protein kinase RNA-like ER kinase induces unfolded protein response and inhibits protein synthesis [18]. An increase in free cytosolic Ca^{2+} is a general mediator of cell death. Hypoxia is associated with the influx of extracellular Ca^{2+}. Increased cytosolic Ca^{2+} in hypoxia is caused by increased influx, release of Ca^{2+} in mitochondria, and decreased Ca^{2+} efflux secondary to ATP depletion. A critical link exists between ROS generation and Ca^{2+}. In mitochondria, Ca^{2+} accumulation is associated with ROS generation. In addition, AMP accumulates when ATP is depleted and is an early and sensitive indicator of metabolic deficiency.

Inhibition of protein synthesis is a common adaptation employed by hypoxic cells to survive O_2/ATP depletion [19]. The initial decrease is mediated by activation of the unfolded protein response, a set of pathways activated in response to endoplasmic reticulum stress [12, 20]. Unfolded protein response is activated by Ca^{2+} depletion in the endoplasmic reticulum or by the depletion of ATP. Activation of the endoplasmic reticulum transmembrane protein pancreatic endoplasmic reticulum kinase-like endoplasmic reticulum kinase is mediated by ROS. Hypoxia also inhibits the mechanistic target of rapamycin activation, thereby halting protein synthesis [21]. Due to increased metabolic activity and disrupted perfusion at sites of inflammation, hypoxia also contributes to inflammation through the regulation of gene expression via key oxygen-sensitive transcriptional regulators, including HIF and NF-κB [22]. It has been suggested that the effects of NF-κB during hypoxia induce a number of cytokines and chemokines and promote the adhesion of inflammatory cells [23]. Peroxisome proliferator-activated receptors (PPARs), including PPARα, PPARβ/δ, and PPARγ, are nuclear hormone receptor superfamily members [24, 25]. PPARα and PPARγ agonists inhibit iNOS and TNF-α, while negatively regulating NF-κB [26].

The intestinal mucosa actively participates as an innate immune sensor against microbial pathogens and commensal organisms. It undergoes multiple large fluctuations in blood perfusion and metabolism daily with a dynamic oxygenation profile [27]. Because of the high energy requirements of the gastrointestinal tract and the integral role of the epithelium in maintaining intestinal homeostasis, these cells have evolved many molecular mechanisms to match the challenging metabolic conditions [28, 29]. Furthermore, the intestinal epithelium is remarkably resistant to hypoxia, and the lower levels of oxygen within this cell layer can be altered to regulate mucosal integrity and barrier function. During active mucosal inflammation, nutrients and local oxygen are rapidly depleted, resulting in hypoxia, hypoglycemia, lactate accumulation, and acidosis [30]. Gut bacteria are critical for intestinal immunity. IL-22 is an important anti-inflammatory cytokine in the gut. Yang *et al.* [31] found that microbiota-derived short-chain fatty acids promote IL-22 production to maintain intestinal homeostasis. Another study reported that intestinal ischemia/reperfusion injury induces gut microbial alterations, such as an increase in the relative abundance of *Bacteroidetes* and *Firmicutes*, leading to epithelial damage [32]. It has recently been shown that melatonin can alleviate chronic intermittent hypoxia-induced intestinal barrier dysfunction by regulating flora dysbiosis [33].

Inflammatory mucosal lesions observed in mouse models of colitis are highly hypoxic or anoxic. Moreover, additional data indicate that microvascular deficits in inflammatory bowel disease (IBD) may cause mucosal hypoxia [34]. Based on available evidence, integration of intestinal epithelial and mucosal immune cells within the hypoxic inflammatory microenvironment, and the effect of hypoxia and HIF signaling on immune cell metabolism and effector function in IBD seem to be probable mechanisms [35, 36]. ROS, nitric oxide (NO), NF-κB, and cytokines in immune cell and microenvironment are also major players [37–39].

HIF-transcriptional regulators in response to hypoxia in IBD

Hypoxia-inducible factor (HIF) is a member of the Per-ARNT-Sim family of basic helix-loop-helix transcription factors that bind to hypoxia response elements at target gene loci under hypoxic conditions [40]. They are heterodimers, consisting of HIF-α (hypoxia-inducible α component) and HIF-β (constitutive subunit). The stabilization of the α-subunit is regulated by a family of oxygen and iron-dependent prolyl hydroxylases and asparaginyl hydroxylase [41, 42]. Three α-subunits have been identified and characterized: HIF-1α, HIF-2α, and HIF-3α [43]. Although there is a high level of conserved sequence homology between HIF-1α and HIF-2α, HIF-1 and HIF-2 have non-redundant functions in genetic mouse models, despite their concurrent expression in many cell types, including intestinal epithelial cells [44]. For example, transcriptional regulation of genes encoding glycolytic enzymes appears to be more specifically mediated by HIF-1 [45], whereas HIF-2 selectively regulates the gene expression of factors involved in iron homeostasis and early erythropoiesis [46].

HIF has a protective role in promoting intestinal epithelial barrier function in IBD

HIF-1 is expressed focally (epithelial cells, stromal fibroblasts, and myocytes) in both UC and CD, whereas HIF-2α is expressed focally in UC and diffusely in CD. The role of hypoxia in the pathogenesis of UC is different from that in CD. Crawling fat is a specific feature of CD. Inhibition of HIF-1α was found to alleviate adipose tissue fibrosis in mice models of CD; however, the exact mechanism is not clear [47]. It has also been reported that the deleterious effects of hypoxia on T helper 17 cells (Th17) in CD can be ameliorated by inhibiting HIF-1α [48]. However, it has also been shown that hypoxia reduces intestinal inflammation in CD by inhibiting the mechanistic target of the rapamycin/NLRP3 pathway and promoting autophagy [49]. A recent study showed that hypoxia enhances the pathogenicity of Th1 and Th17 cells and increases intestinal inflammation in mice models of UC [50]. Xue *et al.* [51] discovered that vitamin D signaling prevents colitis by inhibiting HIF-1 activation in colonic epithelial cells. In conclusion, hypoxia appears to have two opposite effects, detrimental or protective, depending on the circumstances. However, for the time being, hypoxia is considered the most damaging element. Hypoxia-inducible factors play various roles in UC and CD owing to their distinct pathogenic characteristics.

HIF-regulated signaling promotes overall tissue integrity, influencing functions that range from increased mucin production [52] by intestinal trefoil factor [53], to xenobiotic clearance by P-glycoprotein, to nucleotide metabolism by 5'-ectonucleotidase (CD73) [54], and nucleotide signaling through the adenosine A_2B receptor [55].

HIF-1 induces the integrin β_1 subunit, which regulates fibroblast contraction, epithelial migration, and mediates restoration of the damaged mucosal barrier [56]. Experiments using a chemical model of colitis revealed that the loss of HIF-1 correlated with

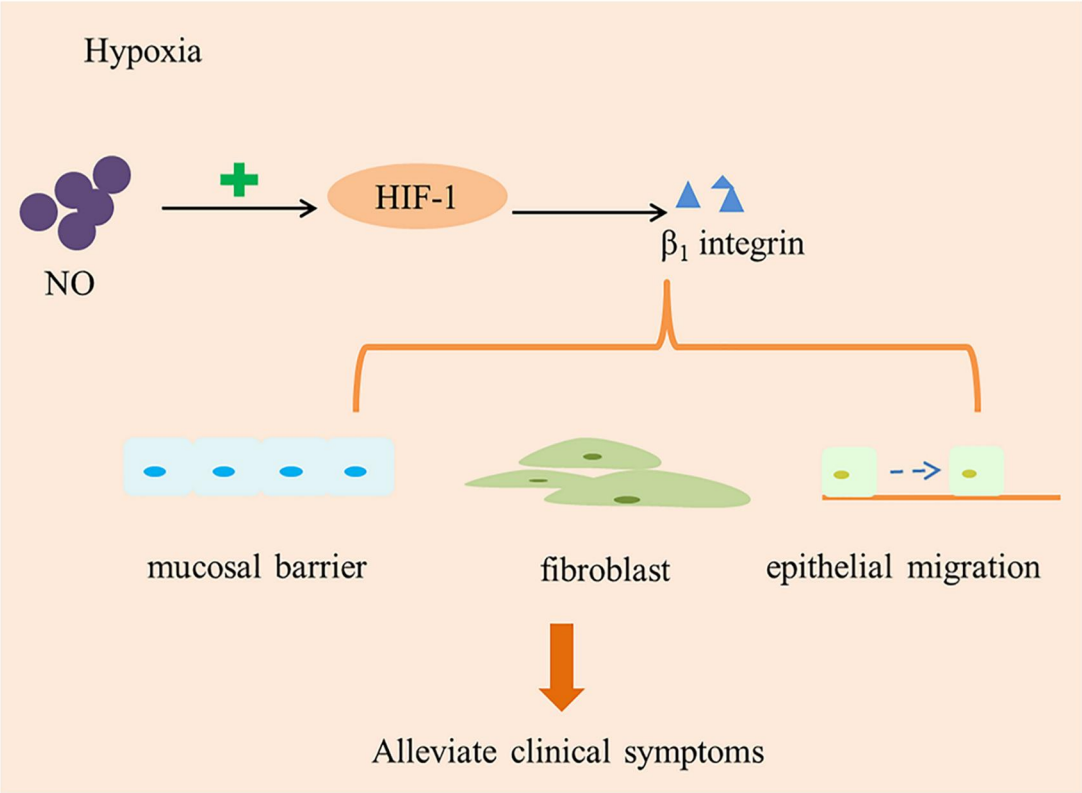

Figure 1. Summary diagram of the protective role of HIF-1 in IBD. NO enhances HIF-1 synthesis and hence integrin β_1 subunit production in hypoxic environments, which regulate fibroblast contraction, and epithelial migration and mediate restitution of the mucosal barrier. HIF-1 = hypoxia-inducible factor-1; IBD = Inflammatory bowel diseases; NO = nitric oxide.

more severe clinical symptoms, including intestinal epithelial permeability [57]. Nitric oxide synthase inhibitors attenuate HIF-1 stabilization and accumulation. The induction of nitric oxide synthase by pro-inflammatory cytokines may contribute to the protection of the mucosal barrier (Figure 1). The overall role of HIF-1 in epithelial wound responses is complex and variable, and is associated with nitric oxide (NO) signaling and pre-existing O_2 conditions. HIF-2α regulates duodenal iron uptake through the apical iron uptake pathway, via discrete regulation of Duodenal cytochrome b (Dcytb) and divalent metal transporter 1 (DMT1), rather than via basolateral iron transport [58].

HIF regulates inflammatory response of immune cells in IBD by nitric oxide

Naïve T cells activated by antigen-presenting cells can be differentiated into at least four major types: Th1, Th2, Th17, and inducible regulatory T cells. HIF-1 is associated with Th1, and Th17, whereas HIF-2 is associated with Th2 and regulatory T cells (Figure 2). Increased synthesis of NO by the induction and activation of nitric oxide synthase is a common hallmark of inflammatory diseases, including IBD.

Nitric oxide (NO) is a versatile mediator of inflammatory immune responses. Owing to its considerable similarities to O_2, NO also interferes with O_2 distribution, and senses and regulates the HIF downstream signaling pathways. NO can affect HIF-1 functions at multiple levels through various mechanisms [59]. Many studies have indicated that these regulatory networks of NO are complex and depend on the local NO concentration, variable effects of different NO metabolites or bioactive forms, and oxygen availability. NO can readily react with iron in proteins because it can inhibit prolyl hydroxylases by coordinating its non-heme Fe^{2+} and thereby stabilize HIF. NO and related reactive nitrogen species are involved in these activation mechanisms. Within the range of biological partial arterial oxygen pressure (P_aO_2) (20–70 mmHg), biological NO can be produced by nitric oxide synthase. It reveals that the ability of nitric oxide synthase to affect HIF-1 activation is greater during relative normoxic conditions and may be diminished during hypoxia. Under hypoxic conditions, NO readily interacts with cytochrome C oxidase, modulates its activity, and decreases O_2 consumption [60]. When O2 concentrations are low and cytochrome C oxidase levels are reduced, competitive binding of NO inhibits cytochrome C oxidase activity, resulting in decreased consumption and redistribution of cellular O_2, leading to increased O_2 availability for prolyl hydroxylation of HIF-1α.

In addition to NO, it has also been reported that carbon dioxide and carbon monoxide modulate the production of hypoxia-inducible factors. It has been shown that high carbon dioxide concentrations counter-regulate HIF pathway activation by lowering intracellular pH and promoting lysosomal degradation of the HIF-α subunit [61]. Further, carbon monoxide promotes the expression of HIF-1α [62].

HIF-1-mediated inflammatory response in myeloid cells

Myeloid cells such as neutrophils and macrophages are recruited to inflammatory sites and act as the front line of defense during immune responses. Upon arrival at the inflammatory site, they facilitate microbial killing through the release of antimicrobial peptides and granule proteases, production of reactive oxygen species/reactive nitrogen species, and phagocytosis. Through the release of pro-inflammatory cytokines [63, 64], macrophages recruit more cells to the inflammatory site and, together with

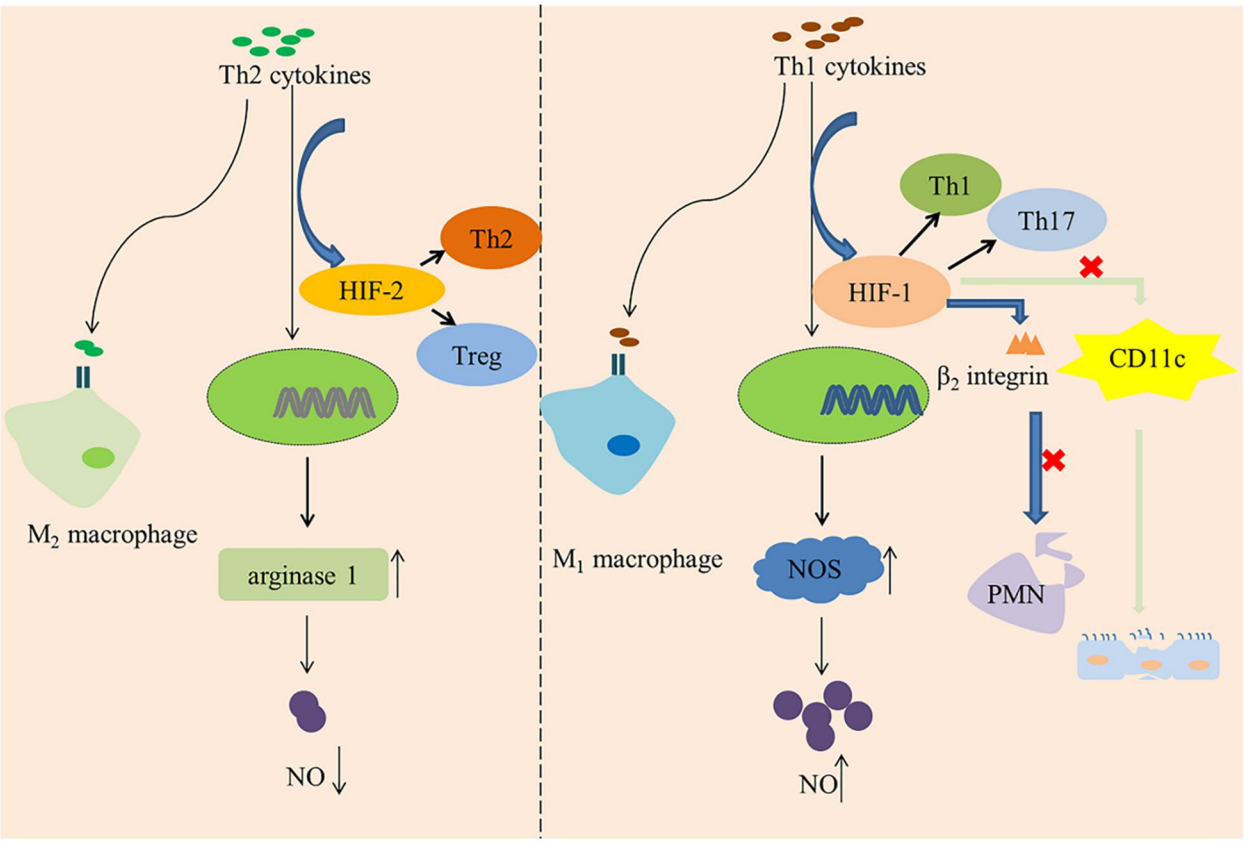

Figure 2. Schematic diagram of the interaction between HIFs and immune cells. M_1 macrophages respond primarily to Th1 cytokines, while the induction of HIF-1α by Th1 cytokines mediates the upregulation of NOS, resulting in increased NO synthesis. M_2 macrophages respond to Th2 cytokines, while the induction of HIF-2 by Th2 cytokines mediates the upregulation of arginase 1, resulting in decreased NO synthesis. HIF-1 is associated with Th1 and Th17; HIF-2 is associated with Th2 and Treg. HIF-1α knockout reduces DC marker CD11c expression, exacerbating intestinal damage. HIF-1 could induce β_2 integrin, inhibiting neutrophil apoptosis. CD11c, integrin alpha X; DC, dendritic cell; HIF, hypoxia-inducible factor; NO, nitric oxide; NOS, nitric oxide synthase; PMN, polymorphonuclear leukocytes; Th1, T-helper 1 cells; Th2, T-helper 2 cells; Th17, T-helper 17 cells; Treg, regulatory T cell.

dendritic cells, participate in antigen presentation, which plays an important role in connecting innate and adaptive immune responses. As mentioned above, inflammatory sites also present the additional challenge of hypoxia; therefore, myeloid cells recruited to these sites must adapt to survive in hypoxia-inflammatory microenvironments.

HIF-1 could widely impact myeloid cell functions [65], including glycolysis, recruitment, migration, phagocytosis, cytokine secretion, neutrophil expression of the anti-microbial molecules (cathepsin G, cathelicidin-related antimicrobial peptide, and neutrophil elastase), and induction of β_2 integrin, which promotes neutrophil epithelial binding and inhibits neutrophil apoptosis (Figure 2). Additionally, dendritic cells play an important role in maintaining intestinal immunity and clearing pathogens. In patients with IBD, the number of dendritic cells in injured intestinal tissue increases, secreting large amounts of inflammatory factors and compromising the intestinal mucosal barrier [66]. Flück *et al.* [67] claimed that HIF-1 promoted gene expression in dendritic cells. In mice with dextran sulfate sodium-induced colitis, knocking down HIF-1 in dendritic cells resulted in a considerably greater loss of body weight and more severe intestinal inflammation with elevated levels of proinflammatory cytokines than in control mice [67]. However, Bäcker *et al.* [68] found that the knockdown of myeloid cell HIF-1α ameliorates the acute pathology in dextran sulfate sodium-induced colitis, and reduced markers for dendritic cells. I believe that the underlying differences should be further investigated.

Interaction between HIFs and nitric oxide in macrophage

The dynamic crosstalk between nitric oxide (NO) and hypoxia signaling has been extensively studied. Recent studies have indicated diverse roles for HIF in macrophage polarization and NO homeostasis [69]. M_1 macrophages respond primarily to Th1 cytokines, whereas M_2 macrophages respond to Th2 cytokines. While induction of HIF-1α by Th1 cytokines was found to mediate upregulation of nitric oxide synthase, induction of HIF-2 by Th2 cytokines was found to mediate upregulation of arginase 1 (Figure 2).

HIF modulates angiogenesis in IBD

An abnormal microcirculatory system has also been implicated in IBD pathogenesis. A high degree of mucosal vascularization was found in active IBD, which did not support an obvious link between HIF upregulation and prolonged hypoxia of vascular origin. The pathological relevance of HIF-α overexpression in IBD should be examined in relation to the lack of vascular endothelial-derived growth factor (VEGF) reactivity; however, HIF-1α and HIF-2α are inducers of VEGF gene expression [70]. The rather focal expression of HIF-1α in the intestinal mucosal and submucosal cells is compatible with the lack of VEGF upregulation. The diffuse expression of HIF-2α by all cellular components in Crohn's disease (CD), including the muscular layer and serosa,

conforms with an intensively activated HIF-2α, which fails to induce VEGF. Therefore, the disruption of the HIF-2α–VEGF pathway is probably part of the pathogenesis of CD. Unlike CD, overexpression of HIF-2α in UC affects mainly the inflammatory component and not the intestinal cell population. Constantly, although low, VEGF production may be essential to maintain tissue integrity by regulating the delicate balance between proliferation and apoptosis, and is required to facilitate tissue regeneration and repair.

In 2014, Bakirtzi *et al.* [71] found that neurotensin (NT) and its receptor (NTR1) were required for colitis-associated neovascularization. NT signaling promotes HIF-1α stabilization, transcriptional activity, and stimulates VEGFα expression. In addition, they claimed that NT signaling increases miR-210 expression by activating HIF-1α, which plays a crucial role in colitis-induced colonic angiogenesis [72].

Conclusions

The etiologies of IBD are complex and still to be fully elucidated. In this review, we aim to establish the axis of the hypoxic-inflammatory microenvironment to model the pathogenesis of IBD. HIF is known to mediate the hypoxic response. HIF-1α reduces intestinal inflammation and does not increase the risk of colon cancer. Based on the pivotal role of HIF, targeting HIF has become an effective therapeutic strategy for IBD.

Authors' Contributions

F.H. and X.B. drafted the manuscript and designed the figures. D. J. revised the manuscript. H.G. and F.Z. conceived the topic. All authors have read and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare that there are no conflicts of interest in this study.

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