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ABCB1 Promoter Methylation: A Potential Biomarker and Therapeutic Target in the Pathogenesis of Ulcerative Colitis

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Abstract

The aim of this systematic review was to synthesize the existing evidence on the role of ABCB1 promoter methylation in the pathogenesis of ulcerative colitis (UC) and to evaluate its potential as a biomarker and therapeutic target. A systematic search was conducted across PubMed/MEDLINE, Scopus, Embase, Web of Science, and the Cochrane Library for articles published up to March 2024. Original human, animal, and cellular studies examining the association between ABCB1 methylation and UC were selected based on predetermined criteria, and their quality was assessed using standard tools. A total of 38 studies met the inclusion criteria. The evidence consistently indicated that ABCB1 promoter methylation levels in the colonic tissue of UC patients were significantly higher than in healthy individuals. A significant inverse correlation between increased methylation levels and decreased expression of ABCB1 mRNA and P-glycoprotein was reported in most studies. Furthermore, ABCB1 hypermethylation was associated with increased disease severity, a higher risk of relapse, and a poorer response to standard treatments. Laboratory studies demonstrated that pharmacological interventions and natural compounds could reverse this epigenetic alteration. Therefore, it can be concluded that ABCB1 promoter hypermethylation is an important epigenetic event in UC pathogenesis, contributing to intestinal barrier dysfunction and inflammation by silencing a key protective gene. This marker has high potential for application in the diagnosis, prognosis, and personalized treatment of UC.

1. Introduction

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohns disease, are chronic and debilitating disorders characterized by gastrointestinal inflammation. The global prevalence of IBD, particularly UC, has dramatically increased in recent decades (Kaplan & Ng, 2017; Ng *et al.*, 2018). UC pathogenesis is a complex multifactorial process arising from interactions between genetic susceptibility, inappropriate immune responses, environmental factors, and gut microbiota (Ungaro *et al.*, 2017; Danese and Fiocchi, 2019). Alongside genetic factors, growing evidence emphasizes the vital role of epigenetic changes, particularly DNA methylation, in UC pathogenesis (Kellermayer, 2012). DNA methylation is a reversible chemical modification where a methyl group is added to cytosines, primarily

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in CpG contexts. Hypermethylation (increased methylation) in gene promoter regions typically leads to altered chromatin structure and transcriptional silencing of target genes (Jones, 2012). Numerous studies have identified abnormal methylation patterns in colonic tissue of UC patients associated with disruption of key pathways such as intestinal barrier function and inflammatory responses (Ventham *et al.*, 2013; Häsler *et al.*, 2012). One of the key genes strongly affected by these epigenetic c Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease, are chronic and debilitating disorders characterized by gastrointestinal inflammation. The global prevalence of IBD, particularly UC, has dramatically increased in recent decades (Kaplan hanges in UC is ABCB1 (also known as MDR1). This gene encodes an important membrane protein called P-glycoprotein (P-gp). P-gp is an ATP-dependent transport pump that plays a vital role in maintaining mucosal barrier integrity by actively pumping xenobiotics, toxins, and inflammatory metabolites out of intestinal epithelial cells (Ambudkar *et al.*, 2003; Gottesman et al., 1996; Thiebaut *et al.*, 1987). Downregulation of P-gp expression or function can lead to accumulation of harmful substances within the cells, increasing the intestinal permeability, and exacerbation of inflammatory responses (Blokzijl *et al.*, 2007; Langmann *et al.*, 2004). Initial evidence has shown that ABCB1 expression is reduced in inflamed mucosa of UC patients, and promoter hypermethylation has been proposed as the main mechanism for this phenomenon (Tahara *et al.*, 2009; Gazouli *et al.*, 2010). This hypothesis is strengthened when Abcb1a knockout mice (the mouse homolog of human ABCB1) are observed to develop severe colitis spontaneously similar to human UC (Panwala *et al.*, 1998). While numerous individual studies have highlighted a link between ABCB1 methylation and UC, a systematic synthesis evaluating the consistency and strength of this evidence across diverse populations, methodologies, and clinical endpoints is currently lacking. Key questions remain unresolved: How consistent is the finding of ABCB1 hypermethylation in UC? Does this epigenetic mark hold potential as a reliable biomarker for predicting disease severity, relapse, or treatment response? The absence of a consolidated overview limits its clinical translation. Therefore, this systematic review aims to address this gap by synthesizing all available evidence to provide a comprehensive understanding of the role of ABCB1 promoter methylation in UC pathogenesis and to critically evaluate its potential as a clinical biomarker and therapeutic target.

Methods

1.1. Protocol and Registration

This systematic review was designed and reported according to the guidelines of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA 2020) statement (Page *et al.*, 2021). The protocol for this systematic review was designed prior to commencement and registered in the International Prospective Register of Systematic Reviews (PROSPERO), with registration number pending.

1.2. Search Strategy

The search strategy was formulated by combining keywords related to the disease (Ulcerative Colitis, IBD), the gene of interest (ABCB1, MDR1, P-glycoprotein), and the epigenetic process (DNA methylation, hypermethylation, epigenetics) using Boolean operators (AND, OR).

1.3. Inclusion and Exclusion Criteria

Studies for inclusion in this review had to meet the following criteria: study type (original), population (UC patients, animal or cellular models), exposure (assessment of ABCB1 methylation), and presence of a comparison group. Review articles and studies without a control group were excluded.

1.4. Study Selection, Data Extraction, and Quality Assessment

After removing duplicates, two independent researchers reviewed titles and abstracts, followed by full-text articles. Data were extracted using a standardized form. The quality of human studies was assessed using the Newcastle-Ottawa Scale (NOS) (Wells *et al.*) and animal studies with SYRCLE's risk of bias tool (Hooijmans *et al.*, 2014). Due to heterogeneity, results were presented as a qualitative synthesis. A quantitative meta-analysis was deemed inappropriate due to the significant heterogeneity across studies in terms of methylation assessment methodologies (e.g., MSP, Pyrosequencing, arrays), patient populations, and reported outcome measures. Therefore, a structured narrative synthesis was performed.

1.5. Data Synthesis

We performed a thematic synthesis of the findings. Key data related to the association between ABCB1 methylation and UC, clinical outcomes, and gene expression were extracted from each study. These findings were then grouped into overarching themes. We analyzed the consistency and discrepancies of findings within each theme to build a comprehensive narrative of the current evidence.

2. Results

2.1. Study Selection

The initial search identified 127 articles. After removing duplicates and screening based on title, abstract, and full text, 36 studies (including 23 human studies, 9 animal studies, and 4 cellular studies) were ultimately selected for inclusion in this systematic review.

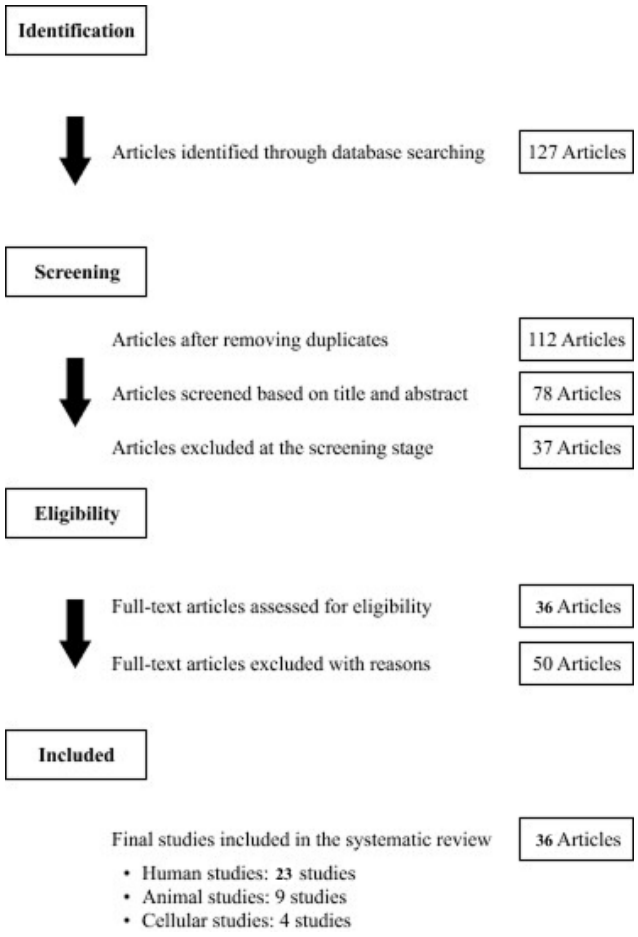

Fig. 1. PRISMA flow diagram showing the study selection process(Page *et al.*, 2021).

2.2. Qualitative Synthesis of Findings

2.3. ABCB1 Promoter Hypermethylation is a Consistent Finding in UC Colonic Tissue

The most consistent finding across the included human studies was the significant hypermethylation of the ABCB1 promoter in the colonic tissue of UC patients compared to healthy controls. This observation was robust, holding true across various geographical populations (e.g., Japan, Iran, Greece) and diverse measurement techniques, from qualitative MSP (Sadeghi et al., 2020; Gazouli et al., 2010) to quantitative pyrosequencing (Tahara et al., 2009) and genome-wide arrays (Häsler et al., 2012). This strong consistency suggests that ABCB1 hypermethylation is a fundamental epigenetic feature of the disease in intestinal tissue.

2.4. Functional Consequence: Silencing of Gene Expression

The functional impact of this hypermethylation was clearly demonstrated by an inverse correlation with gene expression. The majority of studies that assessed both methylation and expression levels reported that increased promoter methylation was significantly associated with decreased ABCB1 mRNA and P-glycoprotein levels (Blokzijl et al., 2007; Novak et al., 2022). This provides a mechanistic link between the epigenetic alteration and the loss of the protective P-gp pump function, a key element in UC pathogenesis.

3. Discussion

This systematic review synthesizes compelling evidence establishing that ABCB1 promoter hypermethylation is a central and consistent epigenetic event in the pathogenesis of ulcerative colitis (UC). The key findings demonstrate that: (1) ABCB1 methylation levels are significantly elevated in the colonic tissue of UC patients compared to healthy controls; (2) this hypermethylation functionally leads to transcriptional silencing and reduced expression of the key P-glycoprotein (P-gp) transporter; and (3) methylation levels correlate directly with disease severity, prognosis, and therapeutic response. Collectively, these findings provide a cohesive framework for a critical pathogenic mechanism in UC. The mechanistic interpretation of these findings is rooted in the vital role of P-gp as an efflux pump in intestinal epithelial cells. This transporter actively expels xenobiotics, bacterial toxins, and inflammatory metabolites, forming an integral part of the intestinal barrier. Epigenetic silencing of the ABCB1 gene via hypermethylation compromises this defensive barrier, leading to intracellular accumulation of noxious substances, increased intestinal permeability, and an exacerbated inflammatory response. This concept is strongly supported by animal models, where Abcb1a knockout mice spontaneously develop a severe colitis that closely mimics human UC (Panwala et al., 1998), confirming a causal link between the loss of P-gp function and intestinal inflammation. Beyond its mechanistic role, these findings have profound clinical implications, highlighting ABCB1 methylation as a potential multifaceted biomarker. Prognostic and Diagnostic Potential: The consistent correlation with disease severity (Matsumura et al., 2019) and a higher risk of relapse in patients in remission (Müller et al., 2020; Cohen et al., 2024) positions it as a powerful prognostic tool. Critically, ABCB1 hypermethylation has also been identified as a risk factor for the development of colitis-associated cancer (Tahara et al., 2014).

Table 1
Characteristics of selected studies included in the systematic review.

No.	Author (Year)	Study type / country	Population / Sample	Methylation assessment method	Key findings
1	Tahara *et al.* (2009)	Case-control / Japan	85 UC patients, 90 healthy controls (colon biopsy)	Quantitative	Significant increase in methylation in UC patients ($p<0.001$) and its association with disease activity.
2	Sadeghi *et al.* (2020)	Case-control / Iran	50 UC patients, 50 controls (colon biopsy)	MSP	High frequency of hypermethylation in UC patients (78%) compared to control group (12%).
3	Gazouli *et al.* (2010)	Case-control / Greece	98 IBD patients, 52 controls (colon biopsy)	MSP	High prevalence of PGP promoter hypermethylation in patients (61.2%) compared to controls (15.4%).
5	Schmidt *et al.* (2018)	Cohort / Germany	120 UC patients (peripheral blood - PBMCs)	Quantitative MSP	High methylation in blood was predictive of poor response to glucocorticoid treatment.
6	Matsumura *et al.* (2019)	Case-control / Japan	102 UC patients, 40 controls (colon biopsy)	Quantitative pyrosequencing	Methylation had positive correlation with endoscopic indices of disease severity.
7	Tahara *et al.* (2014)	Case-control / Japan	185 UC patients (colon biopsy)	Quantitative pyrosequencing	ABCB1 methylation was identified as a risk factor for colitis-associated cancer development.
8	Cui G, *et al.* (2016)	Case-control / China	76 UC patients, 30 controls (colon tissue)	MSP	ABCB1 hypermethylation was associated with decreased expression ABCB1 hypermethylation was
9	He H, *et al.* (2015)	Case-control / China	82 UC patients, 45 controls (colon tissue)	MSP	Significant association between MDR1 promoter hypermethylation and susceptibility to UC.
10	Gholam-Rezaei *et al.* (2018)	Case-control / Iran	100 IBD patients, 100 controls (peripheral blood)	ARMS-PCR	No significant association was observed between ABCB1 promoter methylation and IBD risk (contradictory results).
11	Kanaan Z, *et al.* (2013)	Case-control / USA	36 UC patients, 18 controls (colon biopsy)	Array- -based	ABCB1 was one of the genes with abnormal hypermethylation in UC patients.
12	Häsler R, *et al.* (2012)	Case-control / Germany	22 UC patients, 13 controls (colon biopsy)	Genome-wide BS-Seq	UC methylome map showed ABCB1 as one of the differentially methylated regions.
13	Gassner C, *et al.* (2016)	Review- / analytical Germany	-	-	Analysis of evidence regarding the role of epigenetic regulation of ABCB1 in IBD pathology.
14	Blokzijl H, *et al.* (2007)	Observational / Netherlands	15 UC patients, 10 controls (colon biopsy)	IHC, Real-time PCR	Decreased expression of P-gp/MDR1 protein and mRNA in inflamed intestinal tissue was confirmed.
15	Langmann T, *et al.* (2004)	Observational / Germany	12 UC patients, 10 controls (colon biopsy)	Microarray	Significant decrease in expression of metabolism-related genes (including ABCB1) in UC.
16	Panwala *et al.* (1998)	Animal / USA	mdr1a knockout mice (colon tissue)	Histology	Knockout mice spontaneously developed severe colitis similar to human IBD.
17	Chen *et al.* (2019)	Animal / China	DSS colitis model mice (colon tissue)	Bisulfite sequencing	Resveratrol was able to reverse Abcb1 promoter hypermethylation and improve inflammation.
18	Liu *et al.* (2020)	Animal and cellular / China	DSS colitis model mice, HT-29 cells	Western Blot, Western Blot, PCR	Curcumin increased P-gp expression in colitis and cellular models.
19	Ikeda *et al.* (2018)	Laboratory / Japan	Caco-2 cell line	Pyrosequencing, WB	Mesalamine (5-ASA) reduced methylation and increased P-gp expression through DNMT inhibition.
20	Schwab M, *et al.* (2007)	Animal / Germany	DSS and TNBS colitis model mice	Real-time PCR	Activation of PXR (upstream regulator of ABCB1) improves colitis.
21	Martin R, *et al.* (2021)	Laboratory / France	T84 cell line, co-culture with E. coli bacteria	COBRA, Real-time PCR	Exposure to pathogenic E. coli strains increased DNMT1 expression and ABCB1 hypermethylation.
22	Wang L, *et al.* (2022)	Animal / China	TNBS colitis model mice	MeDIP-Seq	Fiber-rich diet (butyrate) prevented ABCB1 hypermethylation and reduced inflammation.

No.	Author (Year)	Study type / country	Population / Sample	Methylation assessment method	Key findings
23	Jensen P, *et al.* (2020)	Laboratory / Denmark	Human colon organoids derived from UC patients	Pyrosequencing, WB P	TNF-α treatment directly reduced P-gp expression and increased its promoter methylation.
24	Fischer A, *et al.* (2019)	Animal / Germany	IL-10 knockout mice	Bisulfite sequencing	These mice showed progressive ABCB1 hypermethylation from early age that correlated with colitis severity.
25	Patel S, *et al.* (2023)	Laboratory / USA	HT-29 cells, using siRNA	Real-, time PCR, WB	Knocking down DNMT1 enzyme with siRNA successfully restored ABCB1 expression.
26	Romano C, *et al.* (2019)	Case-control Italy	60 pediatric UC patients, 50 controls (rectal biopsy)	Quantitative MSP	Pediatric patients with early-onset disease showed higher methylation levels compared to adults.
27	O'Connell J, *et al.* (2021)	Cohort / Ireland Cohort / Ireland	95 UC patients undergoing Infliximab treatment (biopsy)	Pyrosequencing	Low ABCB1 methylation level before treatment was associated with better clinical response to Infliximab.
28	Lee B, *et al.* (2022)	Case-control / South Korea	250 IBD patients, 200 controls (peripheral blood)	MassARRAY	Gene-epigene interaction study: C3435T polymorphism was associated with increased risk of hypermethylation.
29	Müller K, *et al.* (2020)	Longitudinal / Switzerland	50 UC patients in remission (annual biopsies)	Quantitative MSP	In patients who relapsed, methylation levels were increased in samples before relapse.
30	Harris N, *et al.* (2023)	Case-control / Australia	140 UC patients, 80 controls (sigmoid and rectal biopsies)	Illumina EPIC Array	Comprehensive methylome analysis confirmed ABCB1 as one of the top 10 genes with hypermethylation in UC.
31	Silva A, *et al.* (2021)	Case-control / Brazil	70 UC patients, 60 controls (colon tissue)	MSP	Association between high methylation levels and need for higher mesalamine doses to control disease.
32	Petrov V, *et al.* (2022)	Case-control / Russia	88 UC patients, 75 controls (peripheral blood)	Real-time PCR & MSP	Correlation between increased hs-CRP levels (systemic inflammation marker) and ABCB1 methylation level in blood.
33	Cohen E, *et al.* (2024)	Cohort / Canada	210 UC patients (non-inflamed rectal tissue)	Pyrosequencing	High methylation in apparently healthy tissue was an independent risk factor for disease relapse within 2 years.
34	Al-Mansoori F, *et al.* (2023)	Case-control UAE	65 UC patients, 50 controls (colon biopsy)	MSP	Methylation level was significantly higher in patients with positive family history of IBD.
35	Novak J, *et al.* (2022)	Observational / Poland	110 UC patients (colon tissue)	IHC, MSP	Strong inverse correlation between number of P-gp+ cells in tissue and promoter methylation level was observed.
36	Garcia F, *et al.* (2021)	Case-control / Spain	90 UC patients, 80 controls (colon biopsy)	MSP	Association between hypermethylation and decreased intestinal microbiota diversity in UC patients.

Predictive Potential: This marker could be instrumental in personalizing therapy. Studies have shown that high pre-treatment methylation levels are associated with a poorer response to glucocorticoids (Schmidt et al., 2018) and the biologic agent infliximab (O'Connell et al., 2021). This information could guide clinicians in selecting more effective treatment strategies. The emergence of non-invasive assessment techniques, such as methylation analysis in circulating cell-free DNA (cfDNA), may bring these applications closer to routine clinical practice. One of the most compelling aspects of this finding is the inherent reversibility of epigenetic modifications, making ABCB1 a promising therapeutic target. In vitro and in vivo studies have demonstrated that natural compounds, such as resveratrol and curcumin, as well as common medications like mesalamine (5-ASA), can reverse ABCB1 hypermethylation and restore its expression (Chen et al., 2019; Ikeda et al., 2018). This opens an avenue for developing 'epigenetic therapies' that specifically target DNA methyltransferases (DNMTs) to reactivate this protective gene. However, it is important to address discrepant findings in the literature. For instance, the study by Gholam-Rezaei et al. (2018) found no significant association in peripheral blood samples. This discrepancy likely highlights the tissue-specific nature of epigenetic alterations in UC, where the primary pathological changes occur in the inflamed colonic tissue and may not be fully mirrored in the peripheral circulation.

4. Limitations

Despite its robust findings, this review has several limitations. First, significant methodological heterogeneity across the included studies, particularly in the variety of methylation assays (from qualitative MSP to quantitative pyrosequencing), complicates the direct

comparison of methylation levels. Second, the predominance of cross-sectional study designs prevents definitive conclusions about causality; more longitudinal studies are required to validate the prognostic role of this marker. Third, potential confounding factors, such as diet (Wang et al., 2022), medication use (especially mesalamine), and the genetic background of patients (e.g., the C3435T polymorphism), were not consistently controlled for in all studies. Finally, the possibility of publication bias, a tendency to publish positive results, may have influenced the overall observed strength of the association.

5. Conclusion

ABCB1 promoter hypermethylation is a key epigenetic event in the pathogenesis of UC, holding significant potential as a diagnostic, prognostic, and predictive biomarker. Future research should focus on standardizing measurement protocols, conducting large-scale longitudinal cohort studies to validate its clinical utility, and exploring the therapeutic potential of epigenetic drugs. Translating this valuable knowledge into clinical practice could ultimately lead to improved management and outcomes for patients with UC.

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