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Review

Microvascular Endothelial Barrier Failure in Acute Lung Inflammatory Diseases: From Epigenetic Regulation to Clinical Implications

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ABSTRACT: Pulmonary microvasculature, which is intimately associated with the alveoli, carries the entire cardiac output through an extensive capillary network and plays a pivotal role in gas exchange by maintaining the structural and functional integrity of the alveolar-capillary barrier. Preservation of cell-cell junctions is essential for preventing paracellular leakage and leukocyte infiltration, which are characteristic features of acute lung inflammatory disorders, including acute respiratory distress syndrome (ARDS) and acute exacerbations of chronic lung diseases. Epigenetic regulation serves as a fundamental mechanism linking chromatin dynamics to endothelial barrier function. By modulating gene expression and downstream processes, including protein stability, subcellular localization, and enzymatic activity, epigenetic pathways regulate cell-cell junctions, ultimately determining microvascular endothelial barrier integrity. This review provides an in-depth overview of the molecular regulation of cell-cell junction dynamics in pulmonary endothelial cells under acute inflammatory stress, with a focus on the roles of epigenetic modifications. In addition, it evaluates current therapeutic strategies targeting microvascular endothelial barrier dysfunction and discusses their translational and clinical limitations. By integrating recent advances in cellular and preclinical research with translational efforts, this review identifies key knowledge gaps and outlines future directions for developing precision therapeutics to preserve microvascular endothelial barrier integrity in acute inflammatory diseases.

Keywords: Endothelial cell junctions; Barrier function; Epigenetics; Lung inflammatory diseases

1. Introduction

Edema and neutrophil infiltration into alveolar spaces resulting from alveolar-capillary barrier dysfunction are hallmarks of acute inflammatory lung diseases, such as ARDS, exacerbations of chronic lung disorders, and severe systemic inflammatory conditions [1–5]. Excessive production of cytokine and pathogen- or damage-associated molecular patterns (PAMPs or DAMPs) increases pulmonary microvascular endothelial cell permeability, leading to the leakage of protein-rich fluid and recruitment of

neutrophils into the alveolar compartment [6–8]. The resulting alveolar injury compromises gas exchange and contributes to respiratory failure.

The strength and integrity of junctional contacts between adjacent endothelial cells within the monolayer largely determines microvascular endothelial cell barrier permeability. In general, three major mechanisms regulate endothelial barrier permeability. First, endothelial cell death, resulting from either direct injury or programmed cell death, disrupts the integrity of the endothelial monolayer and compromises barrier function. Second, disruption of intercellular junctions, including tight junctions, adherens junctions, and gap junctions, weakens cell-cell adhesion and increases the gaps between adjacent endothelial cells. Third, endothelial cell contraction decreases cell spreading and surface area, resulting in further expansion of intercellular gaps. Collectively, these processes act in a coordinated manner to increase microvascular endothelial barrier permeability during acute inflammatory conditions (Figure 1).

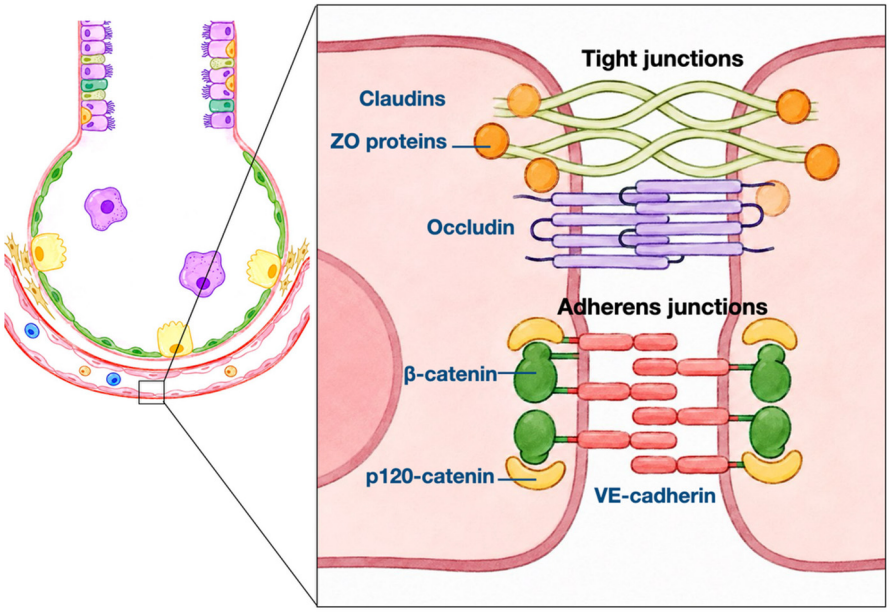

Figure 1. Lung endothelial cell junctions. Schematic illustration of the major junctional structures between lung endothelial cells, including tight junctions, adherens junctions, and associated cell–cell adhesion complexes.

Epigenetic regulation serves as a fundamental mechanism linking chromatin architecture to gene expression. Histone acetylation and DNA and RNA methylation are among the most extensively studied epigenetic modifications and play critical roles in controlling the expression of proteins involved in endothelial barrier function and cell-cell junction assembly [9–12]. Acetylation of lysine residues on histone tails neutralizes their positive charge, weakening histone-DNA interactions and promoting a more open chromatin configuration that facilitates transcription factor access and gene transcription [13–15]. Accordingly, histone acetylation is generally associated with transcriptional activation. This process is tightly controlled by the opposing activities of histone acetyltransferases (HATs), which deposit acetyl groups, and histone deacetylases (HDACs), which remove them. Through coordinated regulation of chromatin accessibility, HATs and HDACs modulate the expression of numerous genes involved in inflammatory signaling and endothelial junctional integrity [14,16–18]. In addition to histone modifications, DNA and RNA methylation provide an additional layer of epigenetic regulation. DNA methylation, which primarily occurs at cytosine residues within CpG-rich regions, is commonly associated with gene silencing [19–21]. RNA methylation regulates post-transcriptional gene expression by influencing RNA processing, stability, localization, and translation [22–24]. These modifications are catalyzed by DNA methyltransferases (DNMTs) and methyltransferase-like (METTL) enzymes, which function as epigenetic methylation writers.

The extent of DNA and RNA methylation is further influenced by the cellular availability of S-adenosylmethionine (SAM), the universal methyl donor required for methylation reactions [25–27].

Epigenetic alterations affect endothelial barrier integrity by modulating cell death, cell junction protein expression and trafficking, as well as cytoskeletal remodeling. However, to maintain a clear and focused scope and avoid complexity associated with discussing multiple pathways, this review primarily focuses on recent advances in understanding the epigenetic regulation of gene expression related to cell-cell junction proteins and the molecular mechanisms that govern epigenetic modifications (Figure 2). The majority of the available literature on epigenetic regulation of cell-cell junction proteins is not directly from pulmonary endothelial cells (Table 1). Therefore, one of the objectives of this review is to highlight a promising research direction by integrating current knowledge of epigenetic modifications regulating cell-cell junction proteins in other cell types and discussing their potential relevance to pulmonary microvascular endothelial cells.

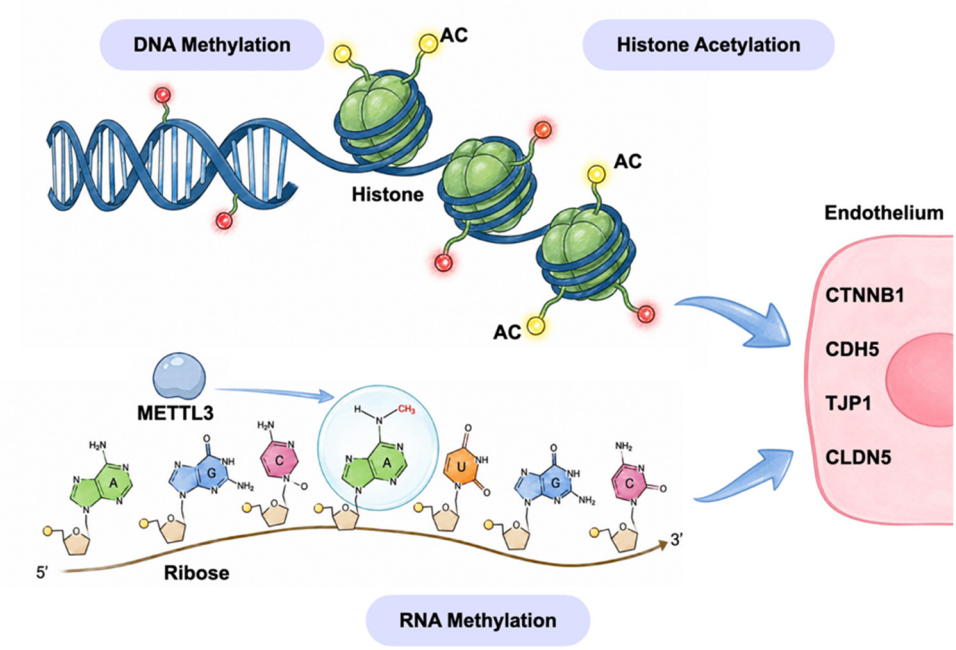

Figure 2. Histone acetylation, DNA, and RNA methylation regulate endothelial cell junction protein expression. Histone acetylation regulates chromatin accessibility and gene transcription; DNA methylation involves the addition of methyl groups to DNA, primarily at cytosine residues; and RNA methylation, particularly N6-methyladenosine (m6A), modifies adenosine residues in RNA and regulates RNA function.

2. Histone Acetylation and Adherens Junction Protein Expression

VE-cadherin is an endothelial-specific adherens junction protein that plays a critical role in maintaining endothelial barrier integrity. The extracellular domains of VE-cadherin molecules on neighboring endothelial cells form calcium-dependent homophilic interactions that zipper adjacent cells together and maintain vascular barrier function. In response to inflammatory stimuli, VE-cadherin undergoes phosphorylation, which promotes its internalization and degradation, thereby increasing endothelial permeability [28–30]. The gene encoding VE-cadherin, *CDH5,* is also regulated by epigenetic mechanisms. Histone H3 located near the *CDH5* promoter can be acetylated at lysine 9 (H3K9ac) and lysine 18 (H3K18ac) by the histone acetyltransferase KAT14 [31]. Ma et al. demonstrated that KAT14 deficiency significantly reduced *CDH5* expression, whereas KAT14 overexpression restored *CDH5* levels [31]. Furthermore, the authors showed that KAT14-mediated histone acetylation facilitates the binding of serum response factor (SRF) to the *CDH5* promoter, thereby enhancing gene transcription [31]. Although this

study was conducted in trophoblast cells rather than endothelial cells, trophoblasts also express VE-cadherin, suggesting a potentially conserved regulatory mechanism. Consistent with this study, Zhang and Ge reported that histone deacetylase 11 (HDAC11) suppresses VE-cadherin expression in human umbilical vein endothelial cells (HUVECs) [32]. Reduced VE-cadherin expression was associated with protease-activated receptor 2 (PAR2)-mediated increases in endothelial permeability [32]. Collectively, these findings support a role for histone acetylation in promoting *CDH5* expression and maintaining endothelial barrier function.

However, not all studies have yielded consistent results. Hrgovic et al. reported that treatment with histone deacetylase inhibitors, including trichostatin A (TSA), reduced VE-cadherin expression [33]. This observation appears to contradict the findings of Zhang and Ge. One possible explanation is that TSA is a broad-spectrum HDAC inhibitor and affects multiple HDAC isoforms in addition to HDAC11 [32]. Therefore, the inhibitory effect of TSA on VE-cadherin expression may result from the suppression of other HDAC family members rather than HDAC11 alone.

Interestingly, lipopolysaccharide (LPS) treatment has been shown to increase H3K9ac and H3K18ac levels in mouse lung endothelial cells [34], suggesting that histone acetylation is dynamically regulated during inflammatory responses. However, direct evidence linking KAT14 or HDAC11 to *CDH5* expression in pulmonary microvascular endothelial cells remains lacking. Likewise, the roles of these epigenetic regulators in controlling lung endothelial barrier integrity have not been investigated. Future studies are needed to determine whether KAT14, HDAC11, or other regulators of histone acetylation modulate *CDH5* expression in pulmonary microvascular endothelial cells and to define their contributions to endothelial barrier dysfunction during acute inflammatory lung diseases.

The cytoplasmic tail of VE-cadherin associates with β-catenin and p120-catenin, two adaptor proteins that stabilize adherens junctions and link VE-cadherin to the actin cytoskeleton [35–38]. Disruption of this multiprotein complex is a key mechanism underlying endothelial barrier dysfunction. Consistent with this concept, expression of both *CDH5* and *CTNNB1* (encoding β-catenin) is reduced in experimental models of LPS-induced acute lung injury [39].

Although histone acetylation has emerged as an important regulator of endothelial barrier function, its role in controlling catenin expression remains incompletely understood. W2A-16-mediated histone acetylation enhanced barrier integrity in cerebral microvascular endothelial cells (hCMEC/D3) without affecting β-catenin expression [40], suggesting that histone acetylation may influence endothelial permeability through mechanisms independent of β-catenin abundance. In addition, HDAC6/7 have been shown to regulate β-catenin acetylation status and nuclear localization, highlighting a complex interplay between epigenetic regulation and β-catenin signaling [41,42]. However, direct evidence linking histone acetylation to the transcriptional regulation of *CTNNB1* or *CTNND1* is currently lacking.

Given the central roles of VE-cadherin, β-catenin, and p120-catenin in maintaining endothelial junctional integrity, future studies should determine whether histone acetylation regulates the expression of these proteins in pulmonary microvascular endothelial cells and how such regulation contributes to endothelial barrier dysfunction during acute inflammatory lung injury. In addition to its structural role within adherens junctions, β-catenin functions as a transcriptional co-activator in the canonical Wnt signaling pathway [43–45], suggesting that epigenetic regulation of β-catenin may influence endothelial barrier function through both junctional and transcriptional mechanisms. Addressing these questions may reveal novel epigenetic mechanisms and therapeutic opportunities for preserving vascular barrier function in diseases such as ARDS.

3. Histone Acetylation and Tight Junction Protein Expression

In addition to adherens junctions, tight junctions play an essential role in maintaining endothelial barrier integrity. Abnormalities in endothelial tight junctions contribute to the disruption of the alveolar-capillary barrier, resulting in pulmonary edema and impaired gas exchange during inflammatory lung diseases [46–48]. Claudins, occludin, and junctional adhesion molecules (JAMs) are the principal transmembrane components of endothelial tight junctions and interact intracellularly with zonula occludens (ZO) proteins to form a functional junctional complex [49–52].

Among the claudin family members, claudin-5, claudin-9, and claudin-11 are prominently expressed in endothelial cells [53]. Epigenetic regulation has emerged as an important mechanism controlling the expression of these proteins. Exposure to high glucose levels suppresses the expression of *CLDN5* and *CLDN11* in endothelial cells through alterations in histone H3 lysine 9 acetylation (H3K9ac) [53]. Further mechanistic studies demonstrated that HDAC3 contributes to the regulation of H3K9ac at the *CLDN5* locus, thereby influencing *CLDN5* expression [54]. Consistent with these findings, HDAC3 has also been implicated in the regulation of claudin expression in intestinal epithelial cells [55]. In addition to HDAC3, HDAC1 regulates *CLDN5* expression through modulation of H3K27 acetylation (H3K27ac) in human brain microvascular endothelial cells [56]. Pharmacological inhibition of class IIa HDACs with TMP269 increases the expression of claudin-5, occludin, and ZO-1 in endothelial cells and preserves blood-brain barrier integrity in murine models of ischemia-reperfusion injury [57]. These findings collectively suggest that HDAC-mediated histone deacetylation plays a critical role in regulating tight junction protein expression and endothelial barrier function.

Sirtuins constitute a family of NAD(+)-dependent deacetylases with diverse functions in chromatin regulation and cellular metabolism. Among them, SIRT1, SIRT6, and SIRT7 are predominantly localized in the nucleus [29,58]. Overexpression of SIRT6 decreased ZO-1, occludin, and claudin-3 mRNA and protein levels in brain tissues [59], which were associated with blood-brain barrier disruption. However, this study did not determine whether SIRT6 directly regulates tight junction protein transcripts. Conversely, SIRT6 has been reported to increase ZO-1 and occludin expression in lung epithelial cells, thereby promoting epithelial barrier integrity [60]. However, these effects do not appear to result directly from histone deacetylation at tight junction gene promoters, suggesting the involvement of alternative transcriptional or signaling mechanisms.

Notably, most studies to date have focused on the role of HDACs as epigenetic “erasers” that remove acetyl groups from histones and regulate tight junction protein expression. In contrast, considerably less is known about the contribution of histone acetyltransferases (HATs) to tight junction gene regulation. CREB-binding protein (CBP) and p300 are major histone acetyltransferases that play central roles in inflammatory gene transcription and the pathogenesis of inflammatory lung diseases [61,62]. In addition to their chromatin-modifying functions, CBP/p300 can cooperate with multiple transcription factors, including β-catenin, to regulate gene expression downstream of canonical Wnt signaling [63]. Given the established importance of Wnt/β-catenin signaling in endothelial barrier maintenance and vascular repair, it is possible that CBP/p300-mediated histone acetylation may influence tight junction protein expression through both chromatin remodeling and Wnt-dependent transcriptional mechanisms.

Despite these observations, significant knowledge gaps remain regarding the role of HATs in regulating tight junction protein expression in pulmonary microvascular endothelial cells. Future studies are needed to determine whether CBP/p300, KAT family members, or other HATs directly control the expression of *CLDN5*, *CLDN11*, *OCLN* (encoding occludin), and *TJP1* (encoding ZO-1) in lung endothelial cells and to define how these epigenetic mechanisms interact with inflammatory signaling and Wnt/β-catenin pathways during acute inflammatory lung injury. Addressing these questions may identify novel

therapeutic targets to preserve endothelial barrier integrity and reduce pulmonary edema in diseases such as ARDS.

4. DNA and RNA Methylation in the Regulation of Cell Adherens Junction Proteins

DNA methylation is generally associated with transcriptional repression [64]. One of the earliest reports linking DNA methylation to *CDH5* regulation demonstrated hypermethylation of the *CDH5* promoter in neuroblastoma cells, which express low or undetectable levels of VE-cadherin [65]. Subsequent analyses using the Infinium HumanMethylation450 BeadChip array identified DNA methylation within the proximal *CDH5* promoter region as a key regulatory mechanism controlling VE-cadherin expression [66].

Increased DNA methylation has also been associated with elevated vascular permeability. For example, enhanced DNA methylation has been reported to increase cortical vascular permeability [67]. DNA methylation contributes to vascular aging [68]. However, whether these effects are mediated through suppression of *CDH5* expression remains unclear. In endothelial cells, bacterial LPS induces DNA methyltransferase 3A (DNMT3A)-dependent DNA methylation [69], suggesting that inflammatory stimuli can directly alter the endothelial epigenetic landscape. Furthermore, pharmacological inhibition of DNA methylation attenuates both LPS-induced and ischemia-reperfusion-induced experimental lung injury [70–72], supporting a pathogenic role for aberrant DNA methylation in pulmonary vascular dysfunction. Although VE-cadherin expression is reduced during acute lung injury, direct evidence linking *CDH5* downregulation to promoter hypermethylation in pulmonary microvascular endothelial cells is currently lacking. Elucidating the molecular mechanisms governing *CDH5* methylation may provide important insights into the epigenetic regulation of endothelial barrier integrity and facilitate the development of targeted therapies to preserve VE-cadherin expression under inflammatory conditions.

Expression of *CTNNB1* is also regulated by DNA methylation. In colon and lung cancers, *CTNNB1* expression is suppressed by promoter hypermethylation [73,74], whereas promoter hypomethylation has been associated with increased *CTNNB1* expression in glioblastoma multiforme [75]. These observations indicate that DNA methylation is an important regulator of β-catenin expression in a cell- and disease-specific manner. However, it remains unknown whether DNA methylation regulates *CTNNB1* expression in endothelial cells during acute inflammatory lung injury.

In addition to DNA methylation, RNA N6-methyladenosine (m6A) modification has emerged as a critical regulator of mRNA stability, splicing, localization, and translation [76,77]. Methyltransferase-like 3 (METTL3) has been reported to function as an m6A “writer” that promotes m6A modification of *CTNNB1* transcripts and suppresses β-catenin expression in hepatoblastoma cells [78]. Recent studies have highlighted a broader role for m6A methylation in endothelial biology. Zhao et al. demonstrated that METTL3-mediated m6A methylation regulates glycolytic gene expression and metabolic reprogramming in endothelial cells under atherogenic conditions [79]. Importantly, both METTL3 expression and global m6A methylation levels are increased in LPS-treated lung endothelial cells [80]. Genetic knockdown or pharmacological inhibition of METTL3 protects against LPS-induced endothelial hyperpermeability [80], suggesting that excessive m6A methylation contributes to barrier dysfunction by suppressing genes involved in endothelial barrier maintenance.

Collectively, these findings suggest that both DNA methylation and m6A RNA methylation participate in the epigenetic regulation of endothelial barrier function. Nevertheless, significant knowledge gaps remain regarding the regulation of *CDH5*, *CTNNB1*, and other junctional genes by DNA and RNA methylation in pulmonary microvascular endothelial cells. Future studies should investigate the methylation status of the *CDH5* and *CTNNB1* promoters, determine whether *CTNNB1* transcripts undergo m6A modification in lung endothelial cells, and identify the specific DNMT, METTL, and demethylase enzymes involved. A deeper understanding of these epigenetic mechanisms may reveal novel therapeutic targets to preserve endothelial barrier integrity and mitigate pulmonary edema in acute inflammatory lung diseases.

5. DNA Methylation in the Regulation of Tight Junction Proteins

DNA methylation has emerged as an important epigenetic mechanism regulating the expression of tight junction proteins and endothelial barrier function. Huls et al. identified multiple DNA methylation sites within the *CLDN5* locus and demonstrated that their methylation status was associated with cognitive trajectory in aging individuals [81]. Because *CLDN5* is highly enriched in brain endothelial cells and is essential for blood-brain barrier integrity, these findings suggest that epigenetic regulation of *CLDN5* may contribute to cerebrovascular dysfunction. Consistent with this concept, recent studies have linked *CLDN5* hypermethylation to an increased risk of neurodegenerative diseases [82,83], further supporting a role for DNA methylation in regulating endothelial barrier function.

In addition to *CLDN5*, alterations in DNA methylation have been reported for other tight junction genes. For example, *OCLN* exhibits promoter hypomethylation in brain microvascular endothelial cells isolated from mice following thromboembolic stroke [84]. DNA methylation has also been implicated in the regulation of *TJP1* (ZO-1) expression. In mouse brain endothelial cells, DNA methyltransferase 3A (DNMT3A)-mediated promoter hypermethylation suppresses *TJP1* expression, leading to endothelial barrier dysfunction following ethanol exposure [67]. These findings collectively indicate that DNA methylation can modulate multiple components of the tight junction complex, thereby influencing endothelial permeability.

Notably, most studies investigating the epigenetic regulation of *CLDN5*, *OCLN*, and *TJP1* have been conducted in brain endothelial cells. Recent studies have demonstrated that inflammatory stimuli such as LPS induce DNMT3A expression and global DNA methylation changes in endothelial cells [69]. However, comparatively little is known about the role of DNA methylation in regulating tight junction proteins in pulmonary microvascular endothelial cells. Nevertheless, the blood-brain barrier and alveolar-capillary barrier share several structural and functional features, including the requirement for tightly regulated intercellular junctions to maintain vascular integrity. Therefore, it is plausible that DNA methylation of tight junction genes, particularly *CLDN5*, also contributes to the regulation of pulmonary endothelial barrier function.

In addition, emerging evidence suggests that DNA methylation may interact with other epigenetic pathways, including histone modifications and RNA methylation, to coordinately regulate endothelial gene expression. Understanding these interactions may be particularly important for tight junction genes, whose expression is tightly controlled during inflammatory stress. Future studies should investigate the methylation status of *CLDN5*, *OCLN*, and *TJP1* promoters in pulmonary endothelial cells and determine whether DNMT-dependent methylation directly contributes to endothelial barrier disruption in acute inflammatory lung diseases.

Table 1. Epigenetic modifications modulate cell-cell junction protein expression in endothelial and non-endothelial cells.

Epigenetic Modifications	Cell-Cell Junction Proteins	Regulators	Cells/Models	Ref.
H3K9ac	CDH5	KAT14	Spiral artery	[31]
	CDH5	HDAC11	HUVECs	[32]
	CDH5	HDACs	HUVECs	[33]
H3K9ac	CLDN5 CLDN11	HDAC3	Cardiac microvascular endothelial cells	[53,54]
	CLDNs	HDAC3	Intestinal epithelial cells	[55]
H3K27ac	CLDN5	HDAC1	Brain microvascular endothelial cells	[56]
H2ac	CLDN5, OCLN, TJP1	Class IIa HADCs	Cerebral ischemia/reperfusion	[57]
	TJP1, OCLN, CLDN3	SIRT6	Brain tissues	[59]
	TJP1, OCLN	SIRT6	Lung epithelial cells	[60]
DNAm	CDH5		Neuroblastoma cells	[65]

DNAm	CDH5		Leukocytes	[66]
DNAm	CTNNB1		Colon cancer, lung cancer, glioblastoma	[73–75]
m6A	CTNNB1	METTL3	Hepatoblastoma cells	[78]
DNAm	CLDN5		Brain barrier, PTSD, Trauma	[81–83]
DNAm	OCLN		Braine microvascular endothelial cells	[84]
DNAm	TJP1	DNMT3A	Brain endothelial cells	[67]

DNAm, DNA methylation, PTSD, post-traumatic stress disorder.

6. Histone Acetylation and DNA Methylation Modifiers in the Treatment of Acute Inflammatory Lung Diseases

As discussed above, significant knowledge gaps remain regarding the epigenetic regulation of cell junction proteins in pulmonary endothelial cells. Nevertheless, accumulating *in vivo* evidence indicates that pharmacological modulation of histone acetylation and DNA methylation can attenuate acute inflammatory lung injury and improve vascular barrier function. These findings suggest that epigenetic regulators may represent promising therapeutic targets for the treatment of acute inflammatory lung diseases. For example, inhibition of histone deacetylases (HDACs) with valproic acid has been shown to attenuate subarachnoid hemorrhage-associated [85] and ischemia/reperfusion-induced acute lung injury [86] in experimental models. The protective effects were associated with reduced inflammation, decreased pulmonary edema, and improved lung function. Similarly, other HDAC inhibitors have demonstrated beneficial effects in preclinical models of lung injury by suppressing inflammatory signaling pathways and preserving endothelial barrier integrity. Wrede et al. comprehensively summarized pathogen-induced epigenetic modifications in the lung and highlighted the importance of epigenetic mechanisms in regulating inflammatory responses during pulmonary infection [87]. However, the specific epigenetic alterations occurring in pulmonary endothelial cells, particularly those involved in the regulation of adherens and tight junction proteins, were not extensively discussed. Given the central role of endothelial barrier dysfunction in the pathogenesis of acute lung injury and ARDS, further investigation into endothelial-specific epigenetic mechanisms is warranted.

In addition to histone acetylation, DNA methylation has emerged as a potential therapeutic target. Thangavel et al. demonstrated that combined treatment with a DNA methyltransferase (DNMT) inhibitor and an HDAC inhibitor significantly reduced pulmonary vascular hyperpermeability in an LPS-induced model of acute inflammatory lung injury [34,88]. These findings suggest that coordinated targeting of multiple epigenetic pathways may provide greater therapeutic efficacy than modulation of a single pathway alone.

7. Knowledge Gaps, Challenges, and Future Perspectives

Although histone acetylation and DNA methylation have been implicated in the regulation of cell junction protein expression, and inhaled pathogens are known to induce epigenetic alterations in the lung, studies specifically investigating these mechanisms in pulmonary endothelial cells remain limited, particularly in the context of acute inflammatory lung diseases. Consequently, the epigenetic regulation of endothelial barrier function in the alveolar-capillary compartment remains incompletely understood.

A major knowledge gap is the lack of direct evidence linking epigenetic modifications to the expression of endothelial junction proteins in injured lungs. Immunohistochemical or immunofluorescence staining using antibodies against histone acetylation markers (e.g., H3K9ac and H3K27ac), DNA methylation markers (e.g., 5-methylcytosine), and cell junction proteins, combined with endothelial-specific markers such as CD31, could help determine whether these epigenetic modifications occur in pulmonary endothelial cells and whether they correlate with alterations in junction protein expression during inflammatory lung injury. Furthermore, chromatin immunoprecipitation sequencing (ChIP-seq), assay for transposase-accessible chromatin sequencing (ATAC-seq), and single-cell multi-omics approaches may provide

mechanistic insights into the relationship between epigenetic remodeling and endothelial barrier dysfunction. Further, research approaches to modulate targeted gain/loss-of-function of writers, erasers, and readers, followed by examination of epigenetic modifications and direct functional measurements such as TEER or endothelial permeability, would provide precise evidence for histone/DNA/RNA modifications regulate cell-cell junction protein expression in pulmonary microvascular endothelial cells in the context of acute inflammatory lung diseases.

Human precision-cut lung slices (hPCLS) offer a particularly valuable translational platform because they preserve the native three-dimensional architecture of the lung and maintain complex interactions among endothelial, epithelial, immune, and stromal cells [89,90]. Combining hPCLS with multiplex immunofluorescence imaging, spatial transcriptomics, and spatial proteomics could enable comprehensive characterization of epigenetic modifications and junction protein expression within pulmonary endothelial cells under physiologically relevant conditions. Such approaches may help bridge the gap between findings obtained in isolated cell cultures and those observed *in vivo*.

Another important challenge relates to the therapeutic targeting of epigenetic regulators. HATs and HDACs are central regulators of chromatin structure and gene expression. However, these enzymes also modify numerous non-histone proteins, including transcription factors, signaling molecules, and cytoskeletal proteins. Consequently, pharmacological modulation of HATs or HDACs can influence a broad spectrum of cellular processes beyond chromatin remodeling. This lack of specificity raises concerns regarding off-target effects and potential toxicities associated with systemic administration of epigenetic therapies. A rare case has been reported that valproic acid induced interstitial pneumonitis [91]. Similar challenges exist for DNA methyltransferase inhibitors and emerging RNA methylation-targeting compounds, which may affect multiple cell types and biological pathways. To date, there are no active clinical trials evaluating drugs that specifically target epigenetic regulators as primary therapeutics for ARDS. To overcome these limitations, future therapeutic strategies should focus on cell-specific delivery approaches. Nanoparticle-based drug delivery systems, lipid nanoparticles, and engineered extracellular vesicles could be utilized to selectively target pulmonary endothelial cells and minimize systemic exposure. In addition, adeno-associated virus (AAV)-based gene delivery systems driven by endothelial-specific promoters, such as the *CDH5* promoter, may provide a means to selectively modulate epigenetic regulators within the pulmonary endothelium. These approaches could improve therapeutic efficacy while reducing unintended effects on other cell populations. Precisely modulating histone methylation at specific histone lysine residues involved in cell junction gene regulation or targeting genome loci responsible for DNA methylation remains a significant technical challenge. Emerging technologies, such as small RNA aptamers combined with guide RNA-based approaches, may offer a more precise strategy for selectively regulating the expression of cell-cell junction genes.

In summary, despite growing evidence that epigenetic mechanisms contribute to endothelial barrier dysfunction, direct studies in pulmonary microvascular endothelial cells remain scarce. Integrating advanced spatial omics technologies, human PCLS models, and endothelial-targeted therapeutic approaches will be critical for defining the epigenetic landscape of endothelial barrier regulation. Addressing these challenges may facilitate the development of precision epigenetic therapies to prevent vascular leakage, pulmonary edema, and respiratory failure in acute inflammatory lung diseases.

Author Contributions

B.B. and J.Z. searched research articles and drafted the manuscript. J.Z. supervised the project and finalized manuscript.

Ethics Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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