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Review Article

Genetic and epigenetic signaling pathways and their clinical outcomes in inflammatory bowel disease

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Abstract

Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are chronic progressive immune-mediated inflammatory conditions of the gastrointestinal tract. The etiology of IBD is multifactorial, involving genetic predisposition, environmental factors, immune dysregulation, and gut microbiota. Genetics has played a pivotal role in elucidating the pathogenesis of IBD, with genome-wide association studies (GWAS) identifying more than 200 susceptibility loci. Additionally, epigenetic mechanisms, such as DNA methylation, histone modifications, and noncoding RNAs, have clarified the role of gene-environment interactions in the pathogenesis of IBD. Epigenetic mechanisms regulate key signaling pathways, dynamically modulating disease onset, progression, and therapy response. By unraveling the complex interactions between genetic and epigenetic factors, we can gain deeper insights into disease mechanisms and uncover novel opportunities for therapeutic and diagnostic advancements. In this review, we examine the contributions of genetic and epigenetic research to our understanding of IBD and explore their potential in diagnosis, monitoring, treatment, and personalized medicine.

Keywords: Epigenetic, genetic, inflammatory bowel disease, signal pathways.

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INTRODUCTION

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic conditions characterized by inflammation of the gastrointestinal tract. These diseases arise from a complex interplay between genetic, environmental, microbial, and immunological factors. Genetics and epigenetics significantly influence IBD predisposition, progression, and treatment outcomes (1). Although the exact etiology of IBD remains elusive, advances in molecular biology have highlighted the pivotal role of signaling pathways in its pathogenesis (2). These pathways coordinate complex interactions among genetic predisposition, environmental triggers, and immune responses, shedding light on potential therapeutic targets. Evidence implicates a complex interplay of genetic, environmental, microbial, and immunological factors in their pathogenesis (2,3).

Signaling pathways in IBD

The genetic predisposition to IBD has been extensively studied, with genome-wide association studies (GWAS) identifying 220 susceptible loci. These loci include genes such as interleukin 23 receptor (IL23R), autophagy related 16 like 1 (ATG16L1), and caspase recruitment domain family member 9 (CARD9), which regulate immune responses, epithelial barrier function, and microbial interactions. The most notable genetic contributor is nucleotide binding oligomerization domain containing 2 (NOD2), which is associated with microbial recognition and autophagy, particularly in CD. Variants in genes like IL23R, ATG16L1, and CARD9 further underscore the genetic basis of immune dysregulation in IBD (4). Despite these discoveries, the heritability of IBD suggests that additional genetic factors remain unidentified. Moreover, genetic predisposition alone cannot fully explain the observed disease heterogeneity, indicating the role of non-genetic factors. The phosphatidylinositol 3-kinase (PI3K) pathway plays a multifaceted role in IBD pathology by regulating immune responses, maintaining epithelial barrier integrity, modulating macrophage and dendritic cell functions, and mediating host–microbe interactions. However, aberrant activation of PI3K in IBD can result in excessive effector T cell responses and diminished regulatory T cell function, thereby sustaining chronic inflammation. Moreover, dysregulated PI3K signaling impairs the epithelial barrier, increasing intestinal permeability and susceptibility to microbial invasion. Consequently, hyperactive PI3K amplifies the inflammatory microenvironment in the mucosa. Additionally, the altered gut microbiota frequently observed in IBD can further dysregulate PI3K signaling, thereby exacerbating inflammation (5-7). Similarly, the janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling is essential for immune homeostasis and epithelial defense. Yet, its dysregulation in IBD leads to immune imbalance and defective barrier function. This imbalance not only promotes the overproduction of pro-inflammatory cytokines but also disrupts T cell differentiation, contributing to a self-perpetuating inflammatory cycle. Furthermore, compromised JAK-STAT signaling increases epithelial permeability, allowing microbial translocation that further drives inflammation (8-11). The nuclear factor kappa B (NF-κB) pathway is another critical regulator that is aberrantly activated in IBD. While NF-κB is normally required for immune defense and epithelial responses, its chronic activation induces a pro-inflammatory cytokine storm—particularly through tumor necrosis factor-alpha (TNF-α), Interleukin 6 (IL-6), and Interleukin 8 (IL-8)—thus creating a feedback loop that intensifies mucosal inflammation. In addition, sustained NF-κB signaling disrupts epithelial barrier integrity and enhances immune cell recruitment, especially of macrophages and T cells, which collectively aggravate intestinal damage (12). Likewise, the mitogen-activated protein kinase (MAPK) signaling pathway supports inflammatory responses in IBD by enhancing cytokine production (TNF-α, IL-1β, IL-6) and modulating immune cell activity. Chronic activation of MAPK components such as extracellular signal-regulated kinase (ERK) and proline-directed serine/threonine kinases of the MAPK family (p38) promotes fibrosis in CD by stimulating fibroblasts. Moreover, MAPK-induced activation of jun N-terminal kinase (JNK) and p38 leads to apoptosis and reduced proliferation in intestinal epithelial cells, thereby impairing barrier integrity and allowing microbial translocation (13). In contrast to these pro-inflammatory pathways, Wnt/β-catenin signaling generally plays a protective role in IBD. It contributes to epithelial barrier maintenance, tissue regeneration, and communication with immune cells. During inflammation, Wnt/β-catenin supports the proliferation and differentiation of intestinal stem cells and promotes mucosal healing. Furthermore,

it facilitates the polarization of macrophages toward the anti-inflammatory M2 phenotype, which is essential for resolving inflammation and restoring intestinal homeostasis (14-21). The role of signaling pathways in the pathogenesis of IBD is summarized in Figure 1.

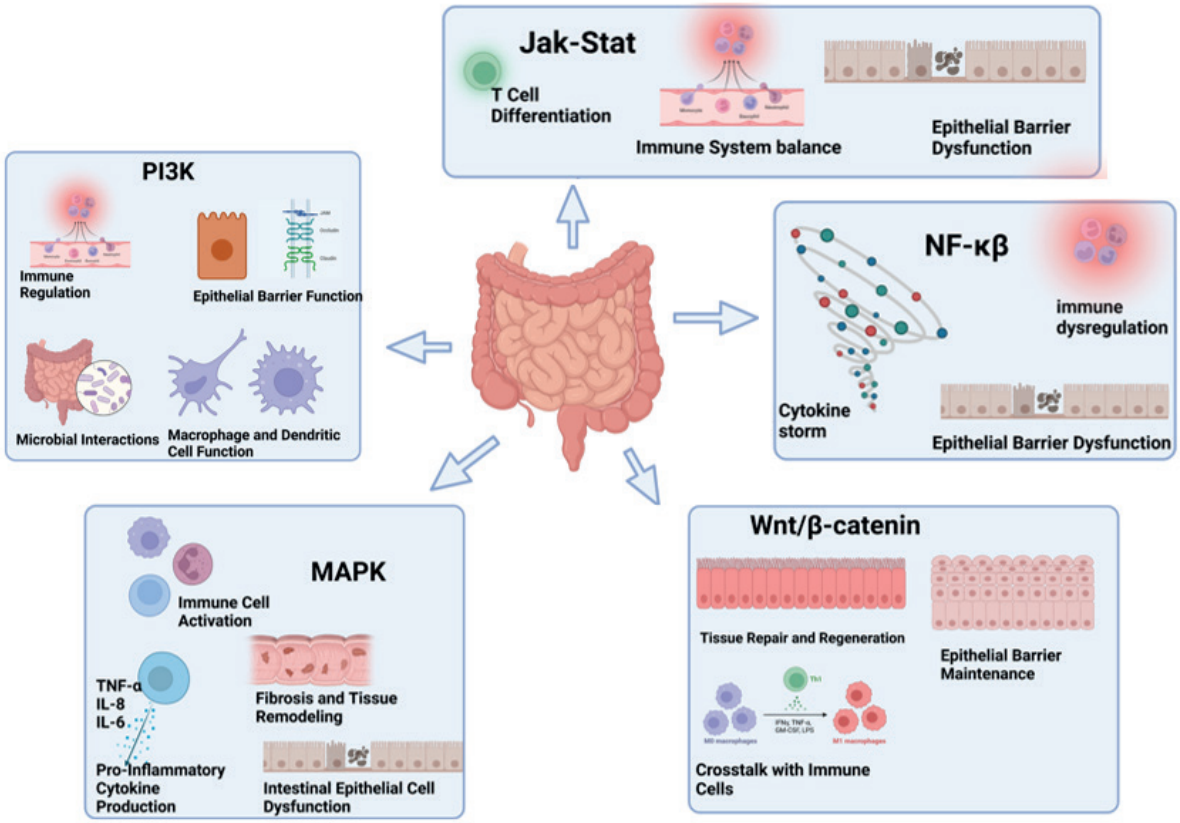

Figure 1. In IBD, dysregulated PI3K signaling weakens the epithelial barrier, leading to bacterial translocation, activating dendritic cells and macrophages, which disrupts immune homeostasis and exacerbates chronic mucosal inflammation. Dysregulated JAK-STAT signaling promotes cytokine overproduction, disrupts epithelial barrier integrity, and distorts T-cell differentiation, contributing to a sustained inflammatory response and immune imbalance. Chronic NF-κB activation promotes proinflammatory cytokine production, disrupts epithelial barrier integrity, and dysregulates immune cell responses, triggering intestinal inflammation. The MAPK pathway contributes to IBD by promoting proinflammatory cytokine production, immune cell activation, epithelial barrier disruption, and intestinal fibrosis, thereby sustaining chronic inflammation and tissue damage. On the other hand, Wnt/β-catenin signaling supports epithelial regeneration, barrier maintenance, and immune crosstalk by promoting stem cell renewal and anti-inflammatory macrophage polarization, aiding in inflammation resolution (Created with BioRender.com).

I. NF-κB pathway and therapeutic implications

NF-κB is a family of transcription factors that modulate the expression of genes involved in immune response, cell survival, and cytokine production. It is activated in response to various stimuli, including microbial products, pro-inflammatory cytokines (e.g., TNF-α, IL-1β), and stress signals. Central to the inflammatory response in IBD is the NF-κB signaling pathway, which acts as a key regulator of immune and inflammatory processes (22-24). NF-κB activation triggers transcription of TNF-α, IL-6, and interleukin 1β (IL-1β), perpetuating inflammation. Dysregulation of this pathway results in sustained inflammation, contributing to mucosal damage and disease progression. Inhibitors targeting NF-κB, including small molecules and biological agents, have shown promise in ameliorating inflammation. The pathway operates via two major mechanisms: the canonical and non-canonical pathways (25). Canonical pathway predominantly mediates acute inflammatory responses, triggered by signals such as TNF-α and IL-1β. The cascade ultimately leads to the nuclear translocation of NF-κB complexes, such as p65/p50, which promote the transcription of pro-inflammatory genes. Non-canonical pathway plays

a crucial role in immune system development and adaptive immunity, primarily involving key regulators such as RelB and p52. Ubiquitin-specific proteases (USPs) are the largest family of deubiquitinating enzymes and are critical in signaling pathway regulation in infections and autoimmune diseases. Therefore, USPs are regarded as key regulators of proinflammatory signaling pathways, such as the NF-κB and transforming growth factor-beta (TGF-β) pathways. Ubiquitin-specific proteases have been shown to regulate signaling pathways associated with inflammatory bowel disease and play critical roles in IBD-associated susceptibility genetics, intestinal epithelial barrier function, immunity, and gut microbiota (26). While targeting NF-κB signaling is promising, its therapeutic modulation must balance reducing inflammation while preserving immune homeostasis. Current therapeutic approaches include biologics, small-molecule inhibitors, and dietary and microbiome interventions (27,28). Among biologics, TNF-α inhibitors such as infliximab and adalimumab indirectly attenuate NF-κB signaling by suppressing upstream proinflammatory cytokines. In parallel, small-molecule inhibitors that target IκB kinase (IKK)—a key activator of NF-κB—are under investigation for their ability to directly inhibit this pathway. Additionally, dietary and microbiome-based approaches, including the use of probiotics, may modulate NF-κB activity and offer supportive therapeutic benefits when used alongside conventional treatments. Studies in the literature emphasize the significance of the non-canonical NF-κB pathway in the pathogenesis of IBD. Its role in maintaining immune system balance suggests that targeting this pathway could offer new therapeutic avenues for IBD treatment (8). Research indicates that deleterious genetic variations in the NOD signaling pathway, particularly those involving the NOD2 gene, are associated with CD. These variations may lead to reduced NF-κB signaling, implicating the pathway's complex role in disease development (29). The NF-κB signaling pathway is a cornerstone in the pathophysiology of IBD, driving inflammation and immune dysregulation (30). Understanding its intricate mechanisms provides insights into disease progression and therapeutic targets. While current treatments partially mitigate NF-κB activation, ongoing research into more selective modulators holds promise for improving outcomes in IBD patients. The key challenge is to achieve effective inhibition of NF-κB while preserving its essential role in host defense and tissue homeostasis (31,32).

II. JAK-STAT pathway and therapeutic implications

The JAK-STAT signaling pathway is a well-characterized intracellular signaling cascade activated by cytokines and growth factors. It involves JAKs, a family of tyrosine kinases, and STAT proteins, which act as transcription factors. When cytokines bind to cell surface receptors, JAKs are activated. This leads to the phosphorylation of STAT proteins. Phosphorylated STATs translocate to the nucleus to modulate gene expression, driving cellular processes such as proliferation, differentiation, and immune regulation (33,34). The JAK-STAT pathway is instrumental in mediating responses to cytokines and growth factors. Dysregulated activation of the JAK-STAT signaling pathway intensifies immune responses in IBD. The development of JAK inhibitors, such as tofacitinib, highlights the therapeutic potential of targeting this pathway for disease management (35). CCAAT/enhancer-binding protein β (C/EBPβ) plays a crucial role in the pathological progression of inflammation-related diseases, such as IBD, by regulating the MAPK and IL-6/STAT3 pathways. A genome-wide association study identified C/EBPβ as a susceptibility-associated factor for IBD (36). Additionally, another study demonstrated that C/EBPβ deficiency induces CD4+ T cell hyperproliferation and impairs Treg functions in colitis (37). The pivotal role of the JAK-STAT pathway in IBD pathogenesis has made it a promising target for therapeutic intervention. Small-molecule JAK inhibitors, such as tofacitinib, upadacitinib, and filgotinib, have shown promising efficacy in managing IBD by dampening excessive cytokine signaling (38). These agents offer advantages such as oral administration and broad-spectrum activity against multiple cytokines. However, their use is associated with risks, including infections, thrombosis, and malignancy. These risks require careful patient selection and ongoing monitoring (39). The JAK-STAT signaling pathway plays a central role in the pathogenesis of IBD as it regulates immune responses and mediating inflammation. Its dysregulation not only exacerbates the disease process but also offers opportunities for targeted therapeutic interventions (40). While JAK inhibitors represent a significant advancement in IBD treatment, further research is required to optimize their use and minimize risks, ultimately improving patient outcomes (41,42). This pathway remains a vital area of exploration for understanding IBD and developing innovative therapies

tailored to individual disease mechanisms (43,44). Ongoing research aims to refine the therapeutic targeting of the JAK-STAT pathway, focusing on improving specificity to reduce adverse effects. Advances in personalized medicine, such as biomarker-based approaches, may help identify patients most likely to benefit from Jak inhibitors. Additionally, understanding the crosstalk between the JAK-STAT pathway and other molecular mechanisms in IBD could lead novel combinatory treatment strategies (39,42).

III. Wnt/β-catenin pathway and therapeutic implications

The Wnt/β-catenin signaling pathway is a conserved cellular signaling mechanism critical for regulating cell proliferation, differentiation, and tissue repair (45,46). In the gastrointestinal system, this pathway ensures the renewal of intestinal epithelial cells (IECs) and supports barrier function (47). Dysregulation of Wnt signaling has been implicated in various diseases, including IBD, where chronic inflammation disrupts epithelial homeostasis and perpetuates disease pathology (48). While it promotes epithelial regeneration and repair, excessive activation can lead to fibrosis and dysplasia. Understanding the fine balance in Wnt signaling is critical for developing therapies aimed at tissue healing without exacerbating pathology (49).

Dysregulation in IBD

1. Aberrant activation: Hyperactivation of the Wnt/β-catenin pathway can contribute to uncontrolled epithelial proliferation, potentially leading to dysplasia and increasing the risk of colorectal cancer in IBD patients (50,51).
2. Impaired signaling: Reduced Wnt/β-catenin activity has been associated with defective barrier function and chronic inflammation in IBD. This impairment may result from genetic mutations or inflammatory cytokines inhibiting pathway components (52).

Targeting the Wnt/β-catenin pathway offers promising therapeutic opportunities for IBD:

1. Enhancing Wnt activity: Pharmacological agents that activate Wnt/β-catenin signaling could promote epithelial repair and restore barrier integrity. Small molecules like CHIR99021 (a GSK-3β inhibitor) have shown potential in preclinical studies (53,54).
2. Inhibiting aberrant activation: For cases with pathway hyperactivation, inhibitors like tankyrase inhibitors could prevent dysplasia while preserving intestinal homeostasis (55).
3. Combination therapies: Given the multifaceted role of the Wnt/β-catenin pathway, combining Wnt-targeting therapies with anti-inflammatory or immunomodulatory agents may enhance treatment efficacy (56).

The Wnt/β-catenin signaling pathway is central to intestinal homeostasis, and its dysregulation contributes significantly to IBD pathogenesis. Therapeutic modulation of this pathway holds promise for addressing the unmet needs in IBD management, including enhancing epithelial repair and mitigating chronic inflammation. Further research is needed to turn preclinical findings into effective clinical interventions (57-59).

IV. PI3K/Akt/mTOR pathway and therapeutic implications

PI3K/Akt/mammalian target of the rapamycin (mTOR) pathway regulates cell survival, proliferation, and metabolism. The PI3K pathway is a critical intracellular signaling cascade involved in regulating diverse cellular processes, including cell proliferation, survival, migration, metabolism, and immune responses. It is activated by various extracellular signals, such as growth factors, cytokines, and microbial products, through receptor tyrosine kinases, G-protein-coupled receptors, or toll-like receptors. PI3Ks catalyze the production of phosphatidylinositol-3,4,5-trisphosphate (PIP3), which recruits and activates downstream effectors such as Akt (protein kinase B) and mTOR (60). In IBD, PI3K/Akt/mTOR dysregulation disrupts tight junction proteins, weakening the epithelial barrier and exacerbating immune hyperactivation. mTOR inhibitors, such as rapamycin, are being explored for their potential to modulate inflammation and restore epithelial integrity (61).

Considering the crucial role of PI3K signaling in IBD, targeting this pathway offers promising therapeutic opportunities. Isoform-specific PI3K inhibitors have been developed to modulate immune responses selectively. For example, PI3Kδ inhibitors show potential in reducing inflammation by dampening T-cell activity while sparing other isoforms involved in essential cellular functions. Additionally, combinatorial strategies targeting both PI3K and other inflammatory pathways, such as NF-κB or JAK-STAT, are being explored to improve therapeutic efficacy (62,63). mTOR plays a crucial role in cellular metabolism and serves as an effective therapeutic target with antimicrobial, anti-inflammatory, and anticancer properties. Inhibiting overactive mTOR signaling can produce a range of beneficial effects, making mTOR inhibitors valuable in clinical trials as potential treatments. However, prolonged use of the same mTOR inhibitors (such as tacrolimus (64) and mesalamine (65)) may lead to tolerance and drug resistance, necessitating the development of new inhibitors. Preclinical studies and clinical trials are exploring inhibitors of this pathway to determine which approaches can restore therapeutic sensitivity. mTOR inhibitors show significant promise for the treatment of infectious diseases and inflammatory bowel disease (66). The PI3K signaling pathway is a cornerstone in the pathogenesis of IBD, influencing immune responses, epithelial integrity, and host-microbiota interactions. As research progresses, targeted modulation of this pathway holds great promise for improving outcomes for IBD patients. However, careful consideration of the pathway's complexity and systemic roles is essential to harness its therapeutic potential fully (55,67). Despite its promising potential, targeting the PI3K pathway poses challenges. Broad inhibition of PI3K can lead to adverse effects, as this pathway is vital for many physiological processes. Isoform-specific inhibitors and tissue-targeted delivery systems are critical to reduce these risks. Furthermore, understanding the interplay between PI3K signaling and other molecular pathways in IBD is essential for developing more precise and effective therapies (55). Advancements in genomics, proteomics, and single-cell technologies are expected to provide deeper insights into the role of PI3K signaling in IBD. These approaches will help identify biomarkers for patient stratification and prediction of therapeutic response, leading to the development of personalized medicine in IBD.

V. MAPK pathway and therapeutic implications

The MAPK signaling pathway is a highly conserved cascade of serine/threonine kinases, including ERKs, JNKs, and p38 MAPKs (66). These kinases are activated in response to extracellular stimuli, such as pro-inflammatory cytokines (e.g., TNF-α, IL-6) and environmental stressors, and regulate diverse cellular processes, including proliferation, differentiation, apoptosis, and inflammatory responses (68). Dysregulation of MAPK signaling is associated with the chronic inflammation and tissue damage seen in IBD (69).

Clinical implications

The integration of signaling pathway research into clinical practice has revolutionized IBD management. Biologic therapies targeting TNF-α and interleukin pathways have significantly improved outcomes. However, many patients remain refractory to current treatments, emphasizing the need for novel therapies. Based on an understanding of individual pathway profiles, personalized medicine is emerging as the pioneering field in IBD treatment (27). Given its central role in IBD pathogenesis, the MAPK pathway is a promising target for therapeutic intervention. Preclinical studies have demonstrated the efficacy of MAPK inhibitors in reducing inflammation and promoting mucosal healing in IBD models. For example, p38 MAPK inhibitors have shown potential in attenuating cytokine production and epithelial cell apoptosis (70). However, the clinical translation of these findings is limited by concerns regarding off-target effects and toxicity. Advances in drug delivery systems, such as nanocarriers and gut-targeted formulations, may overcome these challenges. The MAPK signaling pathway plays a pivotal role in the inflammatory and immune responses underlying IBD. Its involvement in pro-inflammatory cytokine production, epithelial barrier dysfunction, and immune cell activation highlights its importance in disease pathogenesis. Although there are still challenges in turning MAPK inhibitors into clinical practice, ongoing research offers promise for the development of targeted therapies that reduce inflammation while preserving normal cellular functions. Understanding the nuances of this pathway will be essential for advancing IBD treatment and improving patient outcomes (68). IBD, including CD and UC, are

chronic inflammatory conditions of the gastrointestinal tract characterized by episodes of exacerbation and remission. The pathogenesis of IBD is multifactorial, involving genetic predisposition, environmental factors, microbial dysbiosis, and immune dysregulation. The MAPK pathway has emerged as a critical regulator of intestinal inflammation and tissue repair among the many signaling pathways implicated in IBD (13). Signaling pathways play a crucial role in the pathophysiology of IBD, shedding light on the underlying disease mechanisms and paving the way for potential therapeutic advances. Ongoing research in this area holds significant promise for revolutionizing IBD treatment and facilitating the development of targeted therapies that can enhance patients' quality of life.

Further research is needed to elucidate the precise molecular mechanisms by which the MAPK pathway contributes to IBD and to identify biomarkers for patient stratification. Combination therapies targeting MAPKs alongside other key pathways, such as NF-κB or JAK-STAT, may provide a synergistic approach to disease management. Additionally, exploring the interplay between MAPK signaling and the gut microbiota could provide novel therapeutic strategies.

Epigenetics in IBD

The prevalence of IBD has risen globally, with significant socio-economic and health burdens. While genetic factors, such as NOD2 and IL23R mutations, have been associated with IBD susceptibility, these alone cannot explain the disease's phenotypic variability. Epigenetics is crucial in IBD pathophysiology, influencing gene expression through DNA methylation, histone modifications, and non-coding RNAs. These chronic inflammatory disorders of the gastrointestinal tract arise from a complex interplay of genetic susceptibility, environmental triggers, immune dysregulation, and gut microbiota imbalances. As a regulatory layer modulating gene expression without altering the DNA sequence, epigenetics bridges the gap between genetic predisposition and environmental influences, and offers new perspectives for understanding and managing IBD (71). In IBD, epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNAs have emerged as crucial regulators of gene-environment interactions. Environmental factors, such as diet, smoking, infections, and antibiotic use, thereby inducing changes in gene expression profiles associated with IBD. For example, smoking in CD is associated with epigenetic changes that aggravate inflammation, while certain dietary components can modulate histone acetylation, impacting disease severity. The bidirectional interaction between gut microbiota and the host epigenome plays a crucial role in IBD pathogenesis. Dysbiosis can induce epigenetic alterations that amplify inflammation, whereas epigenetic modifications in the host can shape microbiota composition, leading to a vicious cycle of immune dysregulation. The reversibility of epigenetic modifications presents a promising paradigm for the development of novel IBD treatments. Epigenetic therapies, including histone deacetylase (HDAC) inhibitors and DNA methyltransferase inhibitors, are being explored to restore normal gene expression patterns. Additionally, targeting specific miRNAs holds potential for precision medicine approaches in IBD management. Epigenetic insights offer novel diagnostic and therapeutic targets for IBD management. By examining how environmental and genetic factors interact to trigger chronic inflammation, epigenetics offers novel prospects for developing advanced diagnostic and therapeutic methods. Advancing research in epigenetic interventions has the potential to greatly reduce disease burden and improve outcomes for patients (72,73).

Integrating genetics and epigenetics

The interplay between genetics and epigenetics offers a more comprehensive understanding of IBD pathogenesis. Genetic variants can influence epigenetic marks, while epigenetic modifications can modulate the effects of genetic predisposition. For example, individuals with risk alleles may exhibit distinct methylation patterns that affect gene expression and immune responses. This integrative perspective underscores the dynamic nature of IBD and the need for personalized therapeutic approaches. Genetics and epigenetics play a key role in understanding the complex nature of IBD. While genetics provides insights into susceptibility, epigenetics bridges the gap between environmental factors and disease manifestation. Integration of these dimensions will enable us to improve our understanding of IBD pathogenesis and develop more effective, targeted therapies to improve patient outcomes (1).

Epigenetic mechanisms in IBD and therapeutic implications

Epigenetic modifications—such as DNA methylation, histone modifications, and non-coding RNAs—are critical regulators of gene expression in IBD (73,74).

1. DNA methylation: Aberrant DNA methylation patterns are observed in the intestinal tissues of IBD patients. Hypomethylation in pro-inflammatory genes such as TNF-α and IL-6 correlates with their overexpression, driving chronic inflammation. Conversely, hypermethylation in genes responsible for epithelial barrier integrity may impair mucosal defense. Epigenome-wide association studies (EWAS) have identified distinct methylation signatures in IBD patients, suggesting their potential as biomarkers for diagnosis or disease stratification.
2. Histone modifications: Changes in histone acetylation, methylation, and phosphorylation influence chromatin accessibility and transcription. HDACs and histone acetyltransferases (HATs) are implicated in regulating immune responses and epithelial repair mechanisms, which are often dysregulated in IBD. For example, reduced histone acetylation in intestinal epithelial cells may impair mucosal healing, exacerbating disease severity.
3. Non-Coding RNAs: MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) modulate inflammatory signaling pathways and epithelial cell function. Dysregulated expression of specific miRNAs, such as miR-21 and miR-155, upregulated in IBD and are associated with pro-inflammatory pathways. Targeting these ncRNAs offers a novel therapeutic avenue for modulating chronic inflammation.

Role in disease pathogenesis

Epigenetic modifications form the interface between genetic susceptibility and environmental triggers. For instance, smoking - a well-known environmental risk factor for CD - induces epigenetic changes that amplify inflammatory signaling pathways. Similarly, gut microbiome dysbiosis can reshape the host epigenetic landscape, perpetuating chronic inflammation. Epigenetic pathways represent promising therapeutic targets in IBD. Therapies such as HDAC inhibitors, DNA methyltransferase (DNMT) inhibitors, and RNA-based approaches are being investigated for their potential to reprogram inflammatory responses. Furthermore, epigenetic biomarkers may help predict therapeutic responses, paving the way for personalized treatment strategies (74). Epigenetics serves as a crucial mediator in the complex network of factors driving IBD. Understanding the epigenetic mechanisms underlying IBD can provide novel insights into disease pathogenesis and help identify innovative therapeutic targets. The ability to manipulate the epigenome offers promising opportunities to improve outcomes and enhance the quality of life for individuals suffering from these debilitating conditions.

CONCLUSION

Understanding the genetic and epigenetic landscape of IBD has significant implications for diagnosis, prognosis, and treatment. Advances in sequencing technologies and epigenomic profiling have enabled the identification of novel biomarkers and therapeutic targets. Epigenetic therapies, such as histone deacetylase inhibitors and miRNA mimics, have great potential to modulate disease activity. Future research should focus on elucidating gene-environment interactions across diverse populations, conducting longitudinal studies to capture dynamic epigenetic changes over time, and translating these findings into clinical practice to personalized medicine.

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