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Post-Translational Modifications in Respiratory Syncytial Virus Infection: Orchestrating Host-Pathogen Interactions

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Abstract: *Respiratory syncytial virus (RSV) is the leading pathogen worldwide causing lower respiratory tract infections in infants and young children, and it also poses a serious threat to older adults and immunocompromised populations, resulting in a substantial disease burden and deaths each year. Although RSV has a simple structure, its complex interactions with the host are highly dependent on post-translational modifications (PTMs). Acting as molecular switches that rapidly regulate protein function, localization, and stability, these modifications play decisive roles in the viral life cycle and host immune responses. This article systematically reviews the multiple roles of PTMs in RSV infection, with a focus on how glycosylation of the viral G and F proteins influences viral tropism, receptor binding, and immune evasion, and how phosphorylation of the N and P proteins finely regulates the formation and function of the viral replication complex (inclusion bodies). It also analyzes how RSV creates a favorable environment for replication by hijacking host kinase networks and the ubiquitination system to remodel the cytoskeleton, suppress type I interferon responses, and regulate apoptosis. A deeper understanding of these mechanisms will not only help elucidate RSV pathogenesis but also has important translational value, particularly by informing structure-based vaccine antigen design (e.g., optimizing epitope exposure) and providing key strategies for developing novel antiviral drugs that target host PTM enzymes and are less prone to resistance.*

Keywords: *Respiratory syncytial virus, Post-Translational Modifications*

1. Introduction

1.1 Virological characteristics of RSV

Respiratory syncytial virus (RSV) belongs to the family Pneumoviridae, genus Orthopneumovirus, and is an enveloped, single-stranded negative-sense RNA virus[1][2]. Its genome is approximately 15.2 kb in length, contains 10 genes, and encodes 11 proteins[1][3]. These proteins include three transmembrane surface glycoproteins: the fusion protein (F), the attachment glycoprotein (G), and the small hydrophobic protein (SH); the matrix protein (M) located on the inner side of the envelope; the nucleocapsid complex composed of nucleoprotein (N), phosphoprotein (P), and the large polymerase protein (L); additionally, there are transcription regulators M2-1 and M2-2, and two nonstructural proteins NS1 and NS2[1][4].

The RSV life cycle begins with the virus binding to the surface of a host cell. The G protein mediates viral attachment by recognizing host cell surface heparan sulfate proteoglycans (HSPGs) or other receptors (such as nucleolin), after which the F protein undergoes a conformational change that mediates fusion of the viral envelope with the cell membrane, releasing the ribonucleoprotein complex (RNP) into the cytoplasm[1][5]. RSV replication and transcription occur in a distinct cytoplasmic compartment—the inclusion body (IB). IBs are liquid–liquid phase-separated structures formed by aggregation of viral proteins (primarily N and P) with viral RNA, serving as "viral factories" that coordinate genome synthesis and assembly[6].

1.2 Definition and functions of post-translational modifications (PTMs)

Post-translational modifications (PTMs) refer to covalent attachments of chemical groups or small protein molecules to specific amino acid residues of proteins after their synthesis on the ribosome, mediated by enzymatic reactions. Common PTMs include phosphorylation, glycosylation,

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ubiquitination, acetylation, methylation, and palmitoylation, among others[7][8].

PTMs greatly expand the functional diversity of the proteome, enabling cells to respond rapidly to external stimuli without altering the genetic sequence[9].

2. PTMs of Viral Proteins: Molecular Switches for Replication and Assembly

Although the respiratory syncytial virus (RSV) genome is only about 15.2 kb long and its coding capacity is limited to 11 proteins, every step of its life cycle—from receptor recognition and membrane fusion, to genome replication, and ultimately virion assembly and budding—exhibits a high degree of precision and spatiotemporal coordination [1][4]. Because RSV does not encode modifying enzymes such as kinases, glycosyltransferases, or ubiquitin ligases, it has evolved a strategy that is entirely dependent on—and "hijacks"—the host cellular enzyme systems to carry out extensive post-translational modifications (PTMs) on its structural and nonstructural proteins [7][10].

This reliance on the host PTM machinery not only greatly expands the functional diversity of the virus's limited proteome, but also serves as a key "molecular switch" regulating the course of infection [1][10]. These modifications do not occur randomly; rather, they are subject to strict spatiotemporal control within specific cellular compartments:

In the secretory pathway, the host glycosylation enzyme system is used to modify the viral surface glycoproteins (G and F). This is not only a prerequisite for proper protein folding and trafficking, but also a primary strategy by which the virus evades recognition by neutralizing antibodies through "mimicry" of host components [6][11].

In the cytoplasmic viral factories (inclusion bodies, IBs), phosphorylation–dephosphorylation cycles become a central mechanism for regulating the activity of the replication complex. RSV recruits host kinases or phosphatases (such as PP1) to modify the nucleoprotein (N) and phosphoprotein (P), thereby dynamically tuning the balance between viral RNA transcription and replication, as well as the process of nucleocapsid assembly [6][8].

This section will examine in depth how key RSV proteins exploit these host enzyme systems for modification, and how these modifications function as molecular switches that play decisive roles across the stages of viral replication and assembly.

2.1 Glycosylation

Glycosylation is a crucial post-translational modification in the life cycle of respiratory syncytial virus (RSV), occurring mainly on its surface envelope glycoproteins—the fusion protein (F) and the attachment protein (G). This modification not only determines the folding, trafficking, and stability of viral proteins, but also plays a key coordinating role in regulating viral infectivity, syncytium formation, and host immune evasion.

2.1.1 N-glycosylation of the fusion protein (F protein)

The RSV F protein is a highly conserved type I transmembrane glycoprotein. Its precursor F0 is cleaved by the furin protease in the trans-Golgi network into disulfide-linked F1 and F2 subunits, with release of a polypeptide fragment known as p27 during this process [12][13]. Modification of the F protein is primarily N-linked glycosylation. Its sequence contains five conserved N-glycosylation sites: N27 and N70 in the F2 subunit, N500 in the F1 subunit, and N116 and N126 within the p27 peptide segment [12][14].

Studies show that glycosylation of the F protein is functionally site-specific. For example, glycosylation at N500 in the F1 subunit is essential for F-mediated membrane fusion activity; loss of this site leads to a marked reduction in syncytium-forming capacity [12][14]. In addition, glycosylation contributes to the "glycan shield" masking of antigenic epitopes. Although the p27 segment is generally thought to be shed from mature virions, the N116 glycosylation site within p27 appears to play a role in immune modulation; removing the glycosylation at N116 enhances the host blocking-antibody response against the F protein, suggesting that the glycan at this site may sterically hinder antibody recognition of key antigenic epitopes [14]. Moreover, in virus-infected cells, the F2 subunit exists in multiple glycoforms (designated F2a and F2b), indicating heterogeneity in N-glycan processing of the F protein [13].

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2.1.2 O-glycosylation of the attachment protein (G protein) and host cell specificity

Unlike the F protein, the RSV G protein is a type II transmembrane protein. Its ectodomain contains two highly variable mucin-like domains that are rich in serine and threonine residues and undergo extensive O-linked glycosylation [15]. In the mature G protein, more than 60% of its molecular mass is composed of glycans. These dense O-glycan chains form a shielding layer that can mask the protein backbone, thereby protecting the virus from proteolytic degradation and enabling escape from host antibody recognition6.

Notably, glycosylation of the G protein shows pronounced host cell dependence. The G protein produced in primary human bronchial epithelial (HBE) cells (LgG) has a molecular mass of approximately 170 kDa, far larger than the forms produced in HEp-2 or Vero cell lines (approximately 90–100 kDa or smaller). This difference is mainly attributable to more extensive or more complex glycosylation (such as the addition of polylactosamine) [16]. This "high-molecular-weight" glycoform (LgG) significantly alters viral biological properties, making infection less overly dependent on cell-surface heparan sulfate proteoglycans (HSPG), and thus potentially better adapted to the human respiratory tract environment [16]. In addition, restricting O-glycosylation in the mucin-like domains of the G protein has been shown to enhance its immunogenicity: unglycosylated G protein can induce stronger protective immune responses and reduce vaccine-associated immunopathology [15].

2.1.3 Interactions with host glycosaminoglycans

Glycosylation of viral glycoproteins also interacts with glycosaminoglycans (GAGs) on the host cell surface, jointly coordinating viral attachment and entry. RSV infection depends not only on viral glycosylation itself, but also on specific sulfation modifications of host cell-surface heparan sulfate. Studies have confirmed that N-sulfation (rather than O-sulfation) on host GAG chains is a key structural determinant for efficient RSV infection, indicating a high degree of structural specificity in glycosylation-dependent recognition between virus and host [17].

2.2 Phosphorylation: Assembly of Replication Factories

Respiratory syncytial virus (RSV) replication and transcription occur in specialized cytoplasmic compartments known as inclusion bodies (IBs). These "replication factories" are enriched in the viral nucleoprotein (N), phosphoprotein (P), large polymerase protein (L), and the transcription antitermination factor (M2-1). As a dynamic molecular switch, phosphorylation tightly regulates the conformation, oligomeric state, and interactions of these core proteins, thereby coordinating the assembly of the viral ribonucleoprotein complex (RNP) and its functional transitions.

2.2.1 Oligomerization of the Nucleoprotein (N) and RNA Encapsidation

Encapsidation of the RSV genome depends on conversion of nucleoprotein (N) from its monomeric form (N0) to the oligomeric N–RNA form (N-RNA). Newly synthesized N has a strong tendency to self-oligomerize and readily binds host RNA nonspecifically. Studies have shown that phosphorylation of N plays a key role in regulating its oligomerization. Mass spectrometry identified Y88 of N as a specific phosphorylation site [18]. The Y88 residue lies in a structurally critical region of N, and its phosphorylation may stabilize the monomeric N0 form by affecting interactions with key residues (such as R27), preventing premature nonspecific oligomerization before binding to viral genomic RNA [18]. This phosphorylation-mediated stability is essential for maintaining a free pool of N protein (the N0–P complex) available for encapsidating the viral genome and antigenome, constituting the first step of nucleocapsid assembly within replication factories [18].

2.2.2 The Molecular Switch Function of the Phosphoprotein (P)

Phosphoprotein (P) is the central hub of the RSV polymerase complex, linking N to L and recruiting M2-1. P is the primary phosphorylation substrate, mainly mediated by casein kinase II (CK2), and its phosphorylation is hierarchical and function-specific.

Regulatory role of basal phosphorylation: Most P phosphorylation (98%) occurs at S116, S117, S119, and S232. Although these "high-abundance" phosphorylation sites are not absolutely required for basic transcription and replication in vitro, they significantly modulate the efficiency of viral RNA synthesis [19]. S232 is the major C-terminal phosphorylation site, and its mutation leads to fluctuations in transcription and replication efficiency [19].

Interaction switch at T108: Phosphorylation at P residue T108 has a high turnover rate and serves as a decisive molecular switch. Phosphorylation of T108 interferes with binding between P and the

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transcription antitermination factor M2-1 [20]. When T108 is dephosphorylated, P effectively binds M2-1 to form a transcriptionally active complex (Transcriptase); phosphorylation of T108 may instead cause M2-1 to dissociate from the complex, biasing the polymerase complex toward replication (Replicase) [20]. This dynamic phosphorylation cycle allows replication factories to flexibly adjust polymerase complex composition according to the needs of different stages of infection.

2.2.3 Dynamic Cycling of M2-1 and Transcription Elongation

As a transcription antitermination factor, M2-1 is essential for full-length mRNA synthesis and readthrough. M2-1 exists as a tetramer, and S58 and S61 within its core domain are key phosphorylation sites [21]. Similar to P, M2-1 function does not rely on a single phosphorylation state, but rather on dynamic cycling between phosphorylation and dephosphorylation. Mutants that fully mimic phosphorylation (S58D/S61D) or completely abolish phosphorylation (S58A/S61A) both show reduced antitermination activity [21]. This indicates that during replication factory assembly and function, M2-1 must undergo reversible phosphorylation to coordinate its binding to and release from RNA and P.

2.2.4 Nucleocytoplasmic Shuttling of the Matrix Protein (M) and Initiation of Assembly

Although M is primarily considered a structural protein, its phosphorylation state directly determines the switch between its early nuclear transcription-inhibitory function and its late cytoplasmic assembly function. CK2-mediated dual phosphorylation at S95 and T205 regulates M nucleocytoplasmic shuttling [22]. In the late stage of infection, phosphorylation of cytoplasmic M at S95 promotes its oligomerization and its association with nucleocapsids within cytoplasmic inclusion bodies, thereby initiating virion assembly [22]. This phosphorylation-dependent relocalization marks the transition in the viral life cycle from genome replication to virion assembly.

2.3 Ubiquitination

Ubiquitination is a highly dynamic and reversible post-translational modification that plays a crucial role in regulating the early innate immune response induced by RSV. This process involves a cascade of ubiquitin-activating enzymes (E1), conjugating enzymes (E2), and ligases (E3), and it fine-tunes signaling pathways through K48-linked chains (mediating proteasomal degradation) or K63-linked chains (mediating signal activation) [23][24]. During RSV infection, viral proteins evade antiviral immunity by hijacking or disrupting the host ubiquitination system, while the host, in turn, restricts viral replication by using specific E3 ligases to target viral proteins.

2.3.1 Viral inhibition of ubiquitination in the RIG-I pathway

Activation of retinoic acid–inducible gene I (RIG-I) is essential for initiating the antiviral type I interferon (IFN) response, and this depends on TRIM25-mediated K63-linked polyubiquitination of the N-terminal CARD domains of RIG-I [3]. RSV strongly interferes with this process through its nonstructural proteins NS1 and NS2:

Mechanism of NS1: The NS1 protein can directly interact with TRIM25, with the binding site located in TRIM25's SPRY domain (a domain that typically mediates binding to RIG-I) [25]. This interaction does not block the binding between RIG-I and TRIM25; instead, it incorporates NS1 into the RIG-I/TRIM25 complex, thereby inhibiting TRIM25-catalyzed ubiquitination of RIG-I and blocking downstream MAVS signaling [25][26].

Synergistic role of NS2: Although NS1 is the primary inhibitory factor, NS2 can also interact with RIG-I and suppress its ubiquitination. The two may form a complex that cooperatively blocks RIG-I–mediated antiviral signaling [25].

2.3.2 Induction of proteasomal degradation of host signaling molecules

In addition to inhibiting activating ubiquitination, RSV also exploits the ubiquitin–proteasome system to degrade host antiviral factors.

Degradation of STAT2: RSV infection leads to specific degradation of STAT2 protein, thereby blocking the IFN signaling pathway. The RSV NS1 protein contains putative Elongin C– and Cullin 2–binding motifs, enabling it to mimic a host E3 ligase complex substrate-recognition subunit and assemble into an ECS-like (Elongi-Cullin-SOCS box) E3 ubiquitin ligase complex that targets STAT2 for polyubiquitination and degradation [27].

E3 ligase–assisting function of NS2: Although NS2 itself lacks E3 ligase activity, it can enhance

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ubiquitination levels of host proteins during infection and is required for efficient STAT2 degradation [24][27]. Studies indicate that specific residues on NS2 (such as T36, L52, and P92) are critical for its ability to induce ubiquitination and promote STAT2 degradation; mutating these sites restores STAT2 levels and weakens viral replication [24].

Degradation of GBP5: The RSV G protein promotes ubiquitination and subsequent proteasomal degradation of the antiviral protein GBP5 by upregulating expression of the host E3 ligase DZIP3, thereby facilitating virion production [23].

2.3.3 Restriction of viral proteins by host E3 ligases

As part of host defense, the membrane-associated RING-CH family E3 ligase MARCH8 has been identified as an RSV restriction factor.

Targeting the SH protein: MARCH8 can specifically recognize RSV's small hydrophobic protein (SH) and interact with it via its transmembrane domain [28].

Mechanism and consequences: MARCH8 catalyzes ubiquitination at lysine 13 (K13) in the cytoplasmic tail of the SH protein. Unlike typical proteasomal degradation, this modification leads to lysosomal degradation of SH [28]. Because the primary function of SH is to inhibit apoptosis, MARCH8-mediated SH degradation restores apoptosis in infected cells, thereby accelerating clearance of infected cells and reducing viral titers [28]. The virus may evade this restriction mechanism through mutation at the SH K13 site [28].

2.4 Methylation

As a key biochemical modification, methylation plays a dual regulatory role during RSV infection: on the one hand, the virus uses its own methyltransferases or the host methylation machinery to modify its RNA, thereby enhancing replication and evading host immune surveillance; on the other hand, infection reshapes the host epigenetic methylation landscape, influencing long-term pathological changes in the respiratory tract.

2.4.1 N6-methyladenosine (m6A) modification of viral RNA

N6-methyladenosine (m6A) is the most abundant internal modification in eukaryotic mRNA. Studies have shown that the RSV genome, antigenome, and mRNAs all contain m6A modifications, which are mainly enriched in the G gene region [29]. This modification positively regulates RSV replication and pathogenesis.

1) Molecular mechanisms and involvement of host proteins

m6A modification of RSV RNA is catalyzed by host "writer" proteins (Writers, such as METTL3 and METTL14) and recognized by "reader" proteins (Readers, such as YTHDF1–3) [29]. Overexpression of these m6A-related proteins markedly enhances expression of RSV F and G proteins and increases viral titers, whereas knockdown of METTL3/14 or YTHDF1–3 suppresses viral replication [29]. In contrast, the expression levels of m6A "eraser" proteins (Erasers, such as ALKBH5 and FTO) are negatively correlated with viral replication [29].

2) Immune evasion and vaccine potential

m6A modification is an important strategy by which RSV evades recognition by the host innate immune system. Viral RNAs lacking m6A modifications are more effectively recognized by the pattern-recognition receptor RIG-I, which in turn induces RIG-I ubiquitination and IRF3 phosphorylation, leading to a marked increase in secretion of type I interferon (IFN-β) [30]. Animal experiments show that m6A-deficient RSV—obtained either by mutating m6A sites in the G gene or by propagation in METTL3-knockdown cells—exhibits highly attenuated characteristics in cotton rats, yet retains the high immunogenicity of wild-type virus and can induce potent neutralizing antibodies and T-cell responses. This provides a new target for the design of live attenuated RSV vaccines [29][30].

2.4.2 Cap methylation mediated by the viral L protein

The RSV L protein (Large protein) not only has polymerase activity; its C-terminus also contains a methyltransferase (MTase) domain responsible for methylation of the 5′ cap structure of viral mRNA, which is critical for viral mRNA stability and translation [31].

1) Enzymatic activity characteristics

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The MTase domain of the RSV L protein is sequence-specific and preferentially recognizes the 5′ end of viral RNA that begins with a GGG sequence [31]. This domain catalyzes two key reactions in sequence: first, N7 methylation of guanosine, followed by 2′-O methylation of the first nucleotide [31]. Unlike some other single-stranded negative-sense RNA viruses (e.g., Ebola virus), the RSV MTase is mainly strictly cap-dependent, and no obvious cap-independent internal methylation activity has been found [31].

2) Functional significance

N7 methylation is required for initiation of viral mRNA translation, whereas 2'- O methylation mimics the host mRNA "self"signature, preventing recognition and attack by host innate immune sensors (such as IFIT1) [31]. Inhibiting this methyltransferase activity (e.g., using the S-adenosylmethionine analog sinefungin) can markedly block viral methylation, highlighting its potential as an antiviral drug target [31].

2.4.3 Host epigenetic methylation and immune imprinting

RSV infection not only alters the methylation status of the virus itself, but also induces long-term remodeling of DNA and histone methylation profiles in host cells, which is closely associated with long-term post-infection respiratory sequelae (such as recurrent wheezing and asthma).

1) DNA methylation and regulation of gene expression

Genome-wide DNA methylation analyzes show that RSV infection can lead to thousands of differentially methylated positions (DMPs), mainly located in inflammation-related genes [32]. For example, in infants with severe RSV bronchiolitis, hypomethylation appears in the enhancer region of the perforin gene (PRF1), and this change may persist for several years [32]. In addition, abnormal promoter methylation of genes in the transforming growth factor-β (TGF-β) signaling pathway is associated with post-infection airway remodeling and asthma risk [32]. Specific methylation signatures based on genes such as ZNF268, NKIRAS1, and RPL15 can even distinguish children who fully recover after RSV infection from those who develop respiratory sequelae [32].

2) Histone methylation

In addition to DNA methylation, histone methylation also plays a role in host immune responses. RSV infection can induce expression of the histone demethylase KDM5B in dendritic cells, thereby suppressing transcription of type I interferons and innate cytokines; meanwhile, the histone methyltransferase SMYD3 and its regulation of H3K4 methylation in regulatory T cells (Treg) are crucial for controlling pulmonary inflammation [32].

In summary, methylation modifications build a complex regulatory network in RSV infection, spanning precise control of the viral life cycle to long-term memory of host immune defense and pathological damage.

3. Conclusion

As a genome-minimized RNA virus, respiratory syncytial virus (RSV) carries out its complex life cycle and pathogenic mechanisms largely not by relying on an extensive repertoire of virally encoded enzymes, but by finely "hijacking" and manipulating the host post-translational modification (PTM) system. This article systematically reviews the multidimensional regulatory network of PTMs throughout the course of RSV infection, revealing the central role of this "molecular code" in coordinating host–pathogen interactions.

First, PTMs are core molecular switches that enable RSV to complete its replication cycle. Specific modifications of viral proteins directly determine their structural functions and spatiotemporal distribution: glycosylation of the F and G proteins not only helps the virus overcome physical barriers and mediate membrane fusion, but also masks key antigenic epitopes through a "glycan shield" effect, enabling escape from humoral immunity [1][3][4]; meanwhile, the dynamic phosphorylation–dephosphorylation cycles of the nucleoprotein (N) and phosphoprotein (P) are decisive factors regulating liquid–liquid phase separation and assembly of viral inclusion bodies (IBs) and maintaining the balance between viral transcription and replication [4][6]. These modifications ensure efficient amplification and precise assembly of the virus within host cells.

Second, by reshaping the PTM landscape of host proteins, RSV creates a cellular microenvironment favorable to itself and actively evades innate immunity. Virus-induced activation of host kinases (e.g.,

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PI3K, MAPK) leads to phosphorylation of cytoskeletal proteins, promoting viral endocytosis and entry [1][3]; at the same time, by interfering with ubiquitination, ISGylation, and SUMOylation of host signaling molecules, RSV effectively blocks signal transduction in the type I interferon pathway and the functions of antiviral restriction factors, thereby establishing a long-term survival advantage within host cells [7]. In addition, epigenetic histone modifications and RNA methylation (m6A) further reveal how the virus modulates host gene expression to influence inflammatory responses and disease outcomes [7][33].

In summary, in-depth decoding of the "RSV PTM code" is not only crucial for elucidating viral pathogenic mechanisms, but also provides entirely new entry points for developing next-generation intervention strategies. In vaccine development, antigen design based on PTM structural biology (e.g., optimizing glycosylation sites to expose neutralizing epitopes) has become a key strategy for enhancing vaccine protective efficacy [1]. For antiviral therapy, strategies that target host PTM enzymes (e.g., kinase inhibitors) or disrupt specific viral modifications offer a higher barrier to resistance than traditional direct-acting antiviral drugs [9]. Looking ahead, with the combined application of high-throughput PTM-omics technologies and physiologically relevant organoid models, we are likely to map a more complete RSV PTM regulatory network, thereby providing more precise and effective solutions to reduce the global burden of RSV disease.

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