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REVIEW OPEN ACCESS

MiRNA-21 Regulates Multiple Factors in the Pathogenesis of IBD: A Literature Review

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Abstract

Introduction: Inflammatory Bowel Disease (IBD) is characterized by chronic inflammation in the gastrointestinal tract (GIT) via dysbiosis of the gut microbiome and weakening of the epithelial and mucosal barriers. Although the causative nature of IBD remains unknown, several studies have demonstrated that aberrant host-microRNA (miRNA) activity contributes to its pathophysiology. For example, miRNA-21 contributes to IBD through three mechanisms. Firstly, by increasing gut permeability via the ARF4 pathway. Secondly, by decreasing gut mucosal secretions via interfering with host goblet cells. Finally, by regulating proteins that inhibit host autophagy and decreasing immune response via the Phosphatase and Tensin Homolog (PTEN) and Akt pathway.

The proposed study aims to answer the following question: how does aberrant expression of miRNA-21 in IBD contribute to the disease?

Methods: This review highlights and summarizes relevant studies on the miRNA-21 regulation of key pathways in the pathogenesis of IBD. Searches used electronic databases including PubMed, and Google Scholar for keywords such as "Inflammatory bowel disease" and "miRNA-21" and other additional relevant terms from years 2016 to 2022. Review papers that met our criteria and the relevant papers they referenced, regardless of their publication date, were manually searched for. Figures were made in part using KeyNote and Serveir Medical Art.

Discussion: Intracellular pathways contribute to chronic inflammation in IBD such as the PTEN pathway and pro-inflammatory cytokines like TNF-α. These pathways have been shown to influence the mucosal barrier, epithelial barrier, and the immune system in the gut. These pathways are regulated by miRNA-21, demonstrating miRNA-21 as a key regulator in IBD. Both PTEN and TNF-α also contribute to levels of angiogenesis in the gut through the regulation of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF), further demonstrating the intricacies of the miRNA-21 pathway regulation in IBD.

Conclusion: The research highlighted in this review provides insight into the mechanisms of aberrant miRNA expression in IBD. Furthermore, knowledge of such molecular mechanisms has clinical and research applications, including identifying diagnostic biomarkers, less invasive screening techniques, and novel drug therapies.

Keywords: miRNA-21; IBD; CD; UC; PTEN; TNF-α; angiogenesis

Introduction

Inflammatory Bowel Disease (IBD)

Inflammatory Bowel Disease (IBD) is a chronic disease involving relapsing inflammation of the gastrointestinal tract (GIT) [1]. IBD is classified into two forms: ulcerative colitis (UC) and Crohn's disease (CD) [1]. Clinically, both UC and CD present with abdominal pain and diarrhea [2]. UC typically affects the rectum and proximal mucosa, resulting in rectal bleeding, constipation, and tenesmus in patients [3,4]. In contrast, CD results in transmural GIT inflammation anywhere between the mouth and anus manifesting clinically as weight loss, stenosis, abscesses and fistulas [2,5].

IBD was once seen as a disease of the western world but has now affected people in the Middle East, Asia, and South America [6]. IBD typically presents clinically in the second or third decade of life, but patients can also present symptoms between the ages of 40 and 70 [7,8], however, children under the age of 18 contribute to about 25% of cases [2].

IBD and Immunity

The immune system in the GIT consists of gut-associated lymphoid tissue (GALT) which prevents gut inflammation by differentiating pathogenic from beneficial bacteria [9]. To excrete pathogens, pro-inflammatory T helper (Th) cells

induce tissue inflammation causing the host defence mechanism [10,11]. T cell dysregulation can therefore result in chronic inflammation as seen in IBD. GALT Cytotoxic T cells have been found in higher numbers in patients with autoimmune disorders like IBD [12,13].

IBD and Mucosal Barrier

The mucus layer acts as the "first line of defence" in the GIT [14]. It coats the lumen and has two opposing roles: trapping contents of the GIT in a sticky glue-like substance and as a lubricant propelling the intestinal contents distally [14]. The goblet cells are specialized secretory cells, of the epithelial layer which produce gel-forming mucins [15]. Muc2, encoded by the Muc2 gene, is the major mucus protein contributing to the stratification of the mucus layer [16]. The degree of post-transcriptional modifications of MUC2 contributes to the final thickness of the mucus layer [15]. The mucus layer is composed of two layers: the loosely attached outer mucus layer, and the inner mucus layer, tightly bound to the epithelium [17].

In CD, there is a thicker mucus layer which is less functionally active [18] whereas in the context of UC there is a thinner mucus layer resulting in more contact of foreign material with the lumen wall [14]. IBD patients exhibit mucus layer degradation which increases the susceptibility to bacterial invasion while simultaneously altering its permeability [14].

IBD and Microbiome

The GIT harbours a large reservoir of bacteria that allows for the digestion of food and the absorption of nutrients with a multilevel defence system against pathogens [19]. This defence system is comprised of the body's natural immune system, an epithelial barrier, and a mucosal barrier [20].

The microbial flora of the gut varies in both composition and quantity in different areas of the GIT [21]. Microbes are known to provide various health benefits which contribute to the immune system and barrier protection in individuals [21]. The microbiome in IBD patients has an aberrant composition of microbes which promote inflammation such as an increase of Proteobacteria while anti-inflammatory microorganisms are decreased. Genetics and alterations to the gut microbiome can affect the host's immune system and regulatory mechanisms which results in the clinical features listed earlier [1].

IBD and Epithelial Barrier

The epithelial barrier of the gut is a physical barrier of varying permeability to macromolecules [22]. The barrier consists of a brush border lined with finger-like villi allowing for a large surface area functioning to exclude antigenic microbes from passing through into systemic circulation[23]. Tight junction proteins like claudins and occludins also eliminate space between epithelial cells thus maintaining a physical barrier [24].

Relevant Molecular Pathways in IBD

According to Jung H et. al, one of the "most significant" ways in which epithelial barrier defects could result in IBD is related increased barrier permeability [22]. This is likely due to many different cellular signaling pathways (i.e. PTEN/PI3K/Akt pathway (figure 1) and TNF-α signaling (figure 2) regulating the GIT epithelial barrier. Moreover, these pathways are subject to interference via several mechanisms including non-coding RNA (ribonucleic acids) [22]. A particular interest is miRNA-21 (micro-RNA-12) which will be discussed in later sections.

PTEN/PI3k/Akt Pathway

The Phosphatase and tensin homolog (PTEN) / Phosphoinositide 3-kinase (PI3K) / Protein kinase B (Akt) pathway is involved in metabolism, apoptosis, and cellular proliferation [25]. PIK3 is an intracellular kinase, activated upon binding to the intracellular domain of activated membrane receptors, such as receptor tyrosine kinases (RTKs). Activated PIK3 phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) forming phosphatidylinositol 3,4,5-triphosphate (PIP3), an intracellular signaling molecule. PIP3 activates Akt which phosphorylates its downstream targets, leading the cell into a proliferative rather than an apoptotic state [26]. PTEN plays an inhibitory role in this pathway by converting PIP3 back into PIP2 thereby decreasing Akt activation (Figure 1).

Recent studies have demonstrated the link between PTEN and the immune system in immune-resistance cancer progression. This points to PTEN potentially playing a role IBD, possibly contributing to the aberrant regulation of immune response seen [27].

PTEN's effects on the PI3K/Akt pathway result in downstream activity of the Rho-associated protein kinase (ROCK) pathway [28]. RhoA, which is part of a family of GTPases, regulates ROCK [29]. By increasing PTEN activity, the PI3K/Akt pathway is inhibited, which upregulates ROCK activity. Ultimately, PTEN's effects on ROCK impacts cell proliferation levels which can be essential in the development of colitis [30] since ROCK upregulates cytokine responses [28]. ROCK also stimulates myosin-light chain (MLC) phosphorylation and inhibits myosin-light chain phosphatase (MLCP) [31]. Myosin light chain kinase (MLCK) is impacted by MLC phosphorylation and it responds by inducing contractions of perijunctional apical actomyosin rings [32]. Tight junctions in the gastrointestinal tract are bound to these perijunctional actomyosin rings, therefore, increasing ROCK levels and MLC phosphorylation results in greater contraction levels of these rings and breaking down tight junctions (Figure 2). Interestingly, elevated levels of MLCK have been found in patients with colitis suggesting a link to IBD pathology [32].

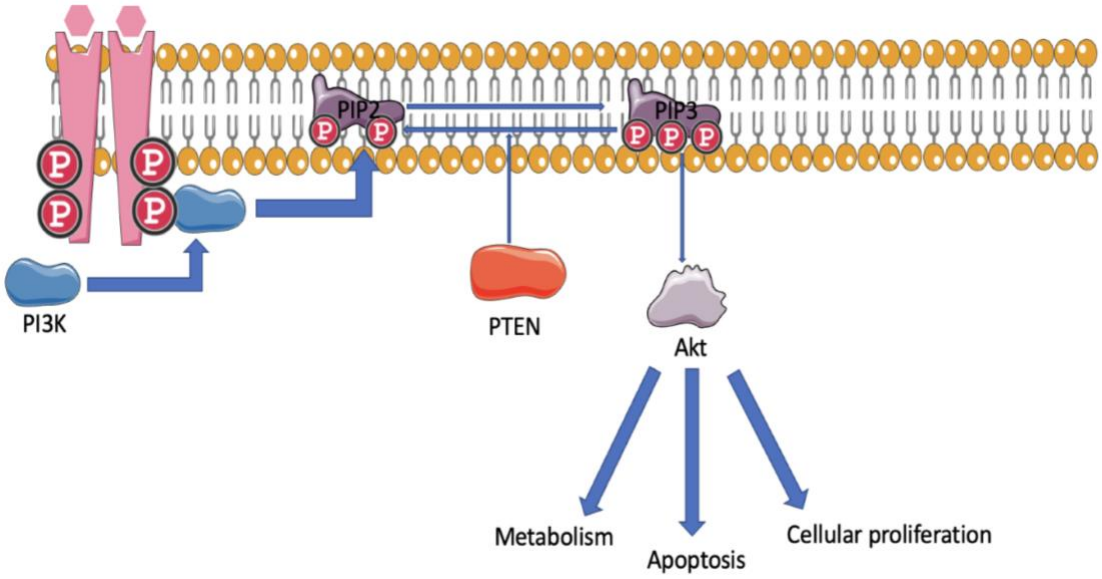

Figure 1. PTEN/PI3K/Akt pathway. Upon binding of an extracellular ligand to membrane receptor tyrosine kinases, there is autophosphorylation of the intracellular tyrosine residues. Intracellular PI3K is activated after binding to these residues where it will then phosphorylates PIP2 forming PIP3 which then results in akt activation thus triggering further downstream cellular responses (such as metabolism, apoptosis, cellular proliferation). PTEN negatively regulates this pathway by promoting the conversion of PIP3 back to PIP2 thereby halting akt activation and further downstream cellular responses. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

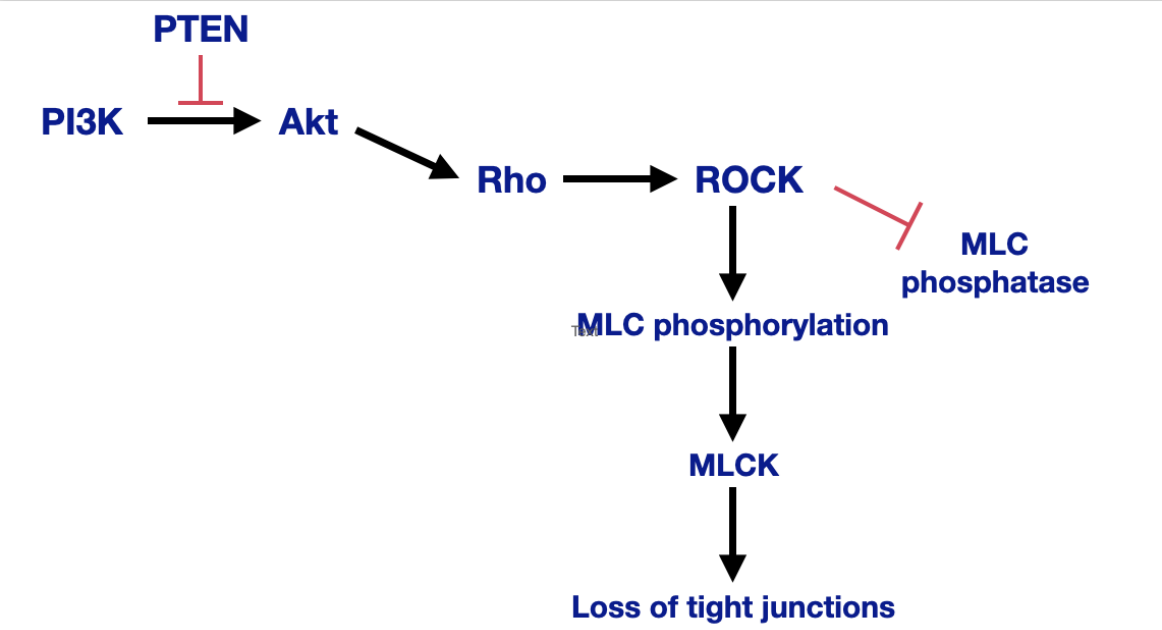

Figure 2. PTEN and the Rho/ROCK pathway. PTEN regulates the ROCK pathway by altering PI3K's ability to produce Akt. As a result, there is a loss of tight junctions in the gut. When the PI3K/Akt pathway is inhibited, the ROCK pathway is up regulated through Rho. ROCK stimulates myosin light chain phosphorylation, increasing myosin light chain kinase and further increasing contractions levels of perijunctional actomyosin rings. Ultimately, this leads to the breakdown of tight junctions. This figure was created with Keynote software.

TNF-α Signaling

Tumour Necrosis Factor-alpha (TNF-α) is a pro-inflammatory cytokine, that is likewise aberrantly regulated in IBD. TNF-α is overexpressed in inflamed colorectal mucosa and stools in UC [33-36]. Cells of monocytic lineage, such as macrophages, are the prominent synthesizers of TNF-α in the body [37].

There are two types of TNF-α receptors TNFR1 (TNF receptor 1), ubiquitously expressed on cells including GIT epithelial cells [38], and TNFR2 (TNF receptor 2), selectively expressed on immune and epithelial cells [39]. When TNF- α binds to a TNFRs on the surface of cells, adaptor proteins are activated resulting in the downstream activation of nuclear factor kappa B (NF- κβ) and Apoptosis protein-1(AP-1). NF- κβ and AP-1 are transcription factors that evoke gene expression of several targets vital for inflammation, cell survival and proliferation [40]. There are also several points of crosstalk within these downstream pathways. For example, the NF-κβ pathway is regulated by other signalling pathways including the Wnt/B-catenin pathway which is dysregulated in IBD [41]. B-catenin blocks NF- κβ DNA binding thereby reducing expression of target genes. However, NF-κβ feeds back into the Wnt/B-catenin pathway, to promote the expression of the B-catenin pathway, ensuing both a positive and negative regulation of the NF-κβ by Wnt/B-catenin (Figure 3).

The regulation of TNF-α is tightly controlled through a variety of mechanisms at the transcription, translation, and protein levels [39]. Importantly, the negative feedback loops controlling the TNF- α are crucial for preventing inflammatory damage during an immune response. TNF-α regulates microRNAs, for example, by inducing miRNA-21 and promoting its downregulation at the translational level in an "autoregulatory" loop [39, 42] (Figure 2).

The discovery of increased serum levels of TNF-α in IBD patients about 30 years ago initiated the thought of utilizing anti-TNF therapies for treatment [43,44]. Today, anti-TNF-α therapy, such as infliximab (IFX), has become mainstream biological therapy for IBD patients [45]. Several studies have demonstrated significant clinical improvement, remission of disease, and mucosal healing in both UC and CD patients with the use of such therapy [46, 47]. However, only one in three patients benefit minimally or not at all from the treatment [48,49].

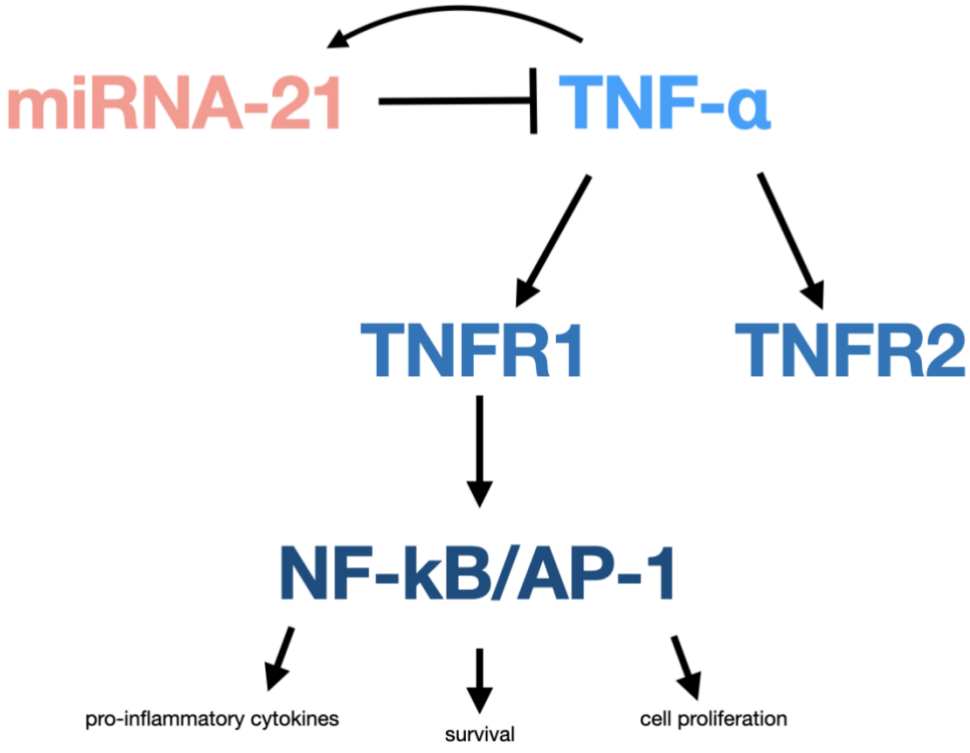

Figure 3. TNF-α Pathway. TNF-α regulates downstream activation of NF- κβ and AP-1 nuclear transcription factors which then go on to promote the expression of genes involved in multiple cellular responses such as pro-inflammatory cytokines, cell survival, and cell proliferation. TNF-α is downregulated at the post-transcriptional level by miRNA-21. Interestingly, TNF-α contributes to its own downregulation through promoting the expression of miRNA-21. This figure was created with Keynote software.

IBD and Angiogenesis

Angiogenesis is the process of the formation of new capillaries from pre-existing blood vessels, and it plays a role in chronic inflammatory conditions such as IBD [50-51]. Hypoxia affects angiogenesis by attracting macrophages and inducing the release cytokines and growth factors, increasing inflammation [52]. Alkim et. al found that hypoxia impacted the secretion of vascular endothelial growth factor (VEGF), a major angiogenic molecule. Inflammatory tissue increases angiogenesis and stimulates release of VEGF, increasing capillary density. VEGF activates NF- κβ which releases proinflammatory cytokines, potentially contributing to the chronic inflammation seen in IBD. Furthermore, hypoxia inhibits the proteasomal degradation of oxygen-sensitive HIF (hypoxia inducible factor)-1α subunit and allows for the subsequent dimerization with the constitutively expressed subunit HIF-1β forming the functional HIF1transcription factor leading to expression of genes with hypoxic response elements (HRE) [53]. HIFs have been found to directly increase VEGF levels [54]. An increase in TNF- α upregulates HIF-1α and increases VEGF, leading to inflammation. Specifically, miRNA-21-5p was found to promote angiogenesis and contribute to the elevated levels of VEGF in IBD cases [55].

MiRNA Synthesis, Mechanism and Dysregulation in IBD

Given the important role that several intracellular pathways play in the pathology of IBD the regulation of proteins expression in the cell is of particular interest in current research as a potential mechanism for their aberrant physiology. There are several ways in which the cell regulates protein expression, one of which is through miRNAs. MiRNAs are small non-coding RNA molecules responsible for the fine-tuning of protein synthesis at the translational level. By targeting mRNA (messenger RNAs) for degradation in a sequence specific manner, miRNAs regulate the amount of protein produced [56-58].

Given its important regulatory function in the cell, the regulation and expression of miRNAs are important. Several miRNAs have been associated in the pathophysiology of IBD, for example, miRNA-16, miRNA -21, miRNA -146, miRNA -151, miRNA -155 and miRNA -362 have all been implicated in causing permeability and decreased functionality of the mucosal barrier of the GIT in IBD patients [42]. Of particular interest is miRNA-21, which has been demonstrated to be a "key switch" in controlling immune responses (regulation of pro- or anti-inflammatory responses); miRNA-21 is involved in the regulation of several key proteins in the immune response such as: PTEN and TNF-α [42, 59-61].

This review will focus on how the aberrant expression miRNA-21 plays a role in the atypical physiology of the immune system, epithelial barrier, mucosal barrier, and angiogenesis in IBD.

Discussion

PTEN as a Regulator of Intestinal Barrier Dysfunction

PTEN is a target of miRNA-21, thus increased miRNA-21 upregulates the activity of the PTEN/PI3K/Akt. Upregulation of the PTEN/PI3K/Akt pathway plays a role in the dysregulation of the immune system and epithelial barrier in IBD, thus contributing to its pathogenesis.

Recent studies have pointed to PTEN playing an important role in T-cell development. Specifically, PTEN- α has been shown to play a direct role in the cell-mediated immune response by two separate mechanisms. PTEN- α reduces T cell function [62] and decreases T-cell infiltration [63] in cancer patients. On the other hand, one study using animal models demonstrated the opposite where the loss of PTEN correlated with decreased T-cell infiltration [63]. PTEN has also been shown to be important in the production and survival of memory CD8 + T cells [64], as well as T-cell activation [65]. Another recent study points to CD8 + T cell dysfunction as one of the initiating triggers of IBD pathogenesis [66].

Interestingly, one study has pointed to miRNA-21 playing a role in intestinal permeability using murine model miRNA-21 knockouts, in which permeability was increased [67]. This suggests that the overactivity of PTEN in these mice promoted the increased intestinal permeability seen. Further studies have also found that the inhibition of PTEN results in the activation of ADP ribosylation factor 4 (ARF4) [68]. ARF4 was further demonstrated to have an inverse correlation to the expression of tight junction proteins claudin-4 and occludin, demonstrating an inverse correlation between ARF4 and the epithelial barrier integrity. This study concludes that miRNA-21 contributes to the weaking of the epithelial barrier by downregulating PTEN, which in turn upregulates ARF4 (Figure 4). It is however important to note that the direct mechanism by which ARF4 regulates expression of these tight junction proteins is yet to be studied, therefore concrete conclusions on the effect of miRNA-21 on ARF4 mediated regulation of tight junction proteins.

The effects of a weakened epithelial barrier also extend to the mucosal barrier of the gut, seen in a study by Zhang et al. which explored the Sishen Pill (SSP) which maintained the mucosal barrier of the colon by upregulating PTEN and subsequently downregulating the PI3K/Akt pathway [69]. Additionally, this study illustrates how PTEN downregulates of the Rho A/Rho kinase (ROCK) pathway which when stimulated decreases the integrity of the mucosal barrier.

This is due to ROCK pathways effects on myosin light chain (MLC) phosphorylation which impacts tight junction structure in the intestine and the permeability of the gut. When ROCK levels increase, MLC phosphorylation increases, leading to more inflammation as tight junction proteins rupture between epithelial cells in the gut making the barrier more permeable [69]. The effects of the therapy were also reflected in the barrier-related protein levels that

resulted, as claudins and cadherins were expressed more readily in the colon with the treatment of SSP [67] This affirms that the permeability of the gut is heavily affected by the involvement of PTEN. Depending on PTEN activity, PI3K/Akt was found to regulate the downstream effects of ROCK, MLC phosphorylation, and myosin light chain phosphatase (MLCP) [65].

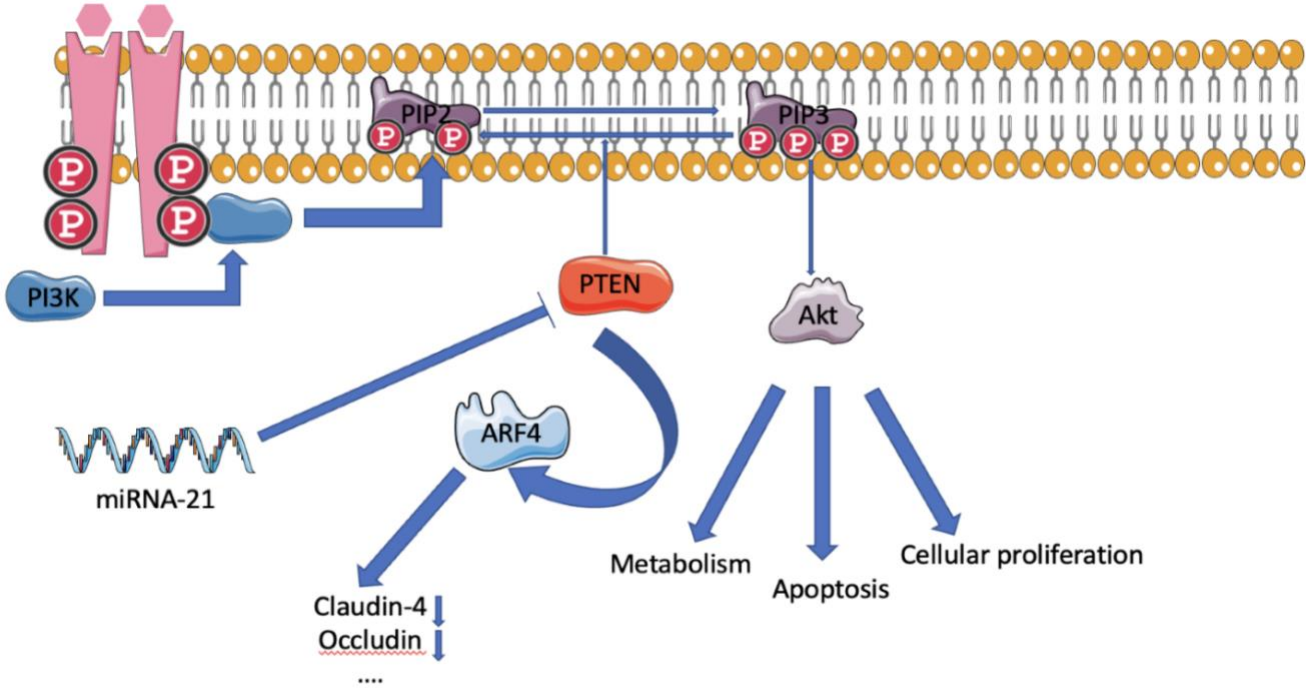

Figure 4. miRNA-21 inhibits PTEN. miRNA-21 inhibits PTEN leading to the downregulation of the akt pathway while simultaneously upregulating ARF4. The upregulation of ARF4 will lead to the further downregulation of tight junction proteins (Claudin-4 and Occludin), thereby increasing epithelial permeability. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

Suppression of the ROCK pathway has shown to improve intestinal fibrosis in CD and maintenance of the mucosal barrier in UC [69,70]. Since PTEN is a miRNA-21 target, we can conclude that miRNA-21 increases the PI3K/Akt signal and stimulates the ROCK pathway, resulting in a compromised mucosal intestinal barrier [91].

TNF-α/ Wnt Signalling Pathway as a Regulator of Intestinal Barrier Dysfunction

MiRNA-21-3p has been recently shown to play a role in the regulation of the expression of tight junction proteins responsible for the integrity of the intestinal epithelial barrier in the GIT. A recent 2021 study demonstrates that TNF-α-induced expression of miRNA-21-3p caused decreased levels of metadherin (MTDH) [72]. MTDH is a negative regulator of the Wnt signalling pathway. Its down-regulation by miRNA-21-3p leads to a subsequent decrease in claudin-1 and occludin and increased protein expression of Wnt signalling proteins (i.e. Axin-1, Wnt3a and B-catenin). When activated, the Wnt-signaling pathway stabilizes the protein B-catenin which acts as a transcription factor for the expression of cell proliferation proteins such as c-Myc and cyclin D1 (Figure 5). Inhibition of Wnt-signaling has been shown to result in crypt loss and tissue degeneration in the GIT [73]. The Wnt pathway is also involved in inflammatory signaling pathways, such as NF-kβ, MAPK and AKT suggesting another mechanism by which miRNA-21 plays a role in the pathogenesis of IBD [74]. The involvement of miRNA-21 in this pathway, demonstrates the need for further research in the role of Wnt-signalling in the maintenance of the intestinal barrier as current studies suggest complex downstream effects.

Figure 5. miRNA-21 regulates the Wnt/β-catenin pathway. MiRNA-21 promotes the Wnt/β-catenin pathway via inhibiting MTDH, a negative inhibitor of the Wnt/β-catenin. Once activated in the cell the β-catenin pathway promotes cell proliferation via promoting the expression of c-Myc and cyclin-D1. TNF-α, through promoting the expression of miRNA-21, promotes Wnt/β-catenin. This figure was created with Keynote software.

The effects of the epithelial barrier and how it is impacted by TNF-α extend to the mucosal barrier of the GIT. The mucosal barrier in the intestine depends on the Muc2 protein, secreted by goblet cells [75]. The weakening of the epithelial barrier can affect how Muc2 is expressed in intestinal mucin, thinning out almost 90% of the mucosal barrier. In a study by Wu et. Al, it was mentioned that TNF-α increases miRNA-21 expression and contributes to the dysbiosis of the gut [75]. This can further deplete the mucin produced by goblet cells as the epithelia increases in permeability, showing that there is a negative correlation between TNF-α levels and goblet cell mucin [76]. This in turn causes irregularities in the sustenance of the gut microbiota. Overall, overexpression of miRNA-21 resulting in increased TNF-α levels and a depletion of Muc2 contribute to chronic inflammation in the gut [77].

The Clinical Applications of Anti-TNF-α Therapy in IBD Patients

Recent studies have been done to inform clinicians on anti-TNF therapy in IBD patients. A study done on 738 ethnically Danish IBD patients concluded several SNPs (single nucleotide polymorphisms) associated with TLRs (Toll-like Receptors), inflammasomes or apoptosis and IFN (Interferon) are associated with responsiveness to anti-TNF therapy [78]. Furthermore, the study found that among patients SNPs associated with increased TLR5 activity in CD and increased IL-12 (Interleukin-12) and IL-18 (associated with IFN) activity in UC were associated non-response to anti-TNF therapy. Interestingly TLR5 is a possible target of miRNA-21 [79] and IFN-y is down regulated in stroke associated infection by miRNA-21 [80], though further studies would need to confirm such a relationship in IBD pathogenesis.

Other recent studies have considered the achievement of different therapeutic goals beyond the mere control of symptoms for patients treated with anti-TNF therapy. In a study of 37 pediatric CD patients found that 70.3% of patients treated with a maintenance anti-TNF therapy presented with complete mucosal healing in a 1-year follow up [81]. These results show promise for anti-TNF therapy in pediatric cohorts, who tend to have a severe phenotype of the disease, although further research in a large cohort should also be considered. Another clinical outcome that was assessed in a recent study was the changes in the gut microbiota in Crohn's disease patients. In a study of 27 patients those treated with anti-TNF therapy were found to have a restoration of the microbiome, typically decreased in CD, in relation to healthy participants [82]. These studies demonstrate that anti-TNF therapy can possibly reverse the pathology of the IBD disease process rather than merely controlling the symptoms of IBD. Further studies, long-term studies, on the effects of these therapies and long-term remission is still unexplored.

Angiogenesis as a Regulator of Chronic Inflammation

Studies have shown that angiogenesis contributes to the immune responses displayed by the intestine in IBD [83]. This is observed in CD patients with vascular irregularities near their colon. In a study conducted by An et al., increased levels of miRNA-21 increased the amount of vascularization by upregulating proteins such as the vascular endothelial growth factor (VEGF) [84]. Another study by Xie et al. looked at agomir-21 and antagomir-21, a

small synthetic miRNA-21 agonist and antagonist of miRNA-21, respectively, which were investigated in terms of vascular hyperplasia levels [83]. It was found that agomir-21 levels were significantly greater in cases of severe colitis whereas antagomir-21 alleviated IBD symptoms in mice. This study showed the link between agomir-21 and the PTEN/ PI3K/AKT/VEGF axis, reflecting the crosstalk between these pathways and miRNA-21.

The PI3K/Akt pathway contributes to angiogenesis by activating VEGF. It has been found that HIF-1α can also impact VEGF levels [85]. The down regulation of HIF-1α has been shown to inhibit the PI3K/Akt pathway which decreases VEGF levels and reduces angiogenesis [86]. High levels of HIF-1α in macrophages further increases TNF-α expression [86]. Although there are not many studies conducted on angiogenesis and TNF-α in IBD, current research shows TNF-α levels increase if miRNA-21 or HIF- α levels increase [84,86]. By inhibiting miRNA-21 or down regulating HIF-1α levels, there can be multiple downstream effects of decreasing the PI3K/Akt levels, VEGF production, and TNF-α levels. This can reduce the angiogenic effects in colon tissues, reducing inflammation and alleviating symptoms of IBD in patients. More studies should be conducted in order to explore possible therapeutic effects, perhaps combining techniques of targeting both miRNA-21 and HIF-1α in order to balance the infiltration of immune cells and maintain the intestinal barrier and balance the gut microbiota [86].

Conclusions

To date several studies, point to miRNA-21 playing a vital role in the atypical physiology of the immune system, epithelial barrier, mucosal barrier, and angiogenesis in IBD. Although these relationships are complex, miRNA-21 aberrant expression in IBD can mediate the changes in these systems and if studied, can be applied clinically. MiRNAs can be detected in circulation and have been seen as potential diagnostic tools for several diseases such as cancer [87,88]. The application of using miRNA-21 in diagnostics also is still to be determined as one studied has shown that circulation miRNA-21 is not reflective of alterations of expression in remote tissues [89].

List of Abbreviations Used

AGO: argonaute protein
ARF4: adenosine diphosphate ribosylation factor 4
CD: Crohn's disease
GIT: gastrointestinal tract
GALT: gut-associated lymphoid tissue
HIF: hypoxia inducing factor
HIV: human immunodeficiency virus
IBD: inflammatory bowel disease
IFN: interferon
IFX: infliximab
IL: interleukin
MLC: myosin-light chain
MLCK: myosin-light chain kinase
MLCP: myosin-light phosphatase
MiRNA: micro-ribonucleic acid
MRNA: messenger ribonucleic acid
MTDH: metadherin
NF- κβ: nuclear factor-kappa beta
NSAIDs: non-steroidal anti-inflammatory drugs
PIP2: phosphatidylionsitol 4,5-bisphosphate
PIP3: phosphatidylionsitol 3,4,5-triphosphate
PI3K: phosphoinositide 3-kinase
PTEN: phosphatase and tensin homolog
ROCK: rho-associated protein kinase
RNA: ribonucleic acids
SNPs: single nucleotide polymorphisms
SSP: Sishen pill
TLR: toll-like receptor
TNF-α: tumour necrosis factor
TNFR: tumour necrosis factor receptor
UC: ulcerative colitis
VEGF: vascular endothelial growth factor

Conflicts of Interest

The authors have no conflict of interest to declare.

Ethics Approval and/or Participant Consent

This literature review did not require ethics approval or participant consent.

Authors' Contributions

MB: made contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.
CG: contributed to study design and planning, assisted with the collection and analysis of data, and gave final approval of the version to be published.
SE: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave final approval of the version to be published.

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