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Review

RSV-Induced Epigenetic Reprogramming: Mechanisms and Therapeutic Opportunities

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Clinical Question Box

Can epigenetic biomarkers help determine which infants with respiratory syncytial virus (RSV) infection are at greater risk for severe disease?

RSV infection causes specific epigenetic changes, including variations in DNA methylation, histone modifications, and shifts in noncoding RNA levels. These molecular markers reflect the strength of the antiviral and inflammatory responses and are linked to both immediate disease severity and future respiratory issues. Detecting these epigenetic signals early will enable healthcare providers to identify infants at higher risk of deterioration or long-term respiratory problems, such as recurrent wheeze or asthma. Incorporating epigenetic biomarkers into clinical evaluation could allow earlier risk assessment and more tailored treatment plans compared to symptom-based approaches.

Abstract

Respiratory syncytial virus (RSV) is a leading cause of severe lower respiratory infections in infants and young children, and it significantly contributes to illness in older adults and immunocompromised individuals. Besides established immune evasion mechanisms, growing evidence indicates that

RSV actively reprograms host epigenetic regulation, affecting both antiviral defenses and long-term respiratory health. RSV alters DNA methylation, histone modifications, chromatin accessibility, and noncoding RNA (ncRNA) expression in various immune and structural cell types, including airway epithelial cells, T cells, B cells, and innate immune cells. These epigenetic changes influence transcriptional programs that regulate cytokine responses, cytotoxic activity, and memory development, ultimately impacting disease severity and the risk of chronic issues like recurrent wheeze and asthma. New epigenetic biomarkers offer promising options for early risk assessment and personalized prognosis in clinical settings. Epigenetic-targeted treatments, such as selective histone deacetylase inhibitors and CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-based gene regulation, show therapeutic promise, though challenges remain regarding off-target effects, delivery methods, and cell-specific targeting. Advances in multi-omics integration, spatial and single-cell technologies, and patient-derived airway organoids provide increasingly relevant human models for studying RSV–epigenome interactions and developing precise therapies. Understanding and harnessing epigenetic reprogramming could spawn novel approaches for predicting severe disease and preventing long-term complications.

Keywords: Respiratory syncytial virus, epigenetics, immune evasion, biomarkers, therapeutics

Introduction

Respiratory syncytial virus (RSV) is a single-stranded, negative-sense RNA virus belonging to the Pneumoviridae family. The RSV genome encodes structural and nonstructural proteins that collectively govern viral entry, replication, and immune evasion.[1] The attachment glycoprotein facilitates binding to host cells through receptors such as heparan sulfate proteoglycan and fractalkine receptor (C-X3-C motif chemokine receptor 1 [(CX3CR1)]), enabling fusion and entry mediated by the fusion glycoprotein (F).[2–4] The small hydrophobic protein modulates host immunity,[5] while the matrix protein coordinates viral assembly.[6] The nucleoprotein, phosphoprotein, and polymerase complex carry out genomic replication and transcription.[7,8] Nonstructural proteins 1 (NS1) and 2 (NS2) are key antagonists of the host innate immune response. Through these proteins, RSV disrupts multiple innate immune pathways, including toll-like receptor and retinoic acid–inducible gene I (RIG-I)-like receptor signaling and inflammasome activation.[2,9–16] NS1 and NS2 inhibit type I interferon production by targeting interferon regulatory factors (IRFs) and signal transducer and activator of transcription 2; they also shift the cytokine response toward an immunosuppressive profile. Similarly, the F protein can inhibit interferon (IFN) production and leukocyte recruitment.[3,17,18] These viral strategies foster a T helper type 2 (Th2)–biased immune environment, resulting in long-term effects that elevate the risk of childhood asthma.[19,20] While these classical mechanisms explain much of RSV's effective immune evasion, emerging evidence indicates that the virus also co-opts host epigenetic mechanisms to facilitate persistent replication and immune modulation.

In 2019 alone, RSV caused an estimated 33 million episodes of acute lower respiratory tract infections in young children, leading to 3.6 million hospitalizations.[21] It is a leading global cause of these infections in children under 5. Nearly all children are infected at least once by age 2,[22] and reinfection remains common throughout life because natural immunity does not provide full protection. Severe cases also occur in the elderly and immunocompromised individuals.[23–25] RSV follows a distinct seasonal pattern. In temperate climates of the Northern Hemisphere, outbreaks usually occur from October or November through April or May, peaking in January or February. In the Southern Hemisphere, peaks occur from May to September.[26] In tropical regions, RSV circulation is often linked to rainy seasons.[27] Pandemic-related changes in social behavior altered these patterns, with intense off-season surges documented when coronavirus disease 2019 (COVID-19) mitigation measures were lifted.[28] Transmission occurs mainly through inoculation of the nasopharynx or eyes after direct contact with virus-containing secretions or contaminated surfaces. RSV is highly durable in the environment; it can survive for several hours on hands and fomites, facilitating quick spread in households and healthcare settings. Studies show that 42% of RSV infections may be asymptomatic, but affected individuals still shed the virus for an average of 11 days, posing an ongoing transmission risk.[29]

RSV disease severity varies considerably among individuals and is influenced by host-related factors. Established risk factors include prematurity, chronic lung disease, congenital heart disease, Down syndrome, and immunocompromising conditions.[30] Social and environmental factors also contribute: infants who attend daycare or live with older siblings are more likely to acquire infection, and exposure to secondhand smoke increases severity.[31] Genetic studies further suggest that polymorphisms in cytokine- and immune-regulation genes, including interleukin-4 (IL-4), IL-8, IL-10, IL-13, surfactant proteins A and D, and toll-like receptor genes, are associated with greater susceptibility to severe RSV.[32] Collectively, these epidemiological data demonstrate that RSV is not only ubiquitous but maintains a strong seasonal presence and imposes a disproportionate burden on vulnerable individuals.

Clinical Features

RSV in Adults

Although RSV has traditionally been labeled a "pediatric virus," it is increasingly recognized as a significant pathogen in adults, especially older adults and immunocompromised patients. While healthy adults usually experience a mild upper respiratory infection, outcomes are much worse in high-risk groups. In adults undergoing hematopoietic cell transplantation or with hematologic cancers, progression to a lower respiratory tract infection is common and associated with high mortality.[33] An observational study indicates that among severely immunocompromised adults with RSV who require intensive care unit (ICU) admission, approximately 50% require mechanical ventilation.[34] In these populations, RSV can cause respiratory failure, longer hospital stays, and death.

Treatment in adults remains limited and is primarily supportive, though pharmacological therapy is considered in high-risk situations. Ribavirin, a nucleoside analog with in vitro antiviral activity against RSV, is approved by the Food and Drug Administration (FDA) and can be administered orally or via aerosol.[35] Clinical practice often combines ribavirin with intravenous immune globulin and, occasionally, glucocorticoids, based on observational studies indicating reduced progression from upper to lower respiratory tract infections and lower mortality. However, ribavirin use is restricted by toxicities such as hemolytic anemia, bronchospasm, and teratogenic effects during pregnancy. RSV is also clinically significant in adults with asthma or chronic obstructive pulmonary disease, as infection can trigger exacerbations and worsen underlying conditions. Therefore, although pediatric cases dominate RSV-related statistics, the disease also contributes substantially to adult respiratory morbidity, especially in frail or medically complex populations.

RSV in Infants and Children

RSV causes the highest disease burden in infants and young children and is recognized as the leading cause of hospitalization for lower respiratory tract infections, such as bronchiolitis and pneumonia, in infants aged less than 1 year. Globally, RSV leads to hospitalization in 0.4% of children under 5 each year, with the highest burden among infants under 6 months, reaching hospitalization rates of 2%–6%, especially in preterm infants.[36] In an international multicenter case–control study, RSV accounted for 31% of severe pneumonia hospitalizations among children aged 1–59 months in Africa and Asia.[37] A prospective European birth cohort showed that 2% of healthy full-term infants are hospitalized during their first RSV season.[38]

RSV is also a common cause of outpatient visits. Prospective, population-based surveillance showed that RSV accounted for roughly 10%–15% of medically attended acute respiratory infections in outpatient and emergency department settings among young children, with the highest incidence occurring in early infancy.[39] Mortality rates vary significantly across settings. In high-resource countries, RSV-associated mortality in children under 5 is very low (well below 1 death per 100,000 per year).[21] Conversely, in low-resource regions, RSV is a major cause of childhood mortality, accounting for up to 6.5% of deaths among infants aged 28 days to <6 months,[40] ranking second only to malaria. Importantly, approximately 20% of fatal pediatric RSV cases occur in children without major underlying risk factors,[41] and nosocomial infection accounts for about 20% of reported in-hospital RSV deaths globally (up to ~26% in high-income settings).[30] Due to its high transmissibility and

substantial clinical burden in early infancy, RSV remains a primary target for preventive therapies, especially for neonates and high-risk infants.

Treatment and Prevention Strategies

Management of RSV infection in both adults and children is mainly supportive, focusing on maintaining hydration, oxygenation, and proper ventilation. Supportive care includes regular monitoring, suctioning of secretions, hydration, and escalation to supplemental oxygen or mechanical ventilation when necessary. Among hospitalized infants with RSV, only a small minority require invasive mechanical ventilation (about 2% in a prospective multicountry cohort),[42] whereas among severely immunocompromised adults admitted to the ICU for RSV, approximately half require mechanical ventilation. Antiviral treatments are limited. Ribavirin may be considered for severely ill or immunocompromised pediatric patients, but is not routinely recommended for otherwise healthy infants due to unclear benefit and potential side effects. Intravenous immunoglobulin with high RSV-neutralizing activity has been shown to reduce viral load and prevent disease in animal studies, but is no longer commercially available.

A significant change in RSV prevention is underway. Both Arexvy and Abrysvo are authorized by the FDA for RSV prevention, but only Abrysvo is approved for use in pregnant individuals.[43] Evidence indicates that infants with higher RSV antibody levels have milder disease and are less likely to develop lower respiratory tract infections. Two preventive strategies are now available: maternal RSV vaccination in the third trimester, which enables passive transfer of RSV antibodies to the newborn, and long-acting monoclonal antibody prophylaxis (nirsevimab), administered either before RSV season or at birth to protect infants throughout the season.[44] Both methods significantly decrease RSV-related hospitalizations, representing the most essential progress in RSV prevention in decades. A recent study showed the efficacy of clesrovimab in preventing RSV disease in healthy infants.[45]

Epigenetic Mechanisms in RSV Infection

Epigenetics involves the study of heritable changes in gene expression that occur without alterations to the underlying DNA sequence. Key epigenetic mechanisms include DNA methylation, histone modifications, ncRNAs, and chromatin remodeling.[46–48] DNA methylation entails the covalent addition of a methyl group to cytosine bases in cytosine–phosphate–guanine (CpG) dinucleotides, typically leading to transcriptional silencing by obstructing transcription factor binding.[49] Histone modifications are post-translational changes to histone tails, such as acetylation, methylation, phosphorylation, ubiquitination, and the recently identified lactylation, that dynamically regulate chromatin structure and gene transcription.[47,48,50–52] ncRNAs, including microRNAs (miRNAs) and long ncRNAs (lncRNAs), fine-tune gene expression post-transcriptionally; for instance, miRNAs can inhibit translation or promote messenger RNA (mRNA) degradation by binding to target transcripts.[53] Chromatin remodeling involves ATP-dependent complexes that alter nucleosome positioning to regulate DNA accessibility and transcription.[54] RSV infection disrupts these regulatory layers by interacting with host methyltransferases, histone modifiers, and ncRNA pathways, leading to altered DNA methylation patterns, aberrant histone marks, and dysregulated ncRNA expression. These changes collectively shape antiviral gene networks and viral replication.[50,52] Understanding how RSV exploits host epigenetic machinery may reveal novel antiviral targets.

Epithelial Cell Epigenetic Remodeling and Its Barrier Defense

As the primary target of RSV and the first line of defense against infection, respiratory epithelial cells undergo significant epigenetic reprogramming during infection.[55] RSV modulates the function of these barrier cells through various epigenetic pathways, thereby influencing viral replication, inflammatory responses, and disease severity (Fig. 1).

DNA Methylation: RSV can alter innate immune responses and airway pathology by modulating DNA methylation in respiratory epithelial cells. Similar to rhinovirus, which induces widespread CpG methylation changes in human nasal epithelial cells and activates DNA methyltransferases,[56] RSV may also silence critical antiviral genes. Clinical epigenomic analyses of RSV-infected infants have

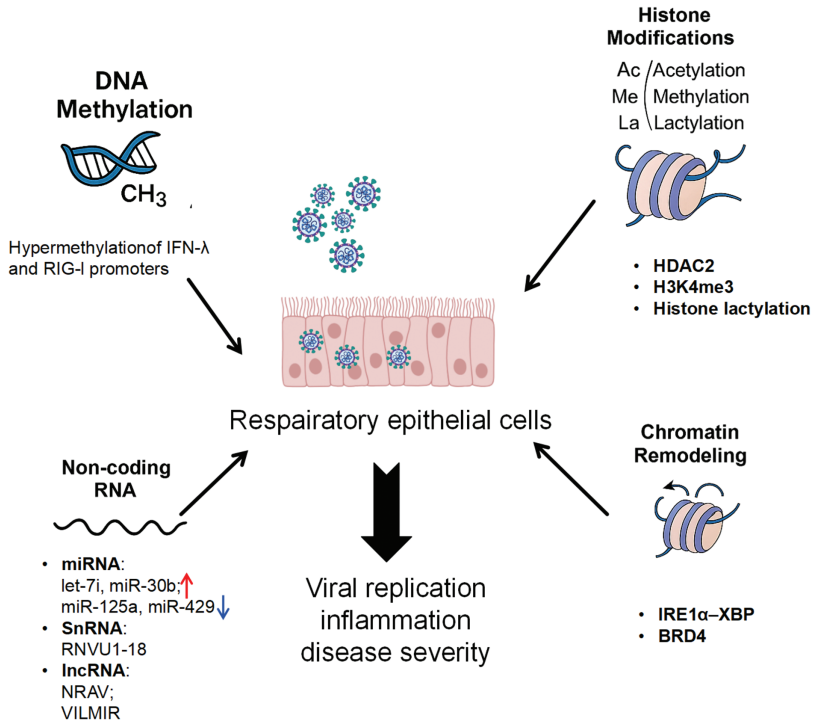

Figure 1. Epigenetic reprogramming of the airway epithelium during RSV infection. RSV reprograms its primary target, the respiratory epithelium, via four interconnected epigenetic axes that collectively govern viral replication, inflammation, and long-term airway pathology.

identified differential host DNA methylation signatures associated with disease severity, consistent with epigenetic modulation of antiviral response pathways rather than random methylation changes.[57] A longitudinal clinical study of children under 2 with RSV infection revealed that those who developed asthma or recurrent wheezing later exhibited significant differences in DNA methylation patterns compared to those who fully recovered, suggesting a link between methylation changes and long-term sequelae.[58] Further, RSV immunoprophylaxis has been shown to alter the methylation profile of nasal epithelial cells in infants, indicating that both natural infection and preventive measures can epigenetically reprogram the airway cells.[59] The clinical findings indicate that RSV and host responses dynamically and reversibly alter DNA methylation in airway epithelial cells, potentially influencing long-term antiviral immunity and respiratory health. While these methylation changes are consistently associated with childhood asthma and wheezing, they may serve as biomarkers for children at risk of these conditions.

Histone Modifications: RSV induces distinct histone modification patterns in respiratory epithelial cells, each differentially regulating antiviral and inflammatory gene expression. In human bronchial epithelial cells (BEAS-2B), RSV increases histone deacetylase 2 (HDAC2) expression. This reduces histone H3 acetylation (e.g., H3K9ac, H3K14ac) at promoters of antiviral genes such as IFN-β and pro-inflammatory genes such as IL-6 and IL-8. The resulting hypoacetylation suppresses transcription and weakens the innate immune response.[60] Treatment with HDAC inhibitors, such as trihydroxypyridine or vorinostat, restores H3 acetylation, reactivates antiviral gene expression, and thus suppresses viral replication and inflammation, underscoring the protective role of histone acetylation during RSV infection. Conversely, in respiratory epithelial cells, RSV infection has been reported to induce enrichment of active chromatin marks (such as H3K4me3 and H3K9ac) at antiviral loci such as RIG-I, and studies in influenza A virus (IAV)–infected epithelial cell models further demonstrate that increased H3K4me3 at the promoters of IFN-β and IFN-stimulated genes (ISGs), including ISG15, augments RIG-I/mitochondrial antiviral-signaling protein–dependent type I IFN responses.[61–63]

The viral NS1 and NS2 proteins can counteract this by inhibiting host methyltransferases. This dual mechanism, suppressing immune gene expression through reduced acetylation while activating antiviral pathways through enhanced methylation, highlights the complex and dynamic regulation of histone marks during RSV infection. Understanding how these modifications are controlled across space and time is crucial for comprehending epithelial immune defense and for developing targeted epigenetic therapies for RSV.

Histone Lactylation: A newly discovered epigenetic modification, histone lactylation, is prevalent in various cell types and plays a crucial role in regulating gene transcription, metabolic processes, and immune responses.[64] It influences inflammatory and immune responses by modifying histone–DNA interactions and transcription factor activity.[65,66] In viral infections, lactylation can play a significant role in host–pathogen interactions; for instance, porcine reproductive and respiratory syndrome virus can increase histone lactylation to suppress IFN-β production.[67,68] RSV infection induces metabolic reprogramming in respiratory epithelial cells in vitro, characterized by enhanced glucose uptake, lactate production, and upregulation of glycolytic enzymes like hexokinase 2.[69] The accumulated lactate serves as a substrate for histone lactylation,[70] positioning this modification as a potential mechanism for RSV to reprogram the epithelial epigenome, influencing both host antiviral immunity and inflammation. Investigating the role of histone lactylation represents a promising frontier in understanding RSV pathogenesis.

ncRNAs: RSV can also significantly alter epithelial cell function by regulating various ncRNAs.[71] Clinical analyses of nasal swab specimens from RSV-infected infants identified distinct miRNA profiles, with miR-34b/c, miR-125b, miR-29c, miR-429, and miR-27b downregulated, and miR-155, miR-31, and let-7d upregulated.[72] Low levels of miR-125a and miR-429 were associated with milder disease, suggesting a potential regulatory role of these miRNAs in influencing infection outcomes and their potential utility as biomarkers for disease progression. In bronchial epithelial models, RSV upregulates let-7i and miR-30b to suppress IFN signaling, while NS1 and NS2 proteins inhibit this upregulation to maintain immune balance.[71] Beyond miRNAs, certain lncRNAs are involved in RSV pathogenesis. The pro-viral lncRNA, NRAV, promotes RSV replication by sequestering miR-509-3p, thereby enhancing Ras-related protein Rab-5C–mediated vesicular transport in infected cells in vitro.[73] Conversely, the IFN-induced lncRNA, VILMIR, is upregulated upon infection and enhances antiviral gene transcription.[74] The pseudogene-derived RNVU1-18, originating from U1 nucleolar RNA, is also upregulated and promotes RIG-I activation by interacting with tripartite motif-containing 25 (TRIM25) to facilitate K63-linked ubiquitination in vitro.[75] This illustrates that ncRNAs form a precise, context-dependent regulatory network during RSV infection, with diverse and occasionally opposing functions governed by their expression timing and interactions with viral and host factors. A comprehensive understanding of the ncRNA landscape may unveil new biomarkers and therapeutic targets.

Chromatin Remodeling: RSV infection induces chromatin restructuring in respiratory epithelial cells, impacting antiviral responses and airway remodeling. Qiao et al. demonstrated, in human small airway epithelial cells in vitro and murine respirovirus lung infection models in vivo, that the activation of the unfolded protein response sensor inositol-dependent endonuclease 1α (IRE1α) and subsequent splicing of X-box binding protein 1s (XBP1s) increase chromatin accessibility at loci encoding hepatocyte-binding protein and epithelial–mesenchymal transition (EMT)-associated genes. This IRE1α–XBP1-driven remodeling boosts expression of antiviral and inflammatory genes and upregulates EMT programs, contributing to long-term pathology like asthma.[76] Another in vitro study showed that RSV induces chromatin remodeling at the promoters of growth factors, such as transforming growth factor-beta (TGF-β), and extracellular matrix genes, including fibronectin-1 and matrix metalloproteinase 9, promoting epithelial proliferation and aberrant matrix deposition linked to airway narrowing and reduced lung function.[77] Bromodomain-containing protein 4 (BRD4), a member of the bromodomain and extra-terminal family, also plays a critical role in these processes in human airway epithelial and basal cell models in vitro. By recognizing acetylated histone tails, BRD4 recruits transcription factors like positive transcription elongation factor b, which contains cyclin-dependent kinase 9, IRF1, and nuclear factor-kappa-light-chain-enhancer of activated B cells to the promoters of pro-inflammatory, antiviral, and remodeling-associated genes. This facilitates RNA polymerase II phosphorylation and efficient transcription elongation.[78,79] These studies underscore that RSV-induced chromatin remodeling, mediated by pathways like IRE1α–XBP1s and BRD4, not

only activates robust innate immunity but also predisposes airway epithelia to long-term structural changes, potentially underpinning the link to asthma.

Epigenetic Reprogramming of T Cell Differentiation and Immune Memory

T cells are central to adaptive immunity against RSV. $CD8^+$ cytotoxic T lymphocytes directly eliminate infected cells and produce IFN-γ to aid viral clearance.[80] Persistent tissue-resident memory $CD8^+$ T cells in the lungs are crucial for protection against reinfection.[81] However, excessive $CD8^+$ T cell activation can cause immunopathology, as seen in mouse models where overproduction of tumor necrosis factor-α and IFN-γ exacerbates lung injury.[82] Establishing a balanced $CD8^+$ T cell response is crucial for effective defense against RSV.

$CD4^+$ helper T cells orchestrate immune responses through cytokine secretion and are equally essential for RSV virus eradication. Th1 cells produce IFN-γ, which activates macrophages and enhances $CD8^+$ T cell function,[83] and helps B cells generate high-affinity antibodies.[84] Dysregulated Th2 responses, however, drive immunopathology by recruiting eosinophils and promoting airway hyperresponsiveness.[85] Th17 cells exacerbate damage through IL-17, which induces mucus overproduction and neutrophil infiltration.[86] Regulatory T cells (Tregs) expand early in RSV infection and help limit tissue damage by secreting anti-inflammatory cytokines like TGF-β and IL-10.[87]

Epigenetic Mechanisms in T Cell Polarization: Epigenetic modifications critically determine T cell fate during RSV infection. RSV increases the expression of Nodal, a TGF-β superfamily ligand, by demethylating CpG sites in its promoter in bronchial epithelial cells in vitro. Elevated Nodal then drives naive $CD4^+$ T cells toward Th2 and Th17 lineages in co-culture systems, worsening airway inflammation and remodeling.[88] Histone modifications further shape T cell responses. RSV activates the Notch pathway through Delta-like ligand 4 on dendritic cells (DCs) in murine models of RSV infection and in Treg differentiation cultures, upregulating the histone methyltransferase MYND domain-containing protein 3 (SMYD3). SMYD3 catalyzes H3K4me3 at the Forkhead box protein 3 promoter and its conserved noncoding sequence 1 region, promoting Treg differentiation and enhancing their suppressive function.[89] Conversely, RSV infection can also reduce levels of the repressive mark H3K27me3 in DCs through the demethylase lysine-specific demethylase 6 in bone marrow–derived DC (BM-DC) and pulmonary DC from RSV-infected mice, thereby alleviating the repression of Th2-promoting genes and facilitating Th2 polarization.[90] Thus, DNA methylation and histone modifications collectively establish an RSV-regulated T cell landscape favoring both inflammatory (Th2/Th17) and Treg phenotypes, ultimately influencing pathology and disease outcomes (Fig. 2).

Fine-Tuning and Long-Term Effects: Epigenetic mechanisms also fine-tune specific T cell responses. N^6-methyladenosine (m^6A) modification of the RSV genome conceals viral pathogen-associated molecular patterns in vitro, helping the virus evade RIG-I detection. In mouse models, removal of this m^6A "camouflage" enhances neutralizing antibody titers and RSV-specific T cell responses.[91] ncRNAs, including miR-155, miR-146a, and the miR-17-92 cluster, modulate T cell activation, proliferation, differentiation, and cytokine production. For instance, miR-155 promotes viral clearance by enhancing Th1 polarization and $CD8^+$ T cell effector function.[92]

RSV infection is associated with lasting epigenetic changes in T cells linked to allergic sensitization and immune memory. In a murine RSV infection model in vivo, RSV triggers demethylation of the Notch homolog 1, translocation-associated (Notch-1) promoter in $CD4^+$ T cells, thereby enhancing the transcription of Th2/Th17 cytokines (such as IL-4, IL-13, and IL-17).[93] This phenomenon may contribute to chronic airway inflammation and asthma susceptibility. Concurrently, RSV increases DNA methylation in the regulatory region of the perforin-1 gene in $CD8^+$ T cells, which reduces perforin-1 expression. This epigenetic silencing impairs cytolytic activity and hinders the development of long-lived memory $CD8^+$ T cells, thereby compromising durable antiviral protection.[94] These coordinated epigenetic changes promote pathogenic $CD4^+$ T cell responses while suppressing cytotoxic $CD8^+$ T cell memory. Together, they create an immune environment skewed toward Th2 activity and reduced antiviral capacity. This imbalance favors chronic airway inflammation, airway remodeling, and ultimately increases the risk of asthma development.

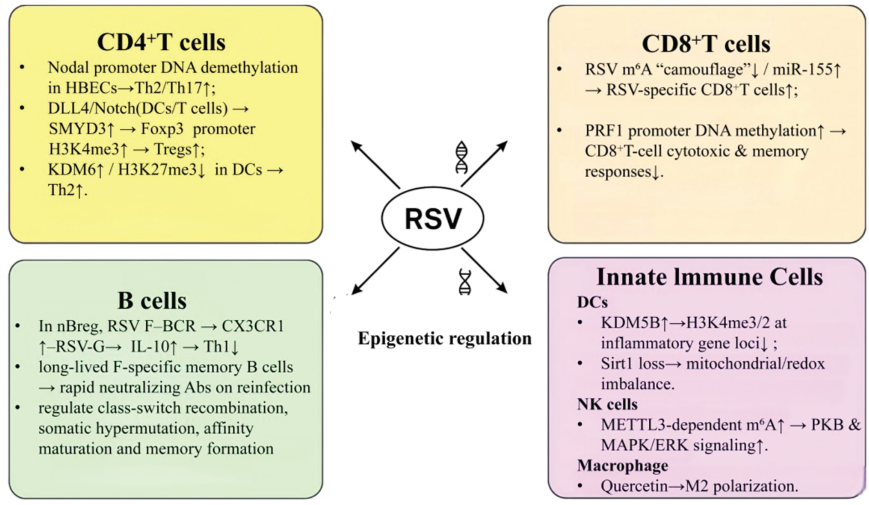

Figure 2. Epigenetic regulation of adaptive and innate immune responses to RSV infection. RSV infection induces a network of cell type–specific epigenetic alterations that collectively skew the immune response toward Th2 inflammation, impair cytotoxic memory, and elevate long-term asthma risk.

Epigenetic Basis of B Cell Differentiation and Humoral Immunity

RSV infection significantly influences B cell differentiation and humoral immunity.[95] Following infection, innate immune cells like neutrophils and macrophages initiate early antiviral responses,[96] while antigen stimulation triggers naive B cells to differentiate into antibody-secreting plasma cells. RSV-specific antibodies neutralize free virus and persist in mucosal tissues and circulation, reducing reinfection risk.[97] Specific B cell subsets exhibit distinct behaviors during RSV infection. For instance, binding of the RSV F protein to the B-cell receptor of natural regulatory B cells (nBreg) activates them, upregulating the chemokine receptor CX3CR1. Interaction between CX3CR1 and the RSV G protein facilitates nBreg infection, inducing IL-10 production that suppresses Th1 responses and contributes to the pathogenesis of severe bronchiolitis.[98] RSV also elicits a robust memory B cell response in mucosa-associated lymphoid tissue. Shehata et al. demonstrated that RSV exposure generates long-lived memory B cells targeting the F protein, which, upon reinfection, produce potent neutralizing antibodies, providing valuable insights into persistent immunity and vaccine development.[99]

Potential Epigenetic Influences: There is no direct evidence linking epigenetic changes to B cell function in RSV infection. Our understanding is inferred from studies on other pathogens or general immunology. In non-RSV models, primarily mouse immunization systems in vivo with ex vivo B cell epigenomic profiling, antigen stimulation leaves an "experiential" epigenetic imprint on memory B cells in an IRF4-dependent manner. This epigenetic imprint progressively increases chromatin accessibility at loci that regulate plasma cell differentiation. Upon subsequent antigen exposure, this chromatin state influences B cell fate. Elevated B lymphocyte–induced maturation protein-1 expression promotes commitment to the plasma cell lineage. Conversely, increased activity of BTB and CNC homology 2 favors B cell re-entry into the germinal center rather than terminal differentiation.[100] Insights from other viruses, such as IAV, show that memory B cells can exhibit sustained chromatin accessibility and transcriptional reprogramming, conferring "epigenetically primed" effector traits correlated with long-lived antibody responses.[101] In a murine lymphocytic choriomeningitis virus infection model, early type I IFN signaling shapes the chromatin properties of memory B cells, and blocking the IFN receptor alters their subset composition, illustrating a mechanistic link between the infectious environment, cytokine signals, B cell epigenetics, and fate/functional preference.[102] These findings suggest that analogous pathways possibly operate during RSV infection, though this requires experimental validation.

Nonviral studies confirm that epigenetic modifications regulate B cell processes, including class-switch recombination, somatic hypermutation, affinity maturation, and memory formation.[103] Given the link between B cell dysfunction and severe RSV disease,[104,105] we propose that RSV may alter B cell immunity through epigenetic mechanisms. Evidence from other viral and nonviral systems reveals that infection context and cytokine signaling can induce lasting chromatin and transcriptional changes in memory B cells. By extension, RSV infection may imprint similar epigenetic programs that influence B cell function and antibody durability. Future studies should apply longitudinal multi-omics approaches to B cells from RSV-infected humans or animal models. These approaches include single-cell ATAC sequencing, DNA methylation profiling, and histone mark analysis. When combined with functional assays, such as antibody repertoire sequencing, cytokine secretion profiling, and fate mapping after antigen reexposure, these data will enable mechanistic evaluation of whether epigenetic remodeling contributes to impaired humoral immunity and clinical outcomes in RSV infection.

Epigenetic Activation and Regulation of Innate Immune Cells

Innate immune cells, including DCs, natural killer (NK) cells, and macrophages, recognize RSV through pattern recognition receptors, triggering cytokine and IFN production.[23,106] RSV infection also induces epigenetic changes in these cells, modulating chromatin accessibility and transcription factor recruitment to shape the course and outcome of the innate immune response.[107,108]

As bridges between innate and adaptive immunity, DCs undergo RSV-induced epigenetic changes. In RSV-infected BM-DCs, the expression of the histone demethylase lysine–specific demethylase 5B (KDM5B) increases. KDM5B removes activation-associated histone marks H3K4me3 and H3K4me2 from inflammatory gene loci. This decreases the transcription of inflammatory genes and, in DC-specific Kdm5b-deficient mice in vivo, prepares DCs to promote a Th 2-biased immune response.[109] Conversely, loss of the NAD^+-dependent deacetylase sirtuin-1 (Sirt1) in RSV-infected BM-DCs disrupts mitochondrial membrane potential and redox balance. This metabolic dysregulation is associated, in DC-specific Sirt1-deficient mice in vivo, with elevated proinflammatory cytokines (IL-1β, IL-6, IL-23) and reduced antiviral mediators (IL-12, IFN-β).[110]

NK cells are crucial effector cells that can rapidly eliminate virus-infected cells.[111] Epigenetic mechanisms underpin their development, effector functions, and memory properties. m^6A RNA methylation, catalyzed by methyltransferase-like 3 (METTL3), is essential for NK cell proliferation, survival, and cytotoxicity both in vivo and in vitro. During IL-15–driven maturation, METTL3-dependent m^6A modification stabilizes Src-like domain 2–containing inositol 5-phosphatase-2 mRNA, activating PKB and mitogen-activated protein kinase/extracellular signal-regulated kinase signaling pathways to maintain NK cell homeostasis and function.[112]

Macrophages execute pathogen clearance through coordinated interactions with $CD8^+$ T cells while preserving pulmonary immunological homeostasis by modulating lung inflammation. Evidence indicates that epigenetic mechanisms influence macrophage polarization during RSV infection. Quercetin, a compound known to modulate epigenetic pathways, including DNA methylation, histone modifications, and miRNA expression, promotes a shift of alveolar macrophages from a classically activated (M1) proinflammatory phenotype to an alternatively activated (M2) anti-inflammatory phenotype both in vitro and in vivo. In RSV-infected mice, this shift markedly reduces lung inflammation.[113] This indicates that epigenetic regulation of macrophage polarization may influence RSV disease severity.

In summary, RSV employs diverse epigenetic strategies to alter the function of innate immune cells, fine-tuning cytokine production, cellular polarization, and maturation processes to establish an immunological equilibrium that often favors viral persistence or immunopathology (Fig. 2).

Translational Prospects and Challenges

Epigenetic Biomarkers for RSV Severity and Prognosis

The current prevention and treatment of RSV face numerous challenges. Preventive strategies primarily rely on monoclonal antibodies, specifically palivizumab and nirsevimab, while various vaccination options,[114] including mRNA-based formulations, are in clinical trials. Infants and young children are

particularly susceptible to severe RSV illness due to their underdeveloped immune systems, narrow airways, and excessive secretions, which may sometimes lead to hospitalization and fatal outcomes. Further, accurate classification of disease severity is essential for optimizing treatment and prognosis. RSV-induced epigenetic alterations in inflammatory and antiviral pathways are linked to clinical severity and long-term outcomes, making them promising biomarker candidates.[58,115] Cohort studies have identified sustained hypomethylation at CpG sites within the zinc finger and BTB domain–containing 38 and TRIM6–TRIM34 loci in infants with severe RSV bronchiolitis, suggesting that these patterns may predict disease progression.[57] Elevated miR-155 levels in blood and sputum from severe RSV cases also highlight its potential as an early warning sign for high-risk individuals.[116] Integrating such epigenetic markers into diagnostic and prognostic workflows could enable earlier interventions and improve clinical outcomes.

Epigenetic Therapeutics: HDAC Inhibitors, CRISPR Tools, and Beyond

Epigenetic pathways, which can govern all stages of RSV infection and replication, represent attractive therapeutic targets. Strategies that modulate host chromatin regulators can inhibit viral replication, potentiate antiviral defenses, and enhance viral clearance, potentially overcoming challenges posed by the high antigenic variability of viral proteins, such as the RSV F protein. HDAC inhibitors can modulate antiviral responses by increasing histone acetylation at select antiviral gene promoters, although these effects depend on enzyme, cell type, and context.[117,118] HDAC inhibition has been shown to reduce RSV replication in vitro and alleviate airway inflammation in mouse models, underscoring its therapeutic potential.[60] Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated protein 9 (CRISPR/Cas9) technology, a versatile gene-editing platform,[119,120] has been applied to engineer B cells to produce RSV-neutralizing antibodies and to directly cleave persistent viral genomes, such as hepatitis B virus and human immunodeficiency virus, within host cells, thereby inhibiting viral replication.[121,122] Looking ahead, CRISPR/Cas9 could be harnessed to establish a sustained antiviral state by epigenetically modifying host cells, particularly airway epithelial or immune cells, through targeted regulation of key epigenetic enzymes such as HDACs. Despite its potential, CRISPR/Cas9 needs further refinement to reduce off-target effects and improve delivery efficiency. While cancer, frequently propelled by epigenetic dysregulation, has been the primary focus of CRISPR/Cas9 therapy, substantial technical obstacles persist.[123]

Challenges, Safety, and Ethical Considerations

The advancement of epigenetic therapies for RSV encounters multiple scientific and translational hurdles. A central methodological challenge arises from the inherent cell-type- and developmental-stage-specificity of epigenetic modifications, which exhibit complex and evolving spatiotemporal dynamics during infection.[124] Comprehensive mapping of these dynamics requires sophisticated high-throughput methodologies, imposing significant technical and financial burdens. This challenge is compounded by the field's traditional reliance on in vitro systems and murine models, which frequently fail to capture key nuances of human-specific immune responses. To address this gap, recent research has increasingly shifted toward more physiologically relevant human models, such as airway organoids and precision-cut lung slices, which facilitate more accurate translational predictions.[125,126]

Equally critical are the safety concerns associated with epigenetic modulators, with off-target effects representing a primary obstacle to clinical development. Many candidate agents, including broad-spectrum HDAC inhibitors, exhibit pleiotropic activity that can disrupt transcriptional homeostasis in healthy, uninfected tissues.[127,128] This risk is markedly amplified in pediatric populations. Infants and young children undergo a phase of exceptionally rapid physiological development, rendering their organ systems uniquely vulnerable to developmental toxicities. Preclinical evidence substantiates this concern, indicating that systemic HDAC inhibition can impair osteoblast maturation and chondrocyte function, thereby posing a tangible risk of skeletal growth impairment—a particularly serious potential adverse outcome in this age group.[129,130] Further complicating the safety profile is the well-established role of HDACs in regulating synaptic plasticity, which raises the possibility of unintended neurodevelopmental consequences—an unresolved issue that necessitates vigilant long-term monitoring. Consequently, establishing a viable therapeutic window for pediatric applications

will likely require the development of next-generation inhibitors with enhanced selectivity or the implementation of sophisticated targeted delivery platforms.

The prospective clinical translation of genome-editing technologies such as CRISPR/Cas9 introduces additional layers of ethical and regulatory complexity. A paramount concern, both scientifically and ethically, is the irreversible nature of heritable genetic edits. In the context of actively proliferating pediatric tissues, even rare off-target mutations may undergo clonal expansion, potentially conferring latent oncogenic risks that might not manifest until adulthood.[131] From a regulatory and ethical standpoint, designing first-in-human trials for infant cohorts presents the dual challenge of securing valid informed consent and ensuring a justifiable risk-benefit ratio. Prevailing ethical frameworks typically stipulate that any research risk exceeding a minimal threshold must be counterbalanced by a clear prospect of direct therapeutic benefit for the participant.[132] Therefore, future clinical protocols must incorporate stringent and prolonged follow-up strategies, designed not only to assess treatment efficacy but also to monitor long-term genomic stability and the potential emergence of delayed adverse events throughout the lifespan.

Future Avenues: Multi-Omics Integration and Organoid Models

While contemporary epigenetic research continues to rely predominantly on bulk cell analyses or immortalized lines, a clear shift is underway toward high-resolution models with direct patient relevance. Integrating multi-omics—spanning epigenomics, transcriptomics, and metabolomics—with human airway organoids now defines the cutting edge of RSV investigation.[133–137] In contrast to conventional two-dimensional cultures, human nasal organoids (HNOs) generated from patient samples faithfully recreate the multicellular architecture, functional ciliary activity, and mucus secretion characteristic of the native airway epithelium.[138,139] This makes them a powerful experimental system for probing age-specific host–virus dynamics.[140]

Emerging primary research underscores the transformative impact of such models. For example, Rajan et al. applied single-cell RNA sequencing—a technique well suited for resolving cellular heterogeneity—to profile RSV-infected HNOs derived from pediatric and adult donors. Their work uncovered pronounced age-dependent differences in cellular responses, including a distinct "proliferative diversity" unique to infant tissues. Moreover, the study revealed an extended cellular tropism of RSV in infants, with the virus targeting a wider array of epithelial cell types—a finding that aligns with the increased clinical severity observed in this age group.[141] Complementing this, Aloisio et al. utilized infant-derived HNOs to demonstrate that pediatric epithelium displays significantly higher susceptibility to RSV infection, along with more vigorous inflammatory responses and greater cytotoxicity, compared to adult-derived counterparts.[142]

Together, these observations highlight the unique value of organoid-based systems combined with single-cell methodologies. Moving forward, epigenetic studies should capitalize on these models to map features such as chromatin accessibility and histone modifications at single-cell resolution. Achieving this level of detail will be crucial for determining whether a persistent "epigenetic memory" of RSV infection resides within specific progenitor cell populations. This mechanism could ultimately explain long-term clinical sequelae, including recurrent wheezing.

Conclusion

This review emphasizes the key role of host epigenetic reprogramming in shaping immune responses and affecting viral replication during RSV infection. RSV manipulates multiple layers of epigenetic regulation, such as DNA methylation, histone modifications, ncRNAs, and chromatin remodeling, across respiratory epithelial cells, T cells, B cells, and innate immune populations. These changes interfere with normal gene expression and influence clinical outcomes, from acute disease severity to long-term respiratory issues like childhood asthma. Although emerging epigenetic-based therapies show promise, further research is needed. Combining multi-omics approaches with advanced human-relevant systems, such as patient-derived airway organoids, will be crucial to fully understand the epigenetic networks driving RSV pathogenesis and to accelerate the development of more targeted therapeutics and vaccines.

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Author Contributions

G. Y., M. W., and H. F. contributed to the conception and design of the study and to drafting the manuscript. Y. L., S. C., J. L., and Z. L. were responsible for the revision and critical review of the article. All authors have agreed on the journal to which the article has been submitted and accept responsibility for all aspects of the work.

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No additional data was necessary for the manuscript.

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Not applicable.

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The authors declare that they have no competing interests.

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