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REVIEW

Phosphorylation Modifications and Their Role in Viral Pneumonia: Mechanisms and Therapeutic Implications

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Abstract: Advances in diagnostic technologies have led to the identification of an increasing number of viruses associated with pneumonia, thereby drawing significant attention to viral pneumonia. The primary viral pathogens implicated in pneumonia include influenza virus, respiratory syncytial virus, coronavirus, adenovirus, parainfluenza virus, human metapneumovirus, and enterovirus. Post-translational modifications, especially phosphorylation, are pivotal in the lifecycle of these viruses. Phosphorylation affects key processes such as viral replication, transcription, assembly, and release, thereby influencing their propagation in host cells. Viral infection can also trigger kinase-associated pathways within host cells, activating host cell phosphatases and related signaling cascades. This results in alterations to host phosphorylation states, aggravating cellular pathology and facilitating viral proliferation. This review examines the common viral pathogens involved in pneumonia and highlights the role of phosphorylation in viral proliferation. Additionally, we explore the potential of phosphorylation inhibitors in controlling viral infections, with the aim of advancing our understanding of viral phosphorylation and promoting the use of these inhibitors in the treatment of viral pneumonia.

Keywords: viral pneumonia, phosphorylation modifications, influenza virus, respiratory syncytial virus, coronaviruses, adenovirus

Introduction

Pneumonia is a prevalent infectious disease that primarily affects the alveoli and distal bronchial tree.[1] According to the 2019 Global Burden of Diseases study, lower respiratory tract infections, including pneumonia, impacted approximately 400 million people globally.[2] The most vulnerable populations include the elderly, children[3] and pregnant women.[4] Pneumonia can be caused by various pathogens, such as bacteria, viruses, fungi, and parasites.[5] Among these, viral pneumonia has been recognized as a major cause of global morbidity and mortality.[6] In terms of timing, the incidence of pneumonia shows recognizable seasonal patterns that vary by climate, with winter–early spring peaks in temperate regions coinciding with increased circulation of influenza and RSV,[7] and rainy or high-humidity periods more often associated with higher incidence in tropical and subtropical settings.[8] Placing the burden in this temporal context helps frame subsequent advances in detection and management. Advances in diagnostic techniques have led to the detection of an increasing number of viruses, resulting in a growing number of diagnosed cases of viral pneumonia. This shift has redirected research focus from bacterial to viral infections in pneumonia studies.[9] The primary viral agents responsible for pneumonia include influenza virus, respiratory syncytial virus (RSV), coronavirus, adenovirus, parainfluenza virus, human metapneumovirus (hMPV), and enterovirus.[10–17]

Post-translational modifications (PTMs) are crucial processes that alter protein structure and function through the addition or removal of chemical groups during and after protein synthesis, such as phosphorylation, ubiquitination, and acetylation.[18–21] These modifications not only affect protein conformation but also play a key role in regulating cellular functions and disease mechanisms. Phosphorylation, in particular, is a significant PTM that modulates protein function by

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adding phosphate groups to specific amino acid residues, thereby influencing viral processes such as replication, transcription, assembly, and release.[22] For example, Glycogen Synthase Kinase-3 (GSK-3) phosphorylates the nucleocapsid protein (N protein) of coronaviruses, and GSK-3 inhibitors have been shown to reduce N protein phosphorylation, disrupt viral replication, and lower viral titers and cytopathic effects.[23] The phosphorylation and dephosphorylation of the influenza virus N protein regulate its nuclear localization, influencing viral replication and assembly.[24] In addition to affecting viral proteins, viral infections can modulate host cell physiological processes. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, for instance, activates host cell kinases and the MAPK pathway.[25] The activated MAPK pathway is involved in various physiological processes, including inflammatory responses and cell cycle regulation, thereby aggravating disease progression while facilitating viral replication.[26–28] Therefore, understanding the phosphorylation dynamics of pneumonia-causing viruses is crucial for gaining deeper insights into viral biology and the pathogenesis of viral pneumonia.

This review provides an overview of the common viral pathogens and their pathological characteristics in viral pneumonia, with a specific focus on the role of phosphorylation PTMs in the life cycle of viruses such as influenza virus, RSV, coronavirus, and adenovirus. Additionally, we discuss recent advances in phosphorylation-targeting therapeutics for treating viral pneumonia, aiming to promote the development of these interventions in clinical settings.

Key Viral Pathogens in Pneumonia: Epidemiology and Pathogenesis

Influenza Virus: Clinical Impact and Mechanisms of Pathogenesis

Influenza viruses are frequently implicated in pneumonia cases, including community-acquired pneumonia (CAP), hospital-acquired pneumonia, and pneumonia in immunocompromised individuals.[29,30] Approximately one-third of patients seeking medical attention for influenza are diagnosed with pneumonia.[31,32] A retrospective study involving 666 patients reported that 185 cases of confirmed influenza progressed to pneumonia, accounting for 27.7% of the total cases. These patients exhibited elevated C-reactive protein levels and reduced blood oxygen saturation.[33] Moreover, severe influenza cases are often complicated by ventilator-associated pneumonia due to secondary infections with antibiotic-resistant bacteria.[34]

Influenza viruses belong to the Orthomyxoviridae family and are classified into four subtypes: influenza A, B, C, and D. Among these, influenza A, B, and C infect humans,[35] while influenza D primarily affects livestock.[36] Influenza A and B are the main causes of seasonal influenza and are RNA viruses prone to frequent antigenic drift due to the lack of proofreading mechanisms in their RNA polymerase, leading to the emergence of novel strains.[37,38] Influenza C, unlike A and B, is less contagious and generally causes milder symptoms.[39] However, all three types—A, B, and C—have been linked to pneumonia. A study of 1,345 influenza patients revealed that 528 had influenza A, and of these, 211 cases developed pneumonia, with a significant association between pneumonia and reduced 30-day survival.[40] The clinical impact of different influenza subtypes varies; for instance, Minney-Smith et al reported that patients infected with influenza A/H1 exhibited longer hospital stays, higher ICU admission rates, and more severe pneumonia compared to other subtypes.[41] Although influenza B is generally associated with milder symptoms, a study involving 1,846 patients demonstrated that both influenza A and B infections can result in pneumonia.[42] Research on influenza C is less extensive; it usually causes only mild respiratory symptoms such as colds or coughs, predominantly in children under the age of 2.[43] Nevertheless, some reports indicate that influenza C can also lead to pneumonia.[44] A study by Principi et al involving 391 children with radiologically confirmed CAP found that respiratory secretions from five patients tested positive for influenza C, and these children exhibited clinical symptoms comparable to those of influenza A, which were more severe than those of influenza B.[45]

RSV: Epidemiology and Clinical Features

RSV is a member of the Paramyxoviridae family and is a non-segmented, negative-sense RNA virus encoding 11 proteins. The G protein and F protein play key roles in its pathogenesis: the G protein facilitates RSV attachment to epithelial cells, while the F protein mediates viral entry into the host cell.[46] RSV is primarily divided into two subtypes, A and B, based on differences in surface antigens, with the G protein being the primary marker for subtype differentiation.[47] Viral infections are a leading cause of CAP in children, with RSV identified as a major pathogen in

approximately 42% of cases.[11,48] RSV is also the most common cause of lower respiratory tract infections in children under one year of age.[49] A two-year study found that 66.9% of pediatric CAP cases were attributed to viral infections, with RSV accounting for 32% of these (67 cases total, with 33 of subtype A, 33 of subtype B, and 1 untyped), making it the most prevalent viral cause.[12] Similarly, a study by Berkley et al on 759 children hospitalized with pneumonia showed that 425 (56%) tested positive for one or more respiratory viruses, with RSV being detected in 260 patients.[50] The study also indicated that RSV detection was associated with severe pneumonia, a correlation not observed with other respiratory viruses.

RSV is not limited to pediatric infections and can cause pneumonia in adults and the elderly as well.[51] In high-risk adults with chronic cardiac or pulmonary conditions, the outpatient visit rates for RSV infection are comparable to those for influenza A, and the rates of ICU admission and mortality are similar for both viruses, underscoring the significant impact of RSV in these populations.[52] PCR-based diagnostic methods have improved the accuracy of detecting viral pathogens in adult CAP cases.[53,54] A study of 340 adult CAP patients using PCR diagnostics revealed that the prevalence of viral infections was comparable to bacterial infections, with influenza A being the most common virus, followed by adenovirus and RSV subtype A.[13] In elderly populations, RSV is a major cause of lower respiratory tract infections, accounting for 2%-9% of annual pneumonia hospitalizations in the United States.[55] Additionally, in those aged 65 and older, RSV-bacterial co-infections are associated with higher hospital mortality rates.[56]

Coronaviruses: Host Interactions and Disease Severity

SARS-CoV and SARS-CoV-2, both members of the Betacoronavirus genus within the Coronaviridae family, are positive-sense single-stranded RNA viruses that share a high genetic homology with coronaviruses found in bats.[57] Their RNA is enclosed within a nucleocapsid formed by the N protein, and the viral envelope is embedded with spike protein (S protein), membrane protein, and envelope protein.[58,59] The S protein is crucial as it facilitates the virus's entry into host cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the cell surface. Notably, the binding affinity of SARS-CoV-2 to ACE2 is significantly higher than that of SARS-CoV, which contributes to the higher transmissibility of SARS-CoV-2.[60] The S protein of SARS-CoV-2 comprises three components: S1, S2, and a transmembrane domain, with the S1 subunit containing the receptor-binding domain that interacts with the ACE2 receptor.[61,62] Binding of the S1 subunit to ACE2 induces conformational changes at the S1/S2 cleavage site, enhancing the susceptibility of these regions to host protease cleavage.[63] Additionally, the binding process triggers a switch-like conformational shift between the κ-helix and the β-strand in the S protein, further promoting viral entry into the host cell.[64]

Coronaviruses are strongly linked to pneumonia. In a study of 338 cases of CAP in children under three years of age, 22 cases (6.5%) tested positive for coronaviruses, with 9 (40.9%) being co-infections.[12] In a Thai study of 734 pneumonia patients, 3% of children and adolescents were found to be infected with human coronaviruses.[65] CAP in children has been associated with human coronaviruses 229E, OC43, NL63, and HKU1.[66,67] However, SARS-CoV-2 primarily affects middle-aged and elderly individuals, with children showing lower susceptibility and fewer severe or fatal cases.[68] A large-scale study involving 41,640 children and adolescents and 268,945 adults found that the seropositivity rate was lower in children than in adults, and children had a lower risk of contracting SARS-CoV-2, with an odds ratio of 0.56 for being an infected contact.[69] Additionally, in household transmission scenarios, adult SARS-CoV-2 patients were found to play a pivotal role in the spread of the virus.[70]

Adenovirus: Pathogenesis and Clinical Manifestations

Adenoviruses are non-enveloped, double-stranded DNA viruses that primarily consist of capsid proteins and a core.[71] During viral entry, the fibers on the adenoviral capsid bind to receptors on the host cell surface,[72,73] triggering endocytosis and vesicle formation. The acidic environment within the vesicle facilitates viral uncoating and the release of viral DNA.[74] This viral DNA then enters the host cell nucleus, where it integrates with the host transcription machinery to initiate gene expression and viral protein synthesis.[75]

Adenoviruses primarily infect the upper respiratory tract, but like other viral agents, they can also cause viral pneumonia.[76–78] A study involving 3,356 patients with acute lower respiratory tract infections (ALRTI) reported that HAdV-B7 and HAdV-B3 were the most prevalent adenovirus types in pediatric ALRTI cases, accounting for 49.0% and

26.3% of infections, respectively, with HAdV-B7 being associated with more severe clinical symptoms.[79] The study also identified cases of co-infection with HAdV-C2 and HAdV-C57.[79] Recent data suggest that adenovirus is a major contributor to respiratory infections in mainland China, responsible for 5.8%-13% of acute respiratory infection cases, predominantly caused by HAdV types B, C, and E.[80] Among these, HAdV-55 is a significant cause of CAP in China.[81] HAdV-55 can result in severe, and even fatal, pneumonia in children, particularly in cases with co-infections involving other pathogens, leading to complications such as plastic bronchitis and post-infectious bronchiolitis obliterans.[82] In elderly patients, HAdV-55 also shows a higher pneumonia severity index, greater systemic hypotension, more pronounced radiographic abnormalities, and increased hospitalization rates compared to HAdV-B7 and HAdV-B3.[83] In contrast, data from the United States collected between 2003 and 2016 indicated that HAdV-3 and HAdV-2 were the most common adenovirus types.[84]

Other Viral Pathogens: Parainfluenza, hMPV, and Enterovirus

In addition to the previously discussed viruses, parainfluenza viruses have also been implicated in pneumonia.[14,15] These viruses initially infect the upper respiratory tract, where they attach to and replicate in ciliated epithelial cells before spreading to the lower respiratory tract.[85] Symptoms of upper respiratory tract infections are typically mild, resembling a common cold, but when the virus reaches the distal airways, it can lead to pneumonia.[86] In adults, parainfluenza virus infections usually present with mild symptoms.[86] However, due to immature immune systems, seasonal epidemics of human parainfluenza virus (HPIV) pose a substantial disease burden for children, with HPIV responsible for 40% of hospitalizations due to lower respiratory tract infections in children.[87] A study involving 4,755 patients found that 160 of 178 HPIV-positive samples were from children under five years old, accounting for 88.9% of cases, with HPIV-3 and HPIV-1 being the most prevalent subtypes.[88] This observation aligns with Knott's findings, which reported peak activity for HPIV-1 in autumn, HPIV-3 in spring and summer, and a lower prevalence of HPIV-2.[89]

hMPV, also a member of the Paramyxoviridae family, can cause lower respiratory tract infections. A study of 124 children with CAP identified hMPV in five cases, three of which involved co-infections. The study further revealed that hMPV seroconversion increases with age, reaching nearly 100% by school age, suggesting that early-life exposure establishes natural immunity.[90] This may explain the relative rarity of hMPV as a cause of CAP in children. A separate study of 2,358 children and 2,320 adults hospitalized with pneumonia detected 298 (12.6%) and 88 (3.8%) hMPV cases, respectively, indicating that hMPV pneumonia is significantly less common in adults than in children. Moreover, the study found that clinical symptoms of hMPV pneumonia were more severe in children than in adults,[16] highlighting the need for vigilant management of this condition despite its lower incidence.

Enteroviruses are small, non-enveloped, positive-sense RNA viruses in the Picornaviridae family. Enteroviruses, particularly EV-D68, have been linked to pneumonia.[91] A report by Imamura et al indicated that 2.6% of severe CAP cases among children aged 7 to 14 years hospitalized in the Philippines between 2008 and 2009 tested positive for EV-D68.[17] Children are the most affected group, with infection rates decreasing with age.[92] In a study of 907 patients, individuals under 20 years of age were found to be more likely to test positive for EV-D68 than those aged 20 and above, with the highest positivity rate observed in the 5–9 years age group.[93] EV-D68 is a primary cause of respiratory illnesses such as CAP. In a screening of respiratory samples from 130 Danish patients, 14 cases were positive for EV-D68, of which 12 presented with respiratory symptoms, including persistent cough, acute respiratory distress, and asthma-like wheezing. Two patients were diagnosed with pneumonia and experienced recurrent hospitalizations.[94]

Phosphorylation Modifications in Viral Pneumonia: Functions and Mechanisms

As shown in Figure 1, PTMs, especially phosphorylation, significantly influence multiple processes such as viral assembly, replication, and transcription, making them indispensable for viral proliferation.[24] The key phosphorylation sites and their respective roles in the proliferation of influenza virus, RSV, coronavirus, and adenovirus are summarized in Table 1.

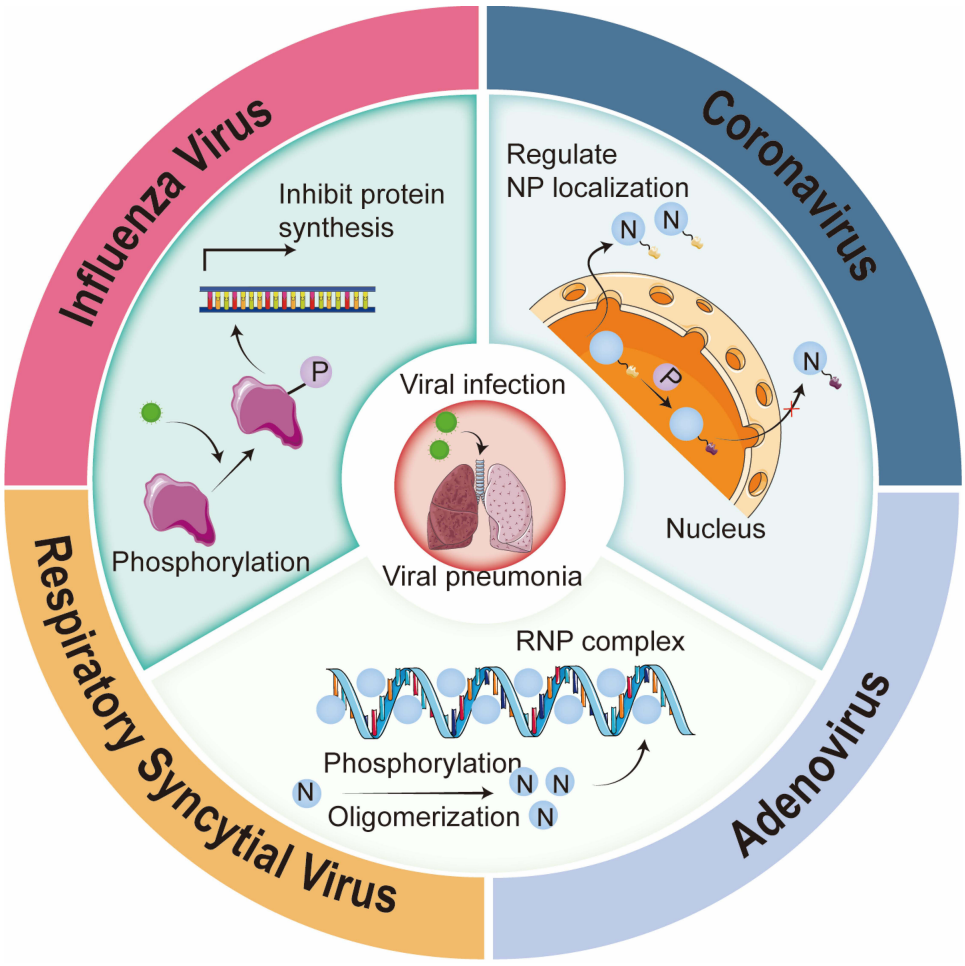

Figure 1 The impact of phosphorylation post-translational modification on viral processes. In pneumonia-causing viruses, including influenza virus, coronavirus, adenovirus, and respiratory syncytial virus, phosphorylation modifications can influence viral transcription and translation. For example, phosphorylation of nucleocapsid proteins promotes the formation of transcriptional complexes, thereby enhancing viral transcription and translation. Additionally, phosphorylation of nucleocapsid proteins affects their intracellular localization, influencing viral assembly. Beyond viral protein phosphorylation, viral infection activates host cell phosphorylation pathways, which in turn suppress host protein synthesis.

Phosphorylation Dynamics in Influenza Virus Replication and Transcription

The phosphorylation modification process and its effects in influenza virus are shown in Figure 2. The transcription of influenza virus involves a unique mechanism known as "cap-snatching," wherein the viral RNA polymerase, consisting of the PA, PB1, and PB2 subunits, interacts with the host RNA polymerase II. The PB2 subunit specifically recognizes and binds to the 5' cap structure of host mRNA, which is then cleaved by the PA subunit to serve as a primer for viral mRNA synthesis.[111,112] The C-terminal domain (CTD) of RNA polymerase II plays a critical role in mRNA transcription and is regulated by phosphorylation during mRNA maturation.[113] Immunoprecipitation studies have demonstrated that the viral RNA polymerase binds to the Ser5-phosphorylated CTD, facilitating the subsequent "cap-snatching" process.[114] The activity of the viral RNA polymerase is crucial for transcription, and PKCα-mediated phosphorylation of PB1 and NS1 enhances its activity.[28] Phosphorylation of the PA subunit is essential for its function. Casein kinase II (CK2), a serine/threonine kinase, phosphorylates several sites on the PA subunit, and mutation of the T157 site results in the loss of cRNA synthesis from the viral RNA template, although viral RNA transcription remains unaffected.[95] The CTD of PA can also interact with pyruvate kinase M2 (PKM2), enabling the transfer of a phosphate group to PA, thereby converting the RNA polymerase from a transcriptase to a replicase.[115] Additionally, non-structural protein 1 (Nsp1) is phosphorylated at threonine 215 by cyclin-dependent kinases (CDKs) and extracellular signal-regulated kinases (ERKs), promoting efficient viral replication.[96]

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Table 1 Phosphorylation Modifications Involved in Viral Pneumonia and Their Functional Roles

Virus	Phosphorylation Site	Involved Enzyme	Effects	Reference
Influenza	PB1, NS1	PKCα	Increases viral RNA polymerase activity and promotes viral replication.	[28]
	PA T157	CK2	The T157 phosphorylation site is crucial for RNA polymerase to synthesize cRNA from the viral RNA template, and its mutation impairs cRNA synthesis without affecting viral RNA transcription.	[95]
	Nsp1 T215	CDKs, ERKs	Promotes efficient viral replication.	[96]
	NP S482	PLK3	Enhances NP oligomerization activity and viral RNA binding to RNP.	[97]
	NP S165, NP S407	PKC	Inhibits NP oligomerization and impairs RNP complex assembly	[98,99]
	NP S486	PKC	Promotes the oligomerization of NP.	[99]
	NP S9, NP Y10	PKG, INSR	Weaken the binding ability of NP to importin-α, preventing NP from entering the nucleus.	[24]
	NP Y296	INSR	Alter the conformation of NES 3, disrupting the interaction between NP and CRM1, thereby inhibiting NP's nuclear export.	[24]
	NP T188	–	Block NP's transport from the nucleus to the cytoplasm, leading to reduced polymerase activity and viral replication.	[100]
RSV	P protein S237	CK2	Promote the phosphorylation of S232.	[101,102]
	P protein S232	CK2	Activate P protein and promote its oligomerization.	[101,102]
	P protein S116, P protein S117, protein P S119	CK2	Promote the interaction between N protein and P protein, ensure the correct folding of N protein and the specific encapsidation of RNA, thereby ensuring the virus's replication capacity.	[101]
	M protein T205	CK2	Promote M protein oligomerization, enhancing viral infectivity.	[103]
	M protein S95	CK2	Inhibit the re-entry of M protein into the nucleus and promote its retention in the cytoplasm, leading to increased oligomerization of M protein, contributing to viral assembly.	[104]
Coronavirus	NP S 177, NP S 189, NP S 207	GSK-3	Enhance the interaction between N protein and 14-3-3 protein, facilitating the localization of N protein with the viral replication complex in the cytoplasm, thereby promoting viral RNA synthesis	[23,105]
	N protein *RS* motif	CDK, MAPK, CK2	Inhibit the multimerization of N protein and its localization in stress granules, thereby reducing its ability to suppress host cell mRNA translation.	[105,106]
	Nsp1-Nsp4	–	Phosphorylation of nsp1 stabilizes its binding to the 40S ribosomal subunit, while phosphorylation of nsp2, nsp3, and nsp4 induces conformational changes, affecting target protein binding and regulating viral replication.	[107]
Adenovirus	E1A S132	CDKs, CK2	Enhance E1A's ability to disrupt E2F/DP-pRB complex, promote host cell entry into S phase, support viral replication	[108]
	E1B S490, E1B S491	CK2	Enhance the inhibition of p53 and increase viral replication.	[109]
	DBP T195	–	Alter the conformation of DBP, thereby changing the replication capacity.	[110]

The nucleoprotein (NP) of influenza virus is a single-stranded RNA-binding protein that encapsulates the viral RNA to form a helical nucleocapsid, which is essential for viral transcription and replication.[116] Inhibition of NP phosphorylation has been shown to delay viral transcription, and phosphorylated nucleocapsids are more sensitive to heat, suggesting that NP phosphorylation alters the nucleocapsid structure and affects viral transcription.[117] Ren et al demonstrated that NP is phosphorylated at serine 482 by polo-like kinase 3 (PLK3), which enhances its oligomerization and promotes ribonucleoprotein (RNP) complex formation with viral RNA.[97] Moreover, PLK3 enhances viral polymerase activity in a dose-dependent manner. Different phosphorylation sites on NP have distinct effects. For example, mutating S165 to glutamic acid (S165E) or aspartic acid (S165D) inhibits NP oligomerization and RNP assembly.[98] Similarly, phosphorylation at S165 and S407 inhibits NP oligomerization, while phosphorylation at S486 promotes excessive oligomerization.[99]

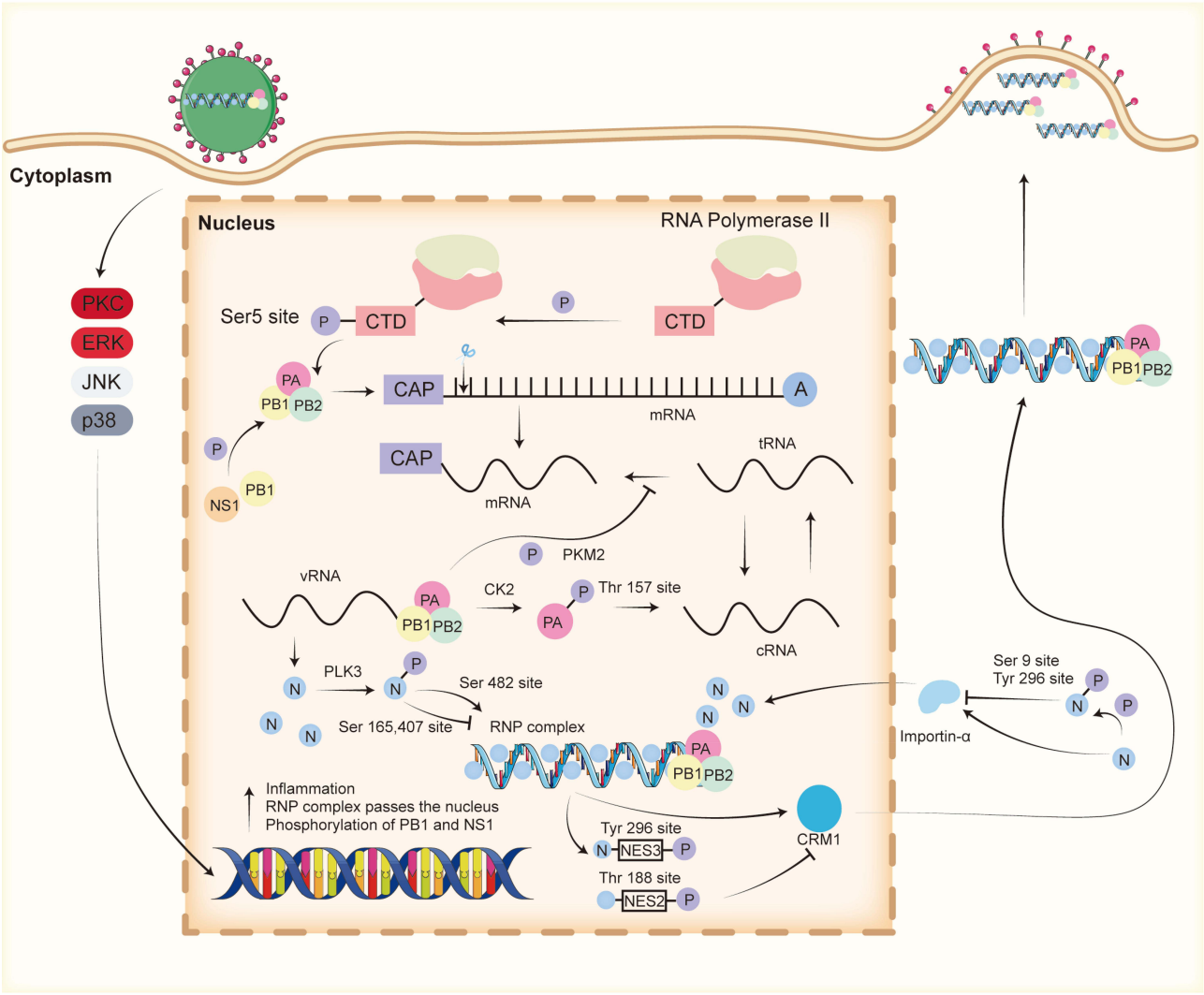

Figure 2 Phosphorylation regulation in influenza virus. Upon infection of host cells by influenza virus, host phosphorylation pathways such as PKC, ERK, JNK, and p38 are activated, leading to an increase in inflammatory cytokines and promoting viral infection and proliferation. The viral RNA polymerase interacts with phosphorylated RNA polymerase II, facilitating host mRNA splicing and viral mRNA maturation. Phosphorylation of the PA subunit of the viral RNA polymerase enhances vRNA synthesis, while phosphorylation of nucleocapsid proteins regulates transcription and replication by promoting RNP complex formation. Additionally, nucleocapsid protein phosphorylation affects CRM1 binding, regulating the nuclear export of RNP complexes, which influences subsequent viral assembly.

Phosphorylation of NP also influences its intracellular transport, thereby affecting RNP formation. For instance, phosphorylation at S9 and Y10 reduces NP's binding affinity to importin-α, preventing its nuclear import, while phosphorylation at Y296 alters the conformation of nuclear export signal 3 (NES3), inhibiting NP's interaction with CRM1 and its nuclear export.[24] Likewise, phosphorylation at T188 within the NES2 region hinders NP's transport from the nucleus to the cytoplasm, reducing polymerase activity and viral replication.[100] Even at the same site, different phosphorylation states can have varying effects; for example, S482E enhances polymerase activity and RNP assembly, whereas S482A negatively impacts viral replication.[97] This dynamic regulation of NP phosphorylation-dephosphorylation ensures precise control of RNP formation, supporting efficient viral replication.

Influenza virus also activates various cellular pathways through phosphorylation to facilitate its replication.[118] For example, PKC activity is significantly increased in mononuclear cells upon influenza infection, and PKC inhibitors reduce viral infection.[119,120] The virus also activates the MAPK pathway (ERK, JNK, and p38) and the PI3K/Akt pathway.[121–124] Activation of p38 and JNK induces the production of pro-inflammatory cytokines like RANTES, triggering inflammatory responses.[121] ERK activation is associated with RNP nuclear translocation in the late stages

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of infection, and ERK inhibition causes RNP retention in the nucleus, thereby suppressing viral replication.[123] The PI3K/Akt pathway promotes the phosphorylation of PB1 and NS1, enhancing viral replication.[28]

Overall, phosphorylation in influenza spans the entire course of replication and transcription. It affects the activity of polymerase subunits PA, PB1, and PB2, and regulates NP oligomerization and nucleo-cytoplasmic trafficking, which together determine the efficiency of RNP assembly. The virus also exploits host signaling pathways, including PKC, MAPK, and PI3K/Akt, to enhance polymerase function and promote genome replication. Phosphorylation at distinct sites is stage dependent and directional, with some events promoting assembly while others restrain excessive aggregation; this fine balance ultimately shapes viral yield and the magnitude of inflammatory responses. Timed interventions that target specific kinases or key sites may reduce replication and mitigate pathology while preserving essential cellular functions.

Phosphorylation and Its Role in RSV Replication and Host Interaction

The replication and transcription of RSV's negative-strand genomic RNA are carried out by the viral RNA-dependent RNA polymerase complex, which primarily comprises the L protein (large RNA polymerase subunit), the P protein (phosphoprotein), and the N protein.[125] The P protein is the major phosphoprotein, and its phosphorylation is mainly mediated by CK2.[126] The main phosphorylation sites on the P protein include S116, S117, and S119 in the central region and S232 and S237 at the C-terminus.[101] These phosphorylation sites are interdependent; phosphorylation at S237 alone does not activate the P protein but promotes phosphorylation at S232, which in turn activates the P protein.[102] Phosphorylation is crucial for P protein oligomerization. P protein expressed in bacterial systems lacks the necessary PTMs and, due to dephosphorylation, fails to oligomerize. In contrast, P protein expressed in HEp-2 cells oligomerizes correctly.[127] Additionally, dephosphorylation of the P protein reduces its interaction with the N protein. Removal of phosphorylation sites S116, S117, S119, S232, and S237 reduces the N-P interaction to only 40% of its original level, impairing the proper folding of the N protein and the specific encapsidation of RNA, thereby decreasing viral replication.[101] Furthermore, the P protein can bind to the cellular phosphatase PP1 and mediate the dephosphorylation of the M2-1 protein, which enhances its binding to newly synthesized viral mRNA in inclusion bodies, thereby increasing RSV transcriptional efficiency.[128]

In RSV, the matrix (M) protein functions as a structural adapter essential for proper viral assembly, bridging the viral envelope and the RNP complex.[129] The T205 site of the M protein can be phosphorylated by CK2. A T205D mutant, which mimics dephosphorylation, disrupts M protein oligomerization, reducing viral infectivity. The S220N mutation partially compensates for the defect caused by T205D, possibly due to the close proximity of T205 and S220 in the M protein crystal structure, suggesting that S220 may influence the phosphorylation of T205.[103,130] During the early stages of RSV infection, the M protein predominantly localizes to the nucleus, where it binds to chromatin and inhibits host cell transcription. Later in the infection, it relocates to the cytoplasm to facilitate viral particle assembly.[131,132] CK2-specific inhibitor TBB has been shown to increase nuclear retention of the M protein in infected cells, indicating that the nuclear-cytoplasmic distribution of the M protein is regulated by phosphorylation. Further studies suggest that phosphorylation at S95 and T205 is critical for this process. M protein lacking phosphorylation at these sites is directed to the nucleus early in infection, but later phosphorylation by CK2 prevents its re-entry into the nucleus and promotes its retention in the cytoplasm, thereby enhancing oligomerization and involvement in viral assembly.[104] Both the absence and excessive phosphorylation of these sites reduce RSV infectivity.[104]

RSV also manipulates host protein phosphorylation to support its replication. Upon viral invasion, cells increase the expression of protein kinase R (PKR), which is activated by phosphorylation. Activated PKR then phosphorylates eIF2α, inhibiting eIF2B and consequently suppressing both cellular and viral protein translation.[133,134] While upregulation of PKR has been observed in RSV-infected epithelial cells,[135] RNA interference silencing of PKR does not affect RSV growth.[136] This is because RSV's N protein binds specifically to PKR, preventing it from interacting with and phosphorylating eIF2α, thus maintaining the translation of viral proteins.[137]

In RSV, phosphorylation of the P protein is central to stabilizing the polymerase complex and sustaining efficient transcription, and it also shapes its interaction with N and the proper assembly of RNPs. The phosphorylation state of M determines its distribution between nucleus and cytoplasm, enabling suppression of host transcription early in infection and promotion of assembly and budding at later stages. The virus further tunes the translation switch governed by PKR and eIF2α

to maintain an environment supportive of viral protein synthesis. Taken together, RSV uses phosphorylation checkpoints across transcription, assembly, and budding to balance replication efficiency against host restrictions. These observations suggest that precise modulation of key nodes such as CK2, or the interaction between P and host phosphatases, may provide a therapeutic window that suppresses the virus without excessive disturbance of the host.

Phosphorylation of Coronavirus N Proteins: Implications for Viral Replication and Host Response

The phosphorylation process in coronavirus, specifically the phosphorylation modifications of the N protein and their effects, are illustrated in Figure 3. The N protein of coronaviruses is a key structural protein crucial for viral replication, transcription, and assembly. It interacts with the coronavirus genome to form RNP complexes, which are encapsulated by the lipid membrane and undergo budding.[138] In infected cells, the N protein is highly phosphorylated, a modification essential for its maturation.[139] Lin et al reported that SARS-CoV exhibits significant phosphorylation at specific sites within the serine-rich region (amino acids 1–256) of the N protein.[140] Wu et al identified that GSK-3 kinase phosphorylates SARS-CoV N protein at S177, S189, and S207, and inhibition of GSK-3 significantly reduces viral RNA synthesis.[23] Additionally, the N protein co-localizes with the viral helicase throughout the infection cycle.[141,142] Apart

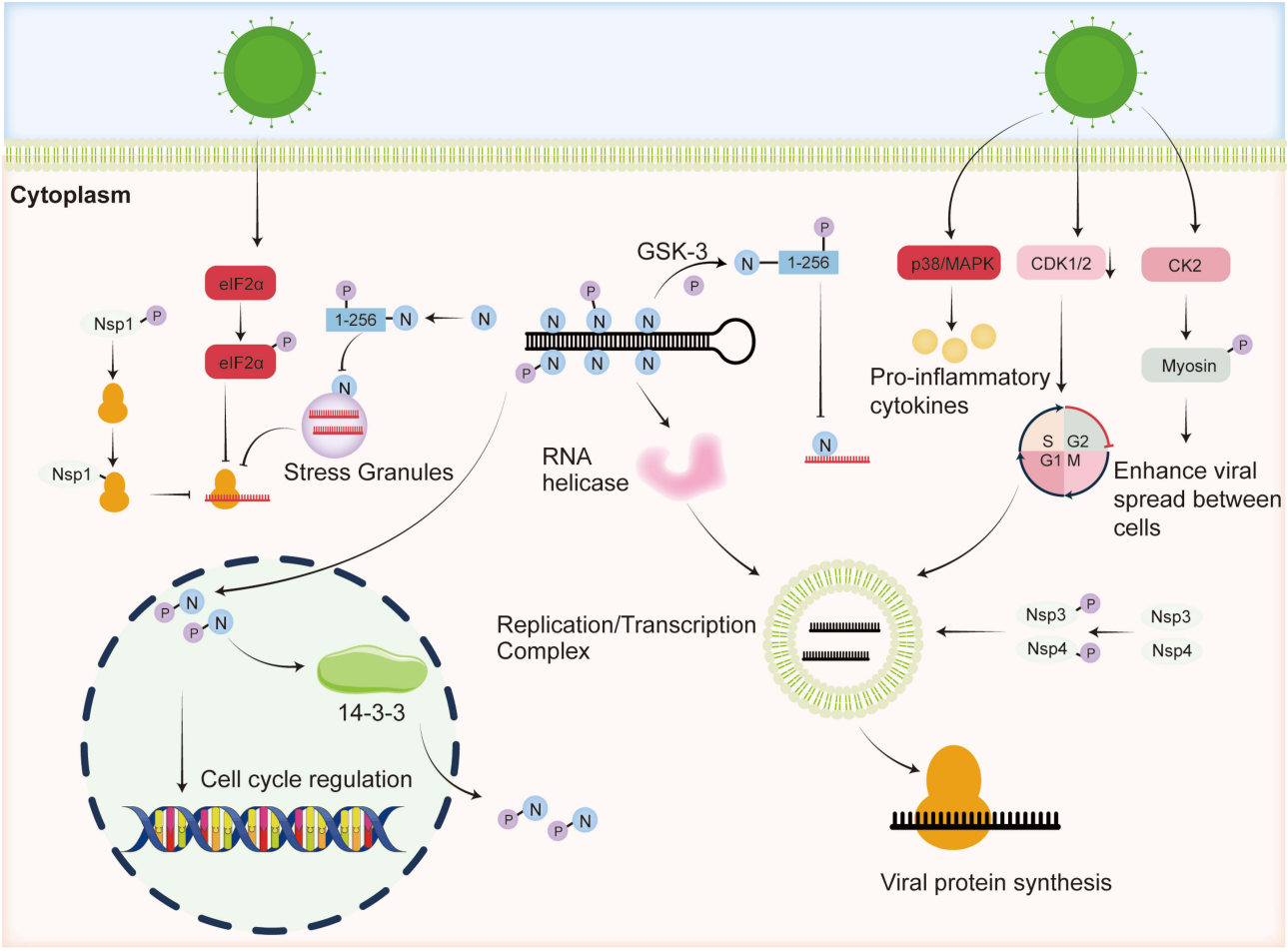

Figure 3 Phosphorylation modifications in coronavirus. Following coronavirus infection, eIF2α phosphorylation is promoted, leading to the formation of stress granules and suppression of host protein translation. Moreover, activation of p38/MAPK and CK2 pathways, along with inhibition of CDK1/2 activation, is observed in infected hosts, which promotes cytokine production, enhances viral spread, and halts cells in the S/G2 phase, thereby facilitating viral replication. Phosphorylation of nucleocapsid proteins is crucial for viral processes, as it enhances specific binding to viral RNA and suppresses stress granule formation, leading to the inhibition of host protein synthesis. Phosphorylated N protein also localizes to the nucleus to regulate the cell cycle. Additionally, within the cell, N protein co-localizes with RNA helicase to promote the release of viral RNA. Phosphorylation of non-structural proteins also affects viral replication, as Nsp1 phosphorylation suppresses host protein transcription, while phosphorylation of Nsp3 and Nsp4 promotes the formation of the transcription/translation complex.

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from GSK-3, other kinases, including CDKs, mitogen-activated protein kinases (MAPKs), and CK2, can phosphorylate the SARS-CoV N protein. Phosphorylated N protein accumulates in the nucleus, binds to 14-3-3 proteins, and translocates to the cytoplasm.[105] This suggests that N protein phosphorylation may enhance its interaction with 14-3-3 proteins, thereby promoting the formation of replication complexes in the cytoplasm and facilitating viral RNA synthesis.

Coronavirus-infected cells have also been shown to increase the phosphorylation of eukaryotic initiation factor 2α (eIF2α), leading to a blockade of translation initiation and an increase in stress granules, which induces host translational arrest without affecting viral replication.[143] Peng et al demonstrated that the SARS-CoV N protein inhibits host mRNA translation in vitro,[106] likely due to its role in stress granule formation. Phosphorylation of the N protein's *RS* motif (rich in arginine [R] and serine [S] dipeptide repeats) reduces its multimerization and accumulation in stress granules. Therefore, phosphorylation of the *RS* motif not only impacts N protein multimerization and localization in stress granules but also weakens its ability to inhibit translation.[106] Moreover, phosphorylated N protein shows higher affinity for viral RNA over non-viral RNA.[144] This indicates that N protein phosphorylation regulates host RNA expression and affects its oligomerization and interaction with viral RNPs.

SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19), hijacks host cell phosphorylation systems to enhance its replication and spread.[145] In SARS-CoV-2-infected cells, the p38/MAPK and CK2-mediated cytoskeletal signaling pathways are upregulated, while CDK1/2 activity is downregulated.[145] Upregulation of the p38/MAPK pathway promotes excessive production of pro-inflammatory cytokines, leading to uncontrolled inflammation and disease exacerbation.[26] Inhibition of CDK1/2 causes cell cycle arrest at the S/G2 phase, ensuring the supply of nucleotides and proteins needed for viral replication.[146] CK2 promotes myosin phosphorylation to drive actin polymerization, facilitating efficient viral spread between cells.[147,148] Additionally, nsps of SARS-CoV-2 play critical roles in viral replication. Nsp1 binds to the 40S ribosomal subunit, inserting its CTD into the mRNA channel, thus interfering with host mRNA synthesis.[149] Mass spectrometry and SILAC analyses revealed that nsp2 interacts with 84 cellular proteins involved in endosomal transport, protein translation, ribosome assembly, and vesicle trafficking, indicating that nsp2 may be crucial for SARS-CoV-2 infection, especially in host processes like protein synthesis and vesicle transport.[150] The interaction between nsp3 and nsp4 induces membrane rearrangement, forming a replication/transcription complex for viral genome replication and mRNA transcription, and disruption of this interaction halts viral replication.[151] Phosphorylation of nsp1 stabilizes its binding to the 40S ribosomal subunit, and significant conformational changes occur in phosphorylated versus dephosphorylated forms of nsp2, nsp3, and nsp4,[107] suggesting that phosphorylation modulates the interactions of SARS-CoV-2 nsps with target proteins, thereby regulating viral replication.

In coronaviruses, phosphorylated N functions as a hub that contributes to replication complex formation and influences RNA preference, subcellular localization, and the state of host translation. These changes are closely linked to pathways governed by GSK-3, CDKs, MAPKs, and CK2, and intersect with stress-granule dynamics and control of host protein synthesis. SARS-CoV-2 leverages these circuits, together with altered interactions of several nsps with host machinery, to expand replication and intensify inflammatory injury. Overall, N and its upstream kinases constitute a key interface between viral replication and host responses. Selective interventions at these nodes may reduce both replicative output and excessive inflammation, provided that disease stage and dosing timing are considered to minimize effects on normal cellular processes.

Adenovirus Phosphorylation Pathways: Viral Replication and Host Defense Evasion

Upon adenovirus infection, the viral genome is transported to the host cell nucleus, initiating the expression of early genes E1 to E4, including E1A and E1B.[152] The E1A protein can immortalize primary cells and push quiescent cells into the S phase, creating a favorable environment for viral replication.[153] This process involves E1A binding to the retinoblastoma protein (pRB) and disrupting the E2F/DP-pRB complex. Phosphorylation of E1A by CDKs or CK2 enhances its ability to disrupt the E2F/DP-pRB complex.[108] A critical phosphorylation site on E1A is Ser132, and mutations at this site (eg, Ser132 to Asp132 or Gly132) significantly reduce its binding affinity for pRB.[154] The E1B protein inhibits apoptosis by binding to the tumor suppressor p53, thereby providing sufficient time for viral replication.[155] Phosphorylation of serine and threonine residues near the C-terminus of E1B by CK2 enhances its

inhibitory effect on p53, and the phosphorylated form of E1B significantly increases viral replication compared to the dephosphorylated mutant (Ser490 and Ser491 mutated to alanine).[109]

The early gene E2 encodes the DNA-binding protein (DBP), which is phosphorylated at tyrosine residues, particularly Tyr195, early in infection.[156] In addition, serine and threonine residues at the N-terminus of DBP are also phosphorylated.[157] The phosphorylation state of DBP varies during infection, ranging from 4 to 7 phosphate groups, and dephosphorylation does not affect its ability to bind DNA.[158] Phosphorylation of DBP alters its sensitivity to chymotrypsin, indicating that phosphorylation may induce conformational changes in DBP that impact adenoviral replication in host cells.[110]

PKR kinase is a host defense mechanism that typically inhibits protein synthesis by phosphorylating eIF2α in response to viral infection. Studies have shown that in the late stages of adenovirus infection, the E1B and E4orf6 complex inhibits PKR activation, preventing eIF2α phosphorylation and thereby promoting efficient viral protein synthesis.[159] Additionally, in the late stages of adenovirus replication, inhibition of eIF-4E phosphorylation suppresses host protein synthesis, allowing preferential translation of viral late mRNA.[160] Adenovirus infection also induces phosphorylation of ERK and activation of the Raf/MEK/ERK signaling pathway in the late stages, which supports high levels of viral protein expression and production of progeny viruses.[161] A model of human adenovirus type 2 (Ad2) infection in IMR-90 cells demonstrated that viral infection triggers phosphorylation changes related to glycolysis, consistent with the activation of the Warburg effect.[162] This suggests that adenovirus modulates host signaling pathways and energy metabolism through phosphorylation to promote viral replication.

In adenoviruses, phosphorylation of E1A, E1B, and DBP sequentially achieves early goals that include driving entry into S phase, suppressing apoptosis, and optimizing nucleic acid replication, and at later stages sustains high levels of structural protein synthesis and progeny production through Raf/MEK/ERK signaling. Regulation of translation initiation and cellular metabolic state gives the virus an advantage in the allocation of host resources. The conformation and function of DBP adjust with its phosphorylation status, which further stabilizes the progression of replication. In summary, adenoviruses connect cell-cycle control, apoptosis, protein synthesis, and metabolic reprogramming into a continuous chain, with phosphorylation serving as a link and amplifier. This framework supports selective targeting of CDKs, CK2, or the ERK pathway, and also indicates the need to monitor potential effects on host proliferation and metabolism when assessing efficacy.

Therapeutic Strategies Targeting Phosphorylation Pathways in Viral Pneumonia

Traditional Chinese medicine (TCM) extracts have been extensively studied for their antiviral effects, particularly against pathogens responsible for viral pneumonia,[163] and given that phosphorylation regulates viral replication, assembly, and host inflammatory responses across respiratory viruses,[145,164] this section briefly summarizes host-directed kinase-targeted strategies and TCM-derived candidates acting on CK2, p38 MAPK, PIKfyve, and CDKs, highlighting their mechanisms, preclinical efficacy, and limitations.

Most of the reported TCM compounds exhibit antiviral activity by inhibiting the phosphorylation of signaling pathways such as p38 MAPK, JNK/SAPK, or ERK, which are activated by pathogens.[165–168] Santin reduced IAV replication in MDCK and THP-1 cell models while dampening phosphorylation of ERK/JNK and NF-κB, with activity observed at micromolar concentrations.[165] Rhein showed in vitro anti-IAV activity with an EC50 of approximately 1.5 μg/mL and, in PR8-infected mice, oral gavage at 25–75 mg/kg/day for 6 days improved survival, lowered lung index and viral titers, and reduced inflammatory cytokines.[166] Emodin inhibited IAV replication at 3.125–25 μg/mL in cell culture and, when given orally at 25–75 mg/kg/day for 6 days in infected mice, decreased pulmonary viral load and cytokine levels and alleviated histopathology.[167] Oxymatrine suppressed IAV replication and airway inflammation in vitro and showed efficacy in PR8-infected mice at 60–120 mg/kg/day by oral gavage, reducing lung index, viral titers, and pro-inflammatory readouts.[168] However, given that TCM compounds often possess additional properties such as anti-inflammatory and antioxidant activities,[165] it remains to be fully understood whether their antiviral effects are solely reliant on the inhibition of phosphorylation pathways. Recent studies have summarized TCM compounds that inhibit viral pneumonia-related pathogens in Table 2. In particular, Bouhaddou et al have investigated phosphorylation inhibitors targeting coronaviruses, especially SARS-CoV-2, and found that several key kinase pathways, including CK2, p38 MAPK, PIKFYVE, and CDKs, play significant roles in SARS-CoV-2 replication and infection. The use of small-molecule inhibitors targeting these pathways significantly reduces viral replication.[145] A summary of the primary small-

Table 2 Role of Phosphorylation Inhibitors in the Treatment of Viral Pneumonia

Virus	Compounds	Model	Effects/Mechanism	Reference
Influenza A	Santin	MDCK and THP-1 cells	Depress the phosphorylation of p38 MAPK, JNK/SAPK and ERK.	[165]
	Rhein	C57BL/6J mice	Decrease IAV-induced activations of Akt, p38 and JNK MAPK pathways.	[166]
	Emodin	C57BL/6J mice	Reduce the phosphorylation of p38/JNK MAPK induced by IAV	[167]
	Oxymatrine	C57BL/6J mice	Inhibit IAV-induced activations of Akt, ERK1/2 and p38 MAPK	[168]
RSV	Berberine	A549 cells	Inhibit the phosphorylation of p38 MAPK and suppress the synthesis of viral proteins and mRNA.	[170]
	Grape Seed Proanthocyanidin	A549 cells	Inhibit the activation of the ERK, JNK, and p38 pathways, and suppress the replication of RSV in airway epithelial cells.	[171]
	Colchicine	Sprague–Dawley rats	Inhibit the phosphorylation of p38.	[172]
SARS-CoV-2	Silmitasertib	Vero E6 and A549-ACE2 cells	Inhibit the CK2 signaling pathway, affecting SARS-CoV-2 replication	[145]
	Gilteritinib		Inhibit AXL kinase (upstream of p38) and provide antiviral effects against SARS-CoV-2.	
	Ralimetinib		Inhibit the p38 MAPK pathway, reducing SARS-CoV-2 replication.	
	MAPK13-IN-1		Inhibit p38δ, preventing viral replication.	
	ARRY-797		Inhibit the p38β signaling pathway, reducing SARS-CoV-2 replication.	
	Apilimod		Inhibit PIKFYVE, disrupting phosphatidylinositol metabolism balance, blocking viral replication.	
	Dinaciclib		Inhibit CDK signaling pathways, preventing SARS-CoV-2 replication and regulating the cell cycle.	
Adenovirus	FIT-039	SCID mice	Inhibit CDK9 kinase and suppress viral replication.	[169]

molecule inhibitors and their mechanisms of action is provided in Table 2. FIT-039, a CDK9 kinase inhibitor, has been reported to inhibit adenovirus replication, but the results indicate that its intracellular EC50 and EC80 values are lower than the IC50 values observed in in vitro biochemical assays,[169] suggesting that its antiviral effects may involve mechanisms beyond CDK9 kinase inhibition.

Beyond strategies already applied in viral pneumonia, several phosphorylation-targeted therapies from oncology and immune-mediated disease settings have been shown in human studies to modulate key kinase pathways and thus hold potential for cross-disease translation.[173] In oncology, the CK2 inhibitor silmitasertib combined with gemcitabine and cisplatin as first-line therapy for cholangiocarcinoma has shown acceptable safety and signals of efficacy, suggesting that inhibiting CK2-mediated phosphorylation networks may dampen pathological signal amplification.[174] Regulation of the PIKfyve pathway, central to endosomal and lysosomal membrane trafficking, has been targeted by the clinical candidate apilimod, which selectively inhibits PIKfyve and has shown activity in hematologic malignancy studies, offering a rationale for interfering with pathogen entry processes that rely on endocytosis.[175] Inhibition of the stress-associated JNK pathway has also been explored in fibrosing lung disease; the selective JNK inhibitor CC-90001 showed good tolerability and encouraging signals in functional outcomes in a randomized controlled trial in idiopathic pulmonary fibrosis, providing a pharmacologic rationale for lung diseases in which inflammation and tissue remodeling coexist.[176] In addition, strategies that act directly on viral kinases merit attention; the pUL97 kinase inhibitor maribavir outperformed control therapy in a Phase 3 study of refractory cytomegalovirus infection in transplant recipients, demonstrating the feasibility of achieving antiviral efficacy by modulating virus-associated phosphorylation events.[177] Taken together, these phosphorylation-related interventions validated outside the context of viral pneumonia offer clear options for drug repurposing and combination regimen design in this field.[178]

Conclusion and Future Perspectives

Viral pneumonia remains a significant global public health concern, with common pathogens such as influenza virus, RSV, coronavirus, and adenovirus contributing to its burden. This review comprehensively discusses the mechanisms by which these viruses facilitate pneumonia development, emphasizing the pivotal role of phosphorylation in

viral replication, transcription, and host interactions. Phosphorylation of viral proteins can regulate their oligomerization, impacting viral nucleic acid replication, transcription, and translation. It also modulates their nuclear-cytoplasmic localization, thereby influencing viral assembly. Furthermore, viruses can activate host cell signaling pathways, such as the MAPK and PI3K/Akt pathways, to promote viral replication and elicit inflammatory responses. These findings suggest that targeting viral phosphorylation may be a promising therapeutic approach to inhibit pathogens and manage viral pneumonia. While TCM extracts have demonstrated efficacy in inhibiting phosphorylation, they currently lack specific phosphatase inhibitors. In addition to TCM-derived agents, hos directed small molecule kinase inhibitors that modulate phosphorylation, targeting CK2, p38 MAPK, PIKfyve, and CDKs, have reduced viral replication and inflammatory readouts in cellular and animal models, providing a translational rationale for clinical testing.

Future research should situate phosphorylation within specific disease contexts, paying attention to differences among viruses, host cell types, and stages of illness, with priority given to time-resolved and single-cell studies that progressively build decision-ready maps for clinical use. We recommend establishing a clear validation chain that links in vitro systems, animal models, and patient specimens, prioritizing a small set of kinases and modification sites that are reproducibly validated and pharmacologically feasible, rather than broad cataloging that lacks translational value. On the therapeutic front, host-targeted kinase inhibition should continue to advance, with greater emphasis on selectivity, dosing timing, and sequencing, and with stage-based combinations alongside direct antivirals or anti-inflammatory agents to balance viral replication control and mitigation of excessive inflammation. In parallel, phosphorylation biomarkers measurable in blood or respiratory samples are needed for patient stratification, pharmacodynamic monitoring, and dose optimization, thereby shortening the path from mechanism to clinic. For candidates derived from TCM, efforts should focus on standardizing composition, clarifying targets and pharmacokinetics, and delineating their true contribution to phosphorylation pathways before entering more rigorous, higher-quality randomized trials. Regarding clinical trial design, adaptive platform frameworks are recommended to compare multiple targets and combinations within a unified structure, with stringent safety surveillance and drug–drug interaction assessment in high-risk populations. Finally, open and reusable data and reporting standards, including harmonized site annotation and functional curation, will improve comparability and evidence synthesis across groups, enabling more precise, stage-specific, and personalized interventions for viral pneumonia.

Ethics Approval and Consent to Participate

Ethics approval does not apply to this article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing interests in this work.

References

1. Torres A, Cilloniz C, Niederman MS, et al. Pneumonia. *Nat Rev Dis Primers*. 2021;7(1):25. doi:10.1038/s41572-021-00259-0
2. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet*. 2020;396(10258):1204–1222. doi:10.1016/S0140-6736(20)30925-9
3. Troeger C, Blacker B, Khalil IA. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the global burden of disease study 2016. *Lancet Infect Dis*. 2018;18(11):1191–1210. doi:10.1016/S1473-3099(18)30310-4
4. Chen YH, Keller J, Wang IT, Lin CC, Lin HC. Pneumonia and pregnancy outcomes: a nationwide population-based study. *Am J Obstet Gynecol*. 2012;207(4):288.e281–287. doi:10.1016/j.ajog.2012.08.023
5. Hooven TA, Polin RA. Pneumonia. *Semin Fetal Neonatal Med*. 2017;22(4):206–213. doi:10.1016/j.siny.2017.03.002
6. Febbo J, Revels J, Ketai L. Viral Pneumonias. *Radiol Clin North Am*. 2022;60(3):383–397. doi:10.1016/j.rcl.2022.01.010

7. Chadha M, Hirve S, Bancej C, et al. Human respiratory syncytial virus and influenza seasonality patterns-Early findings from the WHO global respiratory syncytial virus surveillance. *Influenza Other Respir Viruses*. 2020;14(6):638–646. doi:10.1111/irv.12726
8. Chowdhury FR, Ibrahim QSU, Bari MS, et al. The association between temperature, rainfall and humidity with common climate-sensitive infectious diseases in Bangladesh. *PLoS One*. 2018;13(6):e0199579. doi:10.1371/journal.pone.0199579
9. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. *Lancet*. 2011;377(9773):1264–1275. doi:10.1016/S0140-6736(10)61459-6
10. Almeida A, Boattini M, Christaki E, et al. Comparative virulence of seasonal viruses responsible for lower respiratory tract infections: a Southern European multi-centre cohort study of hospital admissions. *Infection*. 2021;49(3):483–490. doi:10.1007/s15010-020-01569-3
11. Ausina V, Coll P, Sambeat M, et al. Prospective study on the etiology of community-acquired pneumonia in children and adults in Spain. *Eur J Clin Microbiol Infect Dis*. 1988;7(3):342–347. doi:10.1007/BF01962334
12. Cilla G, Oñate E, Perez-Yarza EG, Montes M, Vicente D, Perez-Trallero E. Viruses in community-acquired pneumonia in children aged less than 3 years old: high rate of viral coinfection. *J Med Virol*. 2008;80(10):1843–1849. doi:10.1002/jmv.21271
13. Angeles Marcos M, Camps M, Pumarola T, et al. The role of viruses in the aetiology of community-acquired pneumonia in adults. *Antivir Ther*. 2006;11(3):351–359. doi:10.1177/135965350601100306
14. Moscona A. Entry of parainfluenza virus into cells as a target for interrupting childhood respiratory disease. *J Clin Invest*. 2005;115(7):1688–1698. doi:10.1172/JCI25669
15. Do Carmo Debur M, Raboni SM, Flizikowski FB, et al. Immunohistochemical assessment of respiratory viruses in necropsy samples from lethal non-pandemic seasonal respiratory infections. *J Clin Pathol*. 2010;63(10):930–934. doi:10.1136/jcp.2010.077867
16. Howard LM, Edwards KM, Zhu Y, et al. Clinical features of human metapneumovirus-associated community-acquired pneumonia hospitalizations. *Clin Infect Dis*. 2021;72(1):108–117. doi:10.1093/cid/ciaa088
17. Imamura T, Fuji N, Suzuki A, et al. Enterovirus 68 among children with severe acute respiratory infection, the Philippines. *Emerg Infect Dis*. 2011;17(8):1430–1435. doi:10.3201/eid1708.101328
18. Fu B, Wang L, Ding H, Schwamborn JC, Li S, Dorf ME. trim32 senses and restricts influenza a virus by ubiquitination of pb1 polymerase. *plos pathog*. 2015;11(6):e1004960. doi:10.1371/journal.ppat.1004960
19. Xia C, Wang T, Hahm B. Triggering degradation of host cellular proteins for robust propagation of influenza viruses. *Int J Mol Sci*. 2024;25(9):4677. doi:10.3390/ijms25094677
20. Husain M. Influenza A virus and acetylation: the picture is becoming clearer. *Viruses*. 2024;16(1):131. doi:10.3390/v16010131
21. Meineke R, Rimmelzwaan GF, Elbahesh H. Influenza virus infections and cellular kinases. *Viruses*. 2019;11(2):171. doi:10.3390/v11020171
22. Hu J, Zhang L, Liu X. Role of post-translational modifications in influenza a virus life cycle and host innate immune response. *Front Microbiol*. 2020;11:517461. doi:10.3389/fmicb.2020.517461
23. Wu C-H, Yeh S-H, Tsay Y-G, et al. Glycogen synthase kinase-3 regulates the phosphorylation of severe acute respiratory syndrome coronavirus nucleocapsid protein and viral replication *. *J Biol Chem*. 2009;284(8):5229–5239. doi:10.1074/jbc.M805747200
24. Zheng W, Li J, Wang S, et al. Phosphorylation controls the nuclear-cytoplasmic shuttling of influenza a virus nucleoprotein. *J Virol*. 2015;89(11):5822–5834. doi:10.1128/JVI.00015-15
25. Chatterjee B, Thakur SS. SARS-CoV-2 infection triggers phosphorylation: potential target for anti-covid-19 therapeutics. *Front Immunol*. 2022;13:829474. doi:10.3389/fimmu.2022.829474
26. Jimenez-Guardeño JM, Nieto-Torres JL, DeDiego ML, et al. The PDZ-binding motif of severe acute respiratory syndrome coronavirus envelope protein is a determinant of viral pathogenesis. *PLoS Pathog*. 2014;10(8):e1004320. doi:10.1371/journal.ppat.1004320
27. Daniloski Z, Jordan TX, Wessels HH, et al. Identification of required host factors for SARS-CoV-2 infection in human cells. *Cell*. 2021;184(1):92–105.e116. doi:10.1016/j.cell.2020.10.030
28. Mahmoudian S, Auerochs S, Gröne M, Marschall M. Influenza A virus proteins PB1 and NS1 are subject to functionally important phosphorylation by protein kinase C. *J Gen Virol*. 2009;90(Pt 6):1392–1397. doi:10.1099/vir.0.009050-0
29. Cavallazzi R, Ramirez JA. Influenza and Viral Pneumonia. *Clin Chest Med*. 2018;39(4):703–721. doi:10.1016/j.ccm.2018.07.005
30. Casalino E, Antoniol S, Fidouh N, et al. Influenza virus infections among patients attending emergency department according to main reason to presenting to ED: a 3-year prospective observational study during seasonal epidemic periods. *PLoS One*. 2017;12(8):e0182191. doi:10.1371/journal.pone.0182191
31. Pagliano P, Sellitto C, Conti V, Ascione T, Esposito S. Characteristics of viral pneumonia in the COVID-19 era: an update. *Infection*. 2021;49(4):607–616. doi:10.1007/s15010-021-01603-y
32. Garg S, Jain S, Dawood FS, et al. Pneumonia among adults hospitalized with laboratory-confirmed seasonal influenza virus infection—United States, 2005–2008. *BMC Infect Dis*. 2015;15(1):369. doi:10.1186/s12879-015-1004-y
33. Fullana Barceló MI, Artigues Serra F, Millan Pons AR, et al. Analysis of viral pneumonia and risk factors associated with severity of influenza virus infection in hospitalized patients from 2012 to 2016. *BMC Infect Dis*. 2024;24(1):302. doi:10.1186/s12879-024-09173-8
34. Uyeki TM, Hui DS, Zambon M, Wentworth DE, Monto AS. Influenza. *Lancet*. 2022;400(10353):693–706. doi:10.1016/S0140-6736(22)00982-5
35. Liang Y. Pathogenicity and virulence of influenza. *Virulence*. 2023;14(1):2223057. doi:10.1080/21505594.2023.2223057
36. Liu R, Sheng Z, Huang C, Wang D, Li F. Influenza D virus. *Curr Opin Virol*. 2020;44:154–161. doi:10.1016/j.coviro.2020.08.004
37. Tenforde MW, Kondor RJG, Chung JR, et al. Effect of antigenic drift on influenza vaccine effectiveness in the United States—2019–2020. *Clinl Infect Dis*. 2020;73(11):e4244–e4250. doi:10.1093/cid/ciaa1884
38. Koel BF, Burke DF, Bestebroer TM, et al. Substitutions near the receptor binding site determine major antigenic change during influenza virus evolution. *Science*. 2013;342(6161):976–979. doi:10.1126/science.1244730
39. Sederdahl BK, Williams JV. Epidemiology and clinical characteristics of influenza c virus. *Viruses*. 2020;12(1):89. doi:10.3390/v12010089
40. Maruyama T, Fujisawa T, Suga S, et al. Outcomes and prognostic features of patients with influenza requiring hospitalization and receiving early antiviral therapy: a prospective multicenter cohort study. *Chest*. 2016;149(2):526–534. doi:10.1378/chest.14-2768
41. Minney-Smith CA, Selvey LA, Levy A, Smith DW. Post-pandemic influenza A/H1N1pdm09 is associated with more severe outcomes than A/H3N2 and other respiratory viruses in adult hospitalisations. *Epidemiol Infect*. 2019;147:e310. doi:10.1017/S095026881900195X
42. Sharma Y, Horwood C, Hakendorf P, Thompson C. Clinical characteristics and outcomes of influenza A and B virus infection in adult Australian hospitalised patients. *BMC Infect Dis*. 2020;20(1):913. doi:10.1186/s12879-020-05670-8

43. Matsuzaki Y, Katsushima N, Nagai Y, et al. Clinical features of influenza C virus infection in children. *J Infect Dis*. 2006;193(9):1229–1235. doi:10.1086/502973
44. Calvo C, García-García ML, Centeno M, Pérez-Breña P, Casas I. Influenza C virus infection in children, Spain. *Emerg Infect Dis*. 2006;12 (10):1621–1622. doi:10.3201/eid1210.051170
45. Principi N, Scala A, Daleno C, Esposito S. Influenza C virus–associated community-acquired pneumonia in children. *Influenza Other Respir Viruses*. 2013;7(6):999–1003. doi:10.1111/irv.12062
46. Mejías A, Chávez-Bueno S, Ramilo O. Respiratory syncytial virus pneumonia: mechanisms of inflammation and prolonged airway hyperresponsiveness. *Curr Opin Infect Dis*. 2005;18(3):199–204. doi:10.1097/01.qco.0000168378.07110.72
47. Johnson TR, Varga SM, Braciale TJ, Graham BS. Vbeta14(+) T cells mediate the vaccine-enhanced disease induced by immunization with respiratory syncytial virus (RSV) G glycoprotein but not with formalin-inactivated RSV. *J Virol*. 2004;78(16):8753–8760. doi:10.1128/JVI.78.16.8753-8760.2004
48. Don M, Fasoli L, Paldanius M, et al. Aetiology of community-acquired pneumonia: serological results of a paediatric survey. *Scand J Infect Dis*. 2005;37(11–12):806–812. doi:10.1080/00365540500262435
49. Soni A, Kabra SK, Lodha R. Respiratory syncytial virus infection: an update. *Indian J Pediatr*. 2023;90(12):1245–1253. doi:10.1007/s12098-023-04613-w
50. Berkley JA, Munywoki P, Ngama M, et al. Viral etiology of severe pneumonia among Kenyan infants and children. *JAMA*. 2010;303 (20):2051–2057. doi:10.1001/jama.2010.675
51. Walsh EE, Peterson DR, Falsey AR. Is clinical recognition of respiratory syncytial virus infection in hospitalized elderly and high-risk adults possible? *J Infect Dis*. 2007;195(7):1046–1051. doi:10.1086/511986
52. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med*. 2005;352(17):1749–1759. doi:10.1056/NEJMoa043951
53. Templeton KE, Scheltinga SA, van den Eeden WC, et al. Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. *Clin Infect Dis*. 2005;41(3):345–351. doi:10.1086/431588
54. Saito A, Kohno S, Matsushima T, et al. Prospective multicenter study of the causative organisms of community-acquired pneumonia in adults in Japan. *J Infect Chemother*. 2006;12(2):63–69. doi:10.1007/s10156-005-0425-8
55. Han LL, Alexander JP, Anderson LJ. Respiratory syncytial virus pneumonia among the elderly: an assessment of disease burden. *J Infect Dis*. 1999;179(1):25–30. doi:10.1086/314567
56. Godefroy R, Giraud-Gatineau A, Jimeno MT, et al. Respiratory syncytial virus infection: its propensity for bacterial coinfection and related mortality in elderly adults. *Open Forum Infect Dis*. 2020;7(12):ofaa546. doi:10.1093/ofid/ofaa546
57. Mihaescu G, Chifiriuc MC, Iliescu C, et al. SARS-CoV-2: from structure to pathology, host immune response and therapeutic management. *Microorganisms*. 2020;8(10):1468. doi:10.3390/microorganisms8101468
58. Li Y, Luo C, Li W, et al. Structure-Based Preliminary Analysis of Immunity and Virulence of SARS Coronavirus. *Viral Immunology*. 2004;17 (4):528–534. doi:10.1089/vim.2004.17.528
59. Zawilska JB, Lagodzinski A, Berezinska M. COVID-19: from the structure and replication cycle of SARS-CoV-2 to its disease symptoms and treatment. *J Physiol Pharmacol*. 2021;72(4). doi:10.26402/jpp.2021.4.01
60. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. 2020;367 (6483):1260–1263. doi:10.1126/science.abb2507
61. Xie Y, Du D, Karki CB, et al. Revealing the Mechanism of SARS-CoV-2 spike protein binding with ACE2. *Comput. Sci. Eng*. 2020;22 (6):21–29. doi:10.1109/MCSE.2020.3015511
62. Xie Y, Karki CB, Du D, et al. Spike Proteins of SARS-CoV and SARS-CoV-2 utilize different mechanisms to bind with human ACE2. *Front Mol Biosci*. 2020;7:591873. doi:10.3389/fmolb.2020.591873
63. Raghuvamsi PV, Tulsian NK, Samsudin F, et al. SARS-CoV-2 S protein:ACE2 interaction reveals novel allosteric targets. *eLife*. 2021;10: e63646. doi:10.7554/eLife.63646
64. Meirson T, Bomze D, Markel G. Structural basis of SARS-CoV-2 spike protein induced by ACE2. *Bioinformatics*. 2020;37(7):929–936. doi:10.1093/bioinformatics/btaa744
65. Dare RK, Fry AM, Chittaganpitch M, Sawanpanyalert P, Olsen SJ, Erdman DD. Human coronavirus infections in rural Thailand: a comprehensive study using real-time reverse-transcription polymerase chain reaction assays. *J Infect Dis*. 2007;196(9):1321–1328. doi:10.1086/521308
66. Heugel J, Martin ET, Kuypers J, Englund JA. Coronavirus-associated pneumonia in previously healthy children. *Pediatr Infect Dis J*. 2007;26 (8):753–755. doi:10.1097/INF.0b013e318054e31b
67. Lau SK, Woo PC, Yip CC, et al. Coronavirus HKU1 and other coronavirus infections in Hong Kong. *J Clin Microbiol*. 2006;44(6):2063–2071. doi:10.1128/JCM.02614-05
68. Lu X, Xiang Y, Du H, Wing-Kin Wong G. SARS-CoV-2 infection in children – understanding the immune responses and controlling the pandemic. *Pediatric Allergy Immunol*. 2020;31(5):449–453. doi:10.1111/pai.13267
69. Viner RM, Mytton OT, Bonell C, et al. Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults: a systematic review and meta-analysis. *JAMA Pediatrics*. 2021;175(2):143–156. doi:10.1001/jamapediatrics.2020.4573
70. Maltezou HC, Magaziotou I, Dedoukou X, et al. Children and Adolescents With SARS-CoV-2 infection: epidemiology, clinical course and viral loads. *Pediatr Infect Dis J*. 2020;39(12):e388–e392. doi:10.1097/INF.0000000000002899
71. Gallardo J, Pérez-Illana M, Martín-González N, San Martín C. Adenovirus structure: what is new? *Int J Mol Sci*. 2021;22(10):5240. doi:10.3390/ijms22105240
72. Matthews DA, Russell WC. Adenovirus core protein V is delivered by the invading virus to the nucleus of the infected cell and later in infection is associated with nucleoli. *J Gen Virol*. 1998;79(7):1671–1675. doi:10.1099/0022-1317-79-7-1671
73. Medina-Kauwe LK. Endocytosis of adenovirus and adenovirus capsid proteins. *Adv Drug Deliv Rev*. 2003;55(11):1485–1496. doi:10.1016/j.addr.2003.07.010
74. Medina-Kauwe LK. Development of adenovirus capsid proteins for targeted therapeutic delivery. *Ther Deliv*. 2013;4(2):267–277. doi:10.4155/tde.12.155

75. Ison MG, Hayden RT. Adenovirus. *Microbiol Spectr*. 2016;4(4). doi:10.1128/microbiolspec.DMIH2-0020-2015
76. Febbo J, Revels J, Ketai L. Viral Pneumonias. *Infect Dis Clin North Am*. 2024;38(1):163–182. doi:10.1016/j.idc.2023.12.009
77. Zhang J, Zhu Y, Zhou Y, et al. Pediatric adenovirus pneumonia: clinical practice and current treatment. *Front Med*. 2023;10:1207568. doi:10.3389/fmed.2023.1207568
78. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med*. 2015;372 (9):835–845. doi:10.1056/NEJMoa1405870
79. Liu C, Xiao Y, Zhang J, et al. Adenovirus infection in children with acute lower respiratory tract infections in Beijing, China, 2007 to 2012. *BMC Infect Dis*. 2015;15:408. doi:10.1186/s12879-015-1126-2
80. Mao NY, Zhu Z, Zhang Y, Xu WB. Current status of human adenovirus infection in China. *World J Pediatr*. 2022;18(8):533–537. doi:10.1007/s12519-022-00568-8
81. Sun B, He H, Wang Z, et al. Emergent severe acute respiratory distress syndrome caused by adenovirus type 55 in immunocompetent adults in 2013: a prospective observational study. *Crit Care*. 2014;18(4):456. doi:10.1186/s13054-014-0456-6
82. Zhang D, Chen Y, Shi T, et al. Severe pneumonia caused by human adenovirus type 55 in children. *Front Pediatr*. 2022;10:1002052. doi:10.3389/fped.2022.1002052
83. Cao B, Huang GH, Pu ZH, et al. Emergence of community-acquired adenovirus type 55 as a cause of community-onset pneumonia. *Chest*. 2014;145(1):79–86. doi:10.1378/chest.13-1186
84. Binder AM, Biggs HM, Haynes AK, et al. Human adenovirus surveillance - United States, 2003-2016. *MMWR Morb Mortal Wkly Rep*. 2017;66 (39):1039–1042. doi:10.15585/mmwr.mm6639a2
85. Castleman WL, Brundage-Anguish LJ, Kreitzer L, Neuenschwander SB. Pathogenesis of bronchiolitis and pneumonia induced in neonatal and weanling rats by parainfluenza (Sendai) virus. *Am J Pathol*. 1987;129(2):277–286.
86. Branche AR, Falsey AR. Parainfluenza Virus Infection. *Semin Respir Crit Care Med*. 2016;37(4):538–554. doi:10.1055/s-0036-1584798
87. Marx A, Török TJ, Holman RC, Clarke MJ, Anderson LJ. Pediatric hospitalizations for croup (laryngotracheobronchitis): biennial increases associated with human parainfluenza virus 1 epidemics. *J Infect Dis*. 1997;176(6):1423–1427. doi:10.1086/514137
88. Liu WK, Liu Q, Chen DH, et al. Epidemiology and clinical presentation of the four human parainfluenza virus types. *BMC Infect Dis*. 2013;13:28. doi:10.1186/1471-2334-13-28
89. Knott AM, Long CE, Hall CB. Parainfluenza viral infections in pediatric outpatients: seasonal patterns and clinical characteristics. *Pediatr Infect Dis J*. 1994;13(4):269–273. doi:10.1097/00006454-199404000-00005
90. Don M, Korppi M, Valent F, Vainionpaa R, Canciani M. Human metapneumovirus pneumonia in children: results of an Italian study and mini-review. *Scand J Infect Dis*. 2008;40(10):821–826. doi:10.1080/00365540802227110
91. Bosis S, Esposito S. Enterovirus D68-associated community-acquired pneumonia in the pediatric age group. *Curr Infect Dis Rep*. 2017;19 (3):12. doi:10.1007/s11908-017-0567-8
92. Khan F. Enterovirus D68: acute respiratory illness and the 2014 outbreak. *Emerg Med Clin North Am*. 2015;33(2):e19–32. doi:10.1016/j.emc.2014.12.011
93. Peci A, Winter AL, Warshawsky B, et al. Epidemiology of Enterovirus D68 in Ontario. *PLoS One*. 2015;10(11):e0142841. doi:10.1371/journal.pone.0142841
94. Midgley SE, Christiansen CB, Poulsen MW, Hansen CH, Fischer TK. Emergence of enterovirus D68 in Denmark, June 2014 to February 2015. *Euro Surveill*. 2015;20(17). doi:10.2807/1560-7917.ES2015.20.17.21105
95. Perales B, Sanz-Ezquerro JJ, Gastaminza P, et al. The replication activity of influenza virus polymerase is linked to the capacity of the PA subunit to induce proteolysis. *J Virol*. 2000;74(3):1307–1312. doi:10.1128/JVI.74.3.1307-1312.2000
96. Hale BG, Knebel A, Botting CH, et al. CDK/ERK-mediated phosphorylation of the human influenza A virus NS1 protein at threonine-215. *Virology*. 2009;383(1):6–11. doi:10.1016/j.virol.2008.10.002
97. Ren C, Chen T, Zhang S, et al. PLK3 facilitates replication of swine influenza virus by phosphorylating viral NP protein. *Emerging Microbes Infect*. 2023;12(2):2275606. doi:10.1080/22221751.2023.2275606
98. Turrell L, Hutchinson EC, Vreede FT, Fodor E. Regulation of influenza A virus nucleoprotein oligomerization by phosphorylation. *J Virol*. 2015;89(2):1452–1455. doi:10.1128/JVI.02332-14
99. Mondal A, Potts GK, Dawson AR, Coon JJ, Mehle A. Phosphorylation at the homotypic interface regulates nucleoprotein oligomerization and assembly of the influenza virus replication machinery. *PLoS Pathog*. 2015;11(4):e1004826. doi:10.1371/journal.ppat.1004826
100. Li Y, Sun L, Zheng W, et al. Phosphorylation and dephosphorylation of threonine 188 in nucleoprotein is crucial for the replication of influenza A virus. *Virology*. 2018;520:30–38. doi:10.1016/j.virol.2018.05.002
101. Lu B, Ma CH, Brazas R, Jin H. The major phosphorylation sites of the respiratory syncytial virus phosphoprotein are dispensable for virus replication in vitro. *J Virol*. 2002;76(21):10776–10784. doi:10.1128/JVI.76.21.10776-10784.2002
102. Barik S, McLean T, Dupuy LC. Phosphorylation of Ser232 directly regulates the transcriptional activity of the P protein of human respiratory syncytial virus: phosphorylation of Ser237 may play an accessory role. *Virology*. 1995;213(2):405–412. doi:10.1006/viro.1995.0013
103. Bajorek M, Caly L, Tran KC, et al. The Thr205 phosphorylation site within respiratory syncytial virus matrix (M) protein modulates M oligomerization and virus production. *J Virol*. 2014;88(11):6380–6393. doi:10.1128/JVI.03856-13
104. Ghildyal R, Teng MN, Tran KC, et al. Nuclear transport of respiratory syncytial virus matrix protein is regulated by dual phosphorylation sites. *Int J Mol Sci*. 2022;23(14):7976. doi:10.3390/ijms23147976
105. Surjit M, Kumar R, Mishra RN, Reddy MK, Chow VT, Lal SK. The severe acute respiratory syndrome coronavirus nucleocapsid protein is phosphorylated and localizes in the cytoplasm by 14-3-3-mediated translocation. *J Virol*. 2005;79(17):11476–11486. doi:10.1128/JVI.79.17.11476-11486.2005
106. Peng TY, Lee KR, Tarn WY. Phosphorylation of the arginine/serine dipeptide-rich motif of the severe acute respiratory syndrome coronavirus nucleocapsid protein modulates its multimerization, translation inhibitory activity and cellular localization. *Febs J*. 2008;275(16):4152–4163. doi:10.1111/j.1742-4658.2008.06564.x
107. Alomair L, Mustafa S, Jafri MS, et al. Molecular dynamics simulations to decipher the role of phosphorylation of SARS-CoV-2 nonstructural proteins (nsps) in viral replication. *Viruses*. 2022;14(11):2436. doi:10.3390/v14112436

108. Mal A, Piotrkowski A, Harter ML. Cyclin-dependent kinases phosphorylate the adenovirus E1A protein, enhancing its ability to bind pRb and disrupt pRb-E2F complexes. *J Virol*. 1996;70(5):2911–2921. doi:10.1128/jvi.70.5.2911-2921.1996
109. Teodoro JG, Halliday T, Whalen SG, Takayesu D, Graham FL, Branton PE. Phosphorylation at the carboxy terminus of the 55-kilodalton adenovirus type 5 E1B protein regulates transforming activity. *J Virol*. 1994;68(2):776–786. doi:10.1128/jvi.68.2.776-786.1994
110. Harfst E, Leppard KN. A comparative analysis of the phosphorylation and biochemical properties of wild type and host range variant DNA binding proteins of human adenovirus 5. *Virus Genes*. 1999;18(2):97–106. doi:10.1023/A:1008009630695
111. Plotch SJ, Bouloy M, Ulmanen I, Krug RM. A unique cap(m7GpppXm)-dependent influenza virion endonuclease cleaves capped RNAs to generate the primers that initiate viral RNA transcription. *Cell*. 1981;23(3):847–858. doi:10.1016/0092-8674(81)90449-9
112. Carter T, Iqbal M. The influenza a virus replication cycle: a comprehensive review. *Viruses*. 2024;16(2). doi:10.3390/v16020316
113. Palancade B, Bensaude O. Investigating RNA polymerase II carboxyl-terminal domain (CTD) phosphorylation. *Eur J Biochem*. 2003;270 (19):3859–3870. doi:10.1046/j.1432-1033.2003.03794.x
114. Engelhardt OG, Smith M, Fodor E. Association of the influenza A virus RNA-dependent RNA polymerase with cellular RNA polymerase II. *J Virol*. 2005;79(9):5812–5818. doi:10.1128/JVI.79.9.5812-5818.2005
115. Miyake Y, Ishii K, Honda A. Influenza virus infection induces host pyruvate kinase m which interacts with viral RNA-Dependent RNA Polymerase. *Front Microbiol*. 2017;8:162. doi:10.3389/fmicb.2017.00162
116. Noton SL, Simpson-Holley M, Medcalf E, et al. Studies of an influenza a virus temperature-sensitive mutant identify a late role for np in the formation of infectious virions. *J Virol*. 2009;83(2):562–571. doi:10.1128/JVI.01424-08
117. Kamata T, Watanabe Y. Role for nucleocapsid protein phosphorylation in the transcription of influenza virus genome. *Nature*. 1977;267 (5610):460–462. doi:10.1038/267460a0
118. Ludwig S, Planz O, Pleschka S, Wolff T. Influenza-virus-induced signaling cascades: targets for antiviral therapy? *Trends Mol Med*. 2003;9 (2):46–52. doi:10.1016/S1471-4914(02)00010-2
119. Arora DJ, Gasse N. Influenza virus hemagglutinin stimulates the protein kinase C activity of human polymorphonuclear leucocytes. *Arch Virol*. 1998;143(10):2029–2037. doi:10.1007/s007050050439
120. Sieczkarski SB, Brown HA, Whittaker GR. Role of protein kinase C betaII in influenza virus entry via late endosomes. *J Virol*. 2003;77 (1):460–469. doi:10.1128/JVI.77.1.460-469.2003
121. Kujime K, Hashimoto S, Gon Y, Shimizu K, Horie T. p38 mitogen-activated protein kinase and c-jun-NH2-terminal kinase regulate RANTES production by influenza virus-infected human bronchial epithelial cells. *J Immunol*. 2000;164(6):3222–3228. doi:10.4049/jimmunol.164.6.3222
122. Ludwig S, Ehrhardt C, Neumeier ER, Kracht M, Rapp UR, Pleschka S. Influenza virus-induced AP-1-dependent gene expression requires activation of the JNK signaling pathway. *J Biol Chem*. 2001;276(24):10990–10998. doi:10.1074/jbc.M009902200
123. Pleschka S, Wolff T, Ehrhardt C, et al. Influenza virus propagation is impaired by inhibition of the Raf/MEK/ERK signalling cascade. *Nat Cell Biol*. 2001;3(3):301–305. doi:10.1038/35060098
124. Shin Y-K, Liu Q, Tikoo SK, Babiuk LA, Zhou Y. Effect of the phosphatidylinositol 3-kinase/Akt pathway on influenza A virus propagation. *J Gen Virol*. 2007;88(3):942–950. doi:10.1099/vir.0.82483-0
125. Cao D, Gao Y, Liang B. Structural insights into the respiratory syncytial virus rna synthesis complexes. *Viruses*. 2021;13(5):834. doi:10.3390/v13050834
126. Dupuy LC, Dobson S, Bitko V, Barik S. Casein kinase 2-mediated phosphorylation of respiratory syncytial virus phosphoprotein P is essential for the transcription elongation activity of the viral polymerase; phosphorylation by casein kinase 1 occurs mainly at Ser(215) and is without effect. *J Virol*. 1999;73(10):8384–8392. doi:10.1128/JVI.73.10.8384-8392.1999
127. Asenjo A, Villanueva N. Regulated but not constitutive human respiratory syncytial virus (HRSV) P protein phosphorylation is essential for oligomerization. *FEBS Lett*. 2000;467(2–3):279–284. doi:10.1016/S0014-5793(00)01171-6
128. Richard CA, Rincheval V, Lassoued S, et al. RSV hijacks cellular protein phosphatase 1 to regulate M2-1 phosphorylation and viral transcription. *PLoS Pathog*. 2018;14(3):e1006920. doi:10.1371/journal.ppat.1006920
129. Swain J, Bierre M, Veyrié L, et al. Selective targeting and clustering of phosphatidylserine lipids by RSV M protein is critical for virus particle production. *J Biol Chem*. 2023;299(11):105323. doi:10.1016/j.jbc.2023.105323
130. Money VA, McPhee HK, Mosely JA, Sanderson JM, Yeo RP. Surface features of a Mononegavirales matrix protein indicate sites of membrane interaction. *Proc Natl Acad Sci U S A*. 2009;106(11):4441–4446. doi:10.1073/pnas.0805740106
131. Van Royen T, Rossey I, Sedeyn K, Schepens B, Saelens X. How RSV proteins join forces to overcome the host innate immune response. *Viruses*. 2022;14(2):419. doi:10.3390/v14020419
132. Ghildyal R, Ho A, Dias M, et al. The respiratory syncytial virus matrix protein possesses a Crm1-mediated nuclear export mechanism. *J Virol*. 2009;83(11):5353–5362. doi:10.1128/JVI.02374-08
133. Proud CG. eIF2 and the control of cell physiology. *Semin Cell Dev Biol*. 2005;16(1):3–12. doi:10.1016/j.semcdb.2004.11.004
134. Dever TE. Gene-specific regulation by general translation factors. *Cell*. 2002;108(4):545–556. doi:10.1016/S0092-8674(02)00642-6
135. Groskreutz DJ, Monick MM, Powers LS, Yarovinsky TO, Look DC, Hunninghake GW. Respiratory syncytial virus induces TLR3 protein and protein kinase R, leading to increased double-stranded RNA responsiveness in airway epithelial cells. *J Immunol*. 2006;176(3):1733–1740. doi:10.4049/jimmunol.176.3.1733
136. Zhang P, Samuel CE. Protein kinase PKR plays a stimulus- and virus-dependent role in apoptotic death and virus multiplication in human cells. *J Virol*. 2007;81(15):8192–8200. doi:10.1128/JVI.00426-07
137. Groskreutz DJ, Babor EC, Monick MM, Varga SM, Hunninghake GW. Respiratory syncytial virus limits alpha subunit of eukaryotic translation initiation factor 2 (eIF2alpha) phosphorylation to maintain translation and viral replication. *J Biol Chem*. 2010;285(31):24023–24031. doi:10.1074/jbc.M109.077321
138. Huang Q, Yu L, Petros AM, et al. Structure of the N-terminal RNA-binding domain of the SARS CoV nucleocapsid protein. *Biochemistry*. 2004;43(20):6059–6063. doi:10.1021/bi036155b
139. Stohlman SA, Fleming JO, Patton CD, Lai MM. Synthesis and subcellular localization of the murine coronavirus nucleocapsid protein. *Virology*. 1983;130(2):527–532. doi:10.1016/0042-6822(83)90106-X
140. Lin L, Shao J, Sun M, et al. Identification of phosphorylation sites in the nucleocapsid protein (N protein) of SARS-coronavirus. *Int J Mass Spectrom*. 2007;268(2):296–303. doi:10.1016/j.ijms.2007.05.009

141. Denison MR, Spaan WJ, van der Meer Y, et al. The putative helicase of the coronavirus mouse hepatitis virus is processed from the replicase gene polyprotein and localizes in complexes that are active in viral RNA synthesis. *J Virol*. 1999;73(8):6862–6871. doi:10.1128/JVI.73.8.6862-6871.1999
142. van der Meer Y, Snijder EJ, Dobbe JC, et al. Localization of mouse hepatitis virus nonstructural proteins and RNA synthesis indicates a role for late endosomes in viral replication. *J Virol*. 1999;73(9):7641–7657. doi:10.1128/JVI.73.9.7641-7657.1999
143. Raaben M, Groot Koerkamp MJ, Rottier PJ, de Haan CA. Mouse hepatitis coronavirus replication induces host translational shutoff and mRNA decay, with concomitant formation of stress granules and processing bodies. *Cell Microbiol*. 2007;9(9):2218–2229. doi:10.1111/j.1462-5822.2007.00951.x
144. Chen H, Gill A, Dove BK, et al. Mass spectroscopic characterization of the coronavirus infectious bronchitis virus nucleoprotein and elucidation of the role of phosphorylation in RNA binding by using surface plasmon resonance. *J Virol*. 2005;79(2):1164–1179. doi:10.1128/JVI.79.2.1164-1179.2005
145. Bouhaddou M, Memon D, Meyer B, et al. The global phosphorylation landscape of SARS-CoV-2 Infection. *Cell*. 2020;182(3):685–712.e619. doi:10.1016/j.cell.2020.06.034
146. Chaurushiya MS, Weitzman MD. Viral manipulation of DNA repair and cell cycle checkpoints. *DNA Repair*. 2009;8(9):1166–1176. doi:10.1016/j.dnarep.2009.04.016
147. Fernández-Golbano IM, Idrissi FZ, Giblin JP, et al. Crosstalk between PI(4,5)$P_2$and CK2 modulates actin polymerization during endocytic uptake. *Dev Cell*. 2014;30(6):746–758. doi:10.1016/j.devcel.2014.07.020
148. Alvarez DE, Agaisse H. Casein kinase 2 regulates vaccinia virus actin tail formation. *Virology*. 2012;423(2):143–151. doi:10.1016/j.virol.2011.12.003
149. Schubert K, Karousis ED, Jomaa A, et al. SARS-CoV-2 Nsp1 binds the ribosomal mRNA channel to inhibit translation. *Nat Struct Mol Biol*. 2020;27(10):959–966. doi:10.1038/s41594-020-0511-8
150. Zheng YX, Wang L, Kong WS, et al. Nsp2 has the potential to be a drug target revealed by global identification of SARS-CoV-2 Nsp2-interacting proteins. *Acta Biochim Biophys Sin*. 2021;53(9):1134–1141. doi:10.1093/abbs/gmab088
151. Sakai Y, Kawachi K, Terada Y, Omori H, Matsuura Y, Kamitani W. Two-amino acids change in the nsp4 of SARS coronavirus abolishes viral replication. *Virology*. 2017;510:165–174. doi:10.1016/j.virol.2017.07.019
152. Ip WH, Dobner T. Cell transformation by the adenovirus oncogenes E1 and E4. *FEBS Lett*. 2020;594(12):1848–1860. doi:10.1002/1873-3468.13717
153. King CR, Zhang A, Tessier TM, Gameiro SF, Mymryk JS. Hacking the cell: network intrusion and exploitation by adenovirus E1A. *mBio*. 2018;9(3). doi:10.1128/mBio.00390-18
154. Whalen SG, Marcellus RC, Barbeau D, Branton PE. Importance of the Ser-132 phosphorylation site in cell transformation and apoptosis induced by the adenovirus type 5 E1A protein. *J Virol*. 1996;70(8):5373–5383. doi:10.1128/jvi.70.8.5373-5383.1996
155. Blackford AN, Grand RJ. Adenovirus E1B 55-kilodalton protein: multiple roles in viral infection and cell transformation. *J Virol*. 2009;83(9):4000–4012. doi:10.1128/JVI.02417-08
156. Russell WC, Webster A, Leith IR, Kemp GD. Phosphorylation of adenovirus DNA-binding protein. *J Gen Virol*. 1989;70:3249–3259. doi:10.1099/0022-1317-70-12-3249
157. Bertzbach LD, Seddar L, von Stromberg K, Ip WH, Dobner T, Hidalgo P. The adenovirus DNA-binding protein DBP. *J Virol*. 2024;98(2):e0188523. doi:10.1128/jvi.01885-23
158. Linné T, Jörnvall H, Philipson L. Purification and characterization of the phosphorylated DNA-binding protein from adenovirus-type-2-infected cells. *Eur J Biochem*. 1977;76(2):481–490. doi:10.1111/j.1432-1033.1977.tb11618.x
159. Spurgeon ME, Ornelles DA. The adenovirus E1B 55-kilodalton and E4 open reading frame 6 proteins limit phosphorylation of eIF2alpha during the late phase of infection. *J Virol*. 2009;83(19):9970–9982. doi:10.1128/JVI.01113-09
160. Zhang Y, Feigenblum D, Schneider RJ. A late adenovirus factor induces eIF-4E dephosphorylation and inhibition of cell protein synthesis. *J Virol*. 1994;68(11):7040–7050. doi:10.1128/jvi.68.11.7040-7050.1994
161. Schümann M, Dobbelstein M. Adenovirus-induced extracellular signal-regulated kinase phosphorylation during the late phase of infection enhances viral protein levels and virus progeny. *Cancer Res*. 2006;66(3):1282–1288. doi:10.1158/0008-5472.CAN-05-1484
162. Valdés A, Zhao H, Pettersson U, Lind SB. Phosphorylation time-course study of the response during adenovirus type 2 infection. *Proteomics*. 2020;20(7):e1900327. doi:10.1002/pmic.201900327
163. Somerville VS, Braakhuis AJ, Hopkins WG. Effect of flavonoids on upper respiratory tract infections and immune function: a systematic review and meta-analysis. *Adv Nutr*. 2016;7(3):488–497. doi:10.3945/an.115.010538
164. Yaron TM, Heaton BE, Levy TM, et al. Host protein kinases required for SARS-CoV-2 nucleocapsid phosphorylation and viral replication. *Sci Signal*. 2022;15(757):eabm0808. doi:10.1126/scisignal.abm0808
165. Zhong M, Wang HQ, Yan HY, Wu S, Gu ZY, Li YH. Santin inhibits influenza A virus replication through regulating MAPKs and NF-κB pathways. *J Asian Nat Prod Res*. 2019;21(12):1205–1214. doi:10.1080/10286020.2018.1520221
166. Wang QW, Su Y, Sheng JT, et al. Anti-influenza A virus activity of rhein through regulating oxidative stress, TLR4, Akt, MAPK, and NF-κB signal pathways. *PLoS One*. 2018;13(1):e0191793. doi:10.1371/journal.pone.0191793
167. Dai JP, Wang QW, Su Y, et al. Emodin Inhibition of Influenza A Virus Replication and Influenza Viral Pneumonia via the Nrf2, TLR4, p38/JNK and NF-kappaB Pathways. *Molecules*. 2017;22(10):1754. doi:10.3390/molecules22101754
168. Dai JP, Wang QW, Su Y, et al. Oxymatrine Inhibits Influenza A Virus Replication and Inflammation via TLR4, p38 MAPK and NF-κB Pathways. *Int J Mol Sci*. 2018;19(4):965. doi:10.3390/ijms19040965
169. Tanaka T, Okuyama-Dobashi K, Murakami S, et al. Inhibitory effect of CDK9 inhibitor FIT-039 on hepatitis B virus propagation. *Antiviral Res*. 2016;133:156–164. doi:10.1016/j.antiviral.2016.08.008
170. Shin HB, Choi MS, Yi CM, Lee J, Kim NJ, Inn KS. Inhibition of respiratory syncytial virus replication and virus-induced p38 kinase activity by berberine. *Int Immunopharmacol*. 2015;27(1):65–68. doi:10.1016/j.intimp.2015.04.045
171. Lee JW, Kim YI, Im CN, et al. Grape seed proanthocyanidin inhibits mucin synthesis and viral replication by suppression of AP-1 and NF-κB via p38 MAPKs/JNK signaling pathways in respiratory syncytial virus-infected A549 cells. *J Agric Food Chem*. 2017;65(22):4472–4483. doi:10.1021/acs.jafc.7b00923

172. Lu N, Yang Y, Liu H, et al. Inhibition of respiratory syncytial virus replication and suppression of RSV-induced airway inflammation in neonatal rats by colchicine. *3 Biotech*. 2019;9(11):392. doi:10.1007/s13205-019-1917-z
173. Schor S, Einav S. Repurposing of kinase inhibitors as broad-spectrum antiviral drugs. *DNA Cell Biol*. 2018;37(2):63–69. doi:10.1089/dna.2017.4033
174. Borad MJ, Bai LY, Richards D, et al. Silmitasertib plus gemcitabine and cisplatin first-line therapy in locally advanced/metastatic cholangiocarcinoma: a Phase 1b/2 study. *Hepatology*. 2023;77(3):760–773. doi:10.1002/hep.32804
175. Cai X, Xu Y, Cheung AK, et al. PIKfyve, a class III PI kinase, is the target of the small molecular IL-12/IL-23 inhibitor apilimod and a player in Toll-like receptor signaling. *Chem Biol*. 2013;20(7):912–921. doi:10.1016/j.chembiol.2013.05.010
176. Mattos W, Khalil N, Spencer LG, et al. Phase 2, double-blind, placebo-controlled trial of a c-jun n-terminal kinase inhibitor in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2024;210(4):435–443. doi:10.1164/rccm.202310-1907OC
177. Avery RK, Alain S, Alexander BD, et al. Maribavir for refractory cytomegalovirus infections with or without resistance post-transplant: results from a phase 3 randomized clinical trial. *Clin Infect Dis*. 2022;75(4):690–701. doi:10.1093/cid/ciab988
178. García-Cárceles J, Caballero E, Gil C, Martínez A. Kinase inhibitors as underexplored antiviral agents. *J Med Chem*. 2022;65(2):935–954. doi:10.1021/acs.jmedchem.1c00302