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ANTIVIRAL DRUG DEVELOPMENT POST-PANDEMIC: LESSONS FROM SARS-COV-2

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ABSTRACT

The unprecedented pandemic of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which leads to COVID-19, is threatening global health. Over the past two years, there has been rapid advancement in research aimed at developing new antiviral vaccines and drugs, alongside academic and clinical efforts to better understand the biology and pathology of COVID-19. The development of vaccines and medications, as well as the encouragement of preventive measures, are some of the prevention and control measures that have been put into place globally in response. These tactics have successfully stopped the virus's spread, decreased infection rates, and progressively brought back regular social and economic activities. Nevertheless, the number of fatalities is still rising as a result of SARS-CoV-2 mutations that have caused infectious infections and reinfections. Thus, improving current prevention and control measures is still necessary, with a primary focus on creating new vaccinations and medications, accelerating the medical authorization procedure, and maintaining epidemic surveillance. In order to prevent, manage, and control the coronavirus disease (COVID-19) pandemic and attain long-term, sustained prevention, several actions are essential. Here, we outlined the salient features of current COVID-19 vaccines and medications and proposed possible avenues for further research and development. Moreover, we talked about the COVID-19-related policies that have been put into place in recent years and offered some future plans.

KEYWORDS: SARS-CoV-2, COVID-19, coronavirus disease.

INTRODUCTION

The ongoing evolution of SARS-coV2, the virus responsible for the COVID-19 pandemic, underscores the urgent need for the development of new antiviral therapies. In this work, we used mass spectrometry to undertake a quantitative succinyl proteomics analysis in order to examine SARS-coV-2 infection in Caco-2 cells. The results revealed significant alterations in succinylation patterns affecting both host and viral protiens. Notably, the infection increased Succinylation of several critical enzymes involved in the tricarboxylic acid (TRC) cycle, thereby disrupting cellular metabolic pathways. We discovered that this host protein succinylation is modulated by the viral nonstructural protein NSP14 through its interaction with sirtuin 5 (SIRT5), and that overexpression of SIRT5 markedly reduces viral replication. Additionally, we observed that inhibitors targetting succinylation exhibit strong antiviral activity. The study also identified succinylation modifications on the SARS-coV-2 nucleocapsid and membrane proteins, which are conserved across different variants. Taken together, these findings reveal a novel mechanism by which SARS-coV-2 manipulates host posttranslational modifications and metabolic processes, preventing promising targets for antiviral drug development.[1]

Severe acute respiratory syndrome coronavirus 2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the Coronaviridae family and the Betacoronavirus genus, emerged in late 2019 and is responsible for the global outbreak of coronavirus disease 2019 (COVID-19). In response to the pandemic, vaccines against SARS-CoV-2 were developed at unprecedented speed, with three having received emergency use authorization from the U.S.FDA (Food and Drug Administration) at the time of release. Mutations in the spike protein of the virus, however, have given rise to a number of quickly spreading variations that were initially discovered in Brazil, South Africa, and the United Kingdom. The persistent emergence of such variants poses a potential threat to the long-term effectiveness of current COVID-19 vaccination strategies.[2]

Furthermore, the growing success of vaccination programs worldwide may heighten the selection pressure for the emergence of new SARS-CoV-2 variants. On the other hand, despite significant efforts to develop antiviral therapies for the treatment of COVID-19, only remdesivir—an RNA-dependent RNA polymerase inhibitor—and two monoclonal antibody cocktails have received emergency use authorization from the FDA. It is unclear, nevertheless, how well remdesivir works in later phases of the illness.[3]

Summary of SARS-CoV-2 Virology and Therapeutic Targets

SARS-CoV-2 Virology and Genomic Structure

SARS-CoV-2 is an enclosed, unsegmented, positive-sense single-stranded RNA virus that is a member of the Betacoronavirus genus. Genome sequences obtained from individuals in or who had visited Wuhan revealed a genome length ranging from 29,844 to 29,891 nucleotides, encoding approximately 9,860 amino acids, and notably lacking the haemagglutinin-esterase gene. About 79–82% of the SARS-CoV-2 genome is similar to the human SARS-CoV genome, while the genomes of two bat coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, exhibit a high degree of sequence similarity (89–96.3%).Twenty-seven proteins are encoded by the genome's fourteen open reading frames (ORFs). The largest ORF, located at the 5′ end, produces 15 nonstructural proteins involved primarily in viral replication and possibly in immune system evasion. The genome's 3C end encodes a number of structural and auxiliary proteins. Notably, hypervariable genomic hot spots have been identified, particularly in the spike gene and several ORFs coding for nonstructural proteins.[4]

Structure and Genome Organization of SARS-CoV-2

(A) The general structure of the SARS-CoV-2 virion includes characteristic surface proteins and an enveloped lipid bilayer.(B) The SARS-CoV-2 genome is composed of 14 open reading frames (ORFs).The first two ORFs, located at the 5′ untranslated region (UTR), encode polyproteins (pp1a and pp1ab) essential for viral replication. These are followed by genes that encode structural proteins, such as the spike (S), membrane (M), and nucleocapsid (N) proteins. Toward the 3′ end of the genome, several accessory genes are found—such as 3a, 3b, p6, 7a, 7b, 8b, 9b, and ORF14—positioned among flanking ORFs. These accessory proteins are not required for viral replication or other well-defined functions.[5]

Interestingly, the distinctive features of SARS-CoV-2 are primarily associated with the genes encoding the spike glycoprotein, ORF8, and ORF3b. The spike protein consists of two subunits: the S1 domain, a single polypeptide containing the receptor-binding domain (RBD), and the S2 domain, made up of highly conserved polypeptides linked to the viral envelope. The external subdomain of the spike protein's S1 globular head in SARS-CoV-2 shares only about 40% similarity with corresponding regions in bat and human SARS-CoV viruses. Notably, the outer portion of this subdomain, which directly interacts with the human angiotensin-converting enzyme 2 (ACE2) receptor, exhibits the greatest amino acid variability. These differences are thought to have arisen through homologous recombination between a bat coronavirus and another unidentified coronavirus. However, ORF8 is an auxiliary protein that is shorter than its counterparts in other Beta Coronaviruses and whose function is yet unknown, whilst ORF3b is thought to be a possibly unique protein that may be important in SARS-CoV-2 pathogenesis.[6]

The papain-like protease (PLpro) of SARS-CoV plays a dual role by participating in the viral replication cycle and by counteracting the host's innate immune response

The papain-like protease (PLpro), one of the proteases encoded by the SARS-CoV genome, plays a critical role in viral polyprotein processing. It cleaves three specific sites in the N-terminal region of the polyproteins to generate the mature nonstructural proteins Nsp1, Nsp2, and Nsp3. PLpro recognizes a specific cleavage motif, typically (R/K)L(R/K)GG↓X. Beyond its proteolytic role, PLpro also functions as a deubiquitinase, removing polyubiquitin chains from ubiquitin-tagged host proteins. This aligns with the ubiquitin C-terminal sequence LRLRGG, which corresponds to the recognition motif of the coronavirus PLpro. Additionally, PLpro interferes with the innate immune response by blocking the phosphorylation and nuclear import of interferon regulatory factor 3 (IRF3), thereby inhibiting the production of type I interferons in infected cells. PLpro also exhibits deSIGnating activity, removing ISG15—a product of interferon-stimulated genes (ISGs)—from proteins that have been ISOlated. Moreover, PLpro has been shown to disrupt the NF-κB signaling pathway, further helping the virus evade the host's antiviral defense mechanisms. Thus, SARS-CoV PLpro serves as both a critical enzyme in viral replication and a potent suppressor of host immune responses.[7]

In coronaviruses, the major protease (Mpro), often referred to as 3CLpro, is one of the most thoroughly researched therapeutic targets. Alongside papain-like proteases, Mpro plays a crucial role in processing the polyproteins synthesized from the viral RNA. It specifically cleaves at at least 11 sites within the large polyprotein 1ab (also known as replicase 1ab), which is approximately 790 kDa in size. The usual recognition sequence at these cleavage sites is Leu-Gln↓(Ser, Ala, Gly), with the arrow marking the cleavage location. Inhibiting Mpro would effectively block viral

replication. Importantly, since no known human proteases share this specific cleavage preference, inhibitors targeting Mpro are expected to have minimal toxicity.[8]

Broad-Spectrum Antivirals (BSAs)

Baloxavir marboxil and favipiravir are new antiviral drugs that work by focusing on distinct viral polymerase complex subunits to prevent influenza virus RNA replication. The prodrug baloxavir marboxil works by inhibiting the cap-dependent endonuclease enzyme. Favipiravir, on the other hand, targets the polymerase basic protein 1 (PB1). Given that both SARS-CoV-2 and the influenza virus are RNA viruses, baloxavir acid and favipiravir are considered potential therapeutic options for COVID-19 by disrupting viral RNA synthesis.

In vitro studies have shown that both baloxavir acid and favipiravir exhibit antiviral activity against SARS-CoV-2.Favipiravir, a purine analogue, is metabolized within cells into its active form, favipiravir ribofuranosyl-5'-triphosphate, It can be integrated into the expanding viral RNA strand to prevent replication.Notably, its antiviral efficacy in vivo may be greater than what is observed in vitro. Based on prior clinical use and supporting theoretical evidence, further investigation was undertaken to evaluate their clinical effectiveness in treating COVID-19.[9]

The lopinavir-ritonavir combination is one of the repurposed drugs currently being used for the treatment of COVID-19. Originally developed as protease inhibitors for managing HIV infection, both drugs are believed to inhibit the 3C-like protease (3CLpro), a key enzyme involved in the processing of coronavirus polyproteins. An *in vitro* study by Choy et al. demonstrated that lopinavir could reach an effective concentration of 26.63 μM against SARS-CoV-2 in Vero E6 cells, while ritonavir alone showed no significant antiviral activity. However, a separate *in vitro* investigation by Kang et al.It was reported that the lopinavir-ritonavir combination demonstrated significant antiviral activity against SARS-CoV-2.Despite these findings, an *in vivo* animal study by Park et al. using a ferret model showed no significant therapeutic efficacy of lopinavir-ritonavir against SARS-CoV-2 infection. The current clinical use of this drug combination for COVID-19 is largely based on previous experiences treating SARS and MERS.A systematic review of lopinavir-ritonavir therapy in patients with SARS and MERS demonstrated enhanced clinical outcomes and a decreased risk of acute respiratory distress syndrome (ARDS) or death. However, this evidence primarily stems from case reports and retrospective case series, highlighting the need for more robust clinical data.[10]

Protease Inhibitors

The SARS-CoV papain-like protease (PLpro) inhibitors were found using a screening assay based on yeast.In this assay, expression of SARS-CoV PLpro in Saccharomyces cerevisiae caused a slow-growth phenotype, which was used as a marker to screen a 2,000-compound NIH Diversity Set library. Compounds that reversed this growth inhibition were selected as initial hits and further evaluated for their ability to suppress SARS-CoV replication and inhibit PLpro activity in cell culture. The compound NSC158362 successfully inhibited SARS-CoV replication in cell culture without causing cytotoxic effects.However, it did not inhibit the protease, deubiquitinase, or anti-interferon functions of PLpro, suggesting a novel mechanism of viral inhibition. Another compound, NSC158011, inhibited PLpro protease activity in cell-based assays but failed to block viral replication.

These inhibitors of SARS-CoV PLpro were found by means of a limited screening procedure.Structures of the inhibitors show positions susceptible to covalent modification via nucleophilic attack ("warhead" sites) in red, with

electrophilic carbon atoms marked by an asterisk. Inhibitors found by the yeast-based screen are shown in (a), while thiopurine-based inhibitors are shown in (b).[11]

Reactions of SARS-CoV PLpro Inhibitors with Cys112

Cysteine proteases, including SARS-CoV PLpro, can be targeted by covalent inhibitors containing electrophilic groups, commonly referred to as "warheads." These inhibitors typically first bind noncovalently to the active site of the enzyme, placing the electrophilic warhead close to the catalytic cysteine residue—specifically Cys112 in PLpro. A covalent connection is formed between the inhibitor and the enzyme after the reactive thiolate form of cysteine attacks the electrophilic carbon of the warhead nucleophilically.This covalent modification successfully inactivates the protease. This covalent modification effectively inactivates the protease. Known electrophilic warheads that can irreversibly inhibit cysteine proteases include aldehydes, epoxy-ketones, Michael acceptors, activated ketones and esters, vinyl sulfones, acrylamides, alkynes, alkyl halides, and nitriles.[12]

Development of Antiviral Inhibitors for PLpro Enzymes from Other Coronaviruses

The successful identification of selective, antiviral inhibitors targeting SARS-CoV PLpro highlights the potential for designing similar compounds against PLpro enzymes from other coronaviruses. Naphthalene-based inhibitors, known for their potency and competitive binding within the SARS-CoV PLpro active site, serve as strong candidates for further development. In an effort to expand this approach, over 30 naphthalene-derived compounds were evaluated for their ability to inhibit papain-like protease 2 (PLP2) from human coronavirus NL63 (HCoV-NL63) and PLpro from Middle East respiratory syndrome coronavirus (MERS-CoV). Among these, six compounds showed inhibitory activity against HCoV-NL63 PLP2, with IC_{50} values ranging from 18 to 60 μM. However, none demonstrated activity against MERS-CoV PLpro.

These differences in inhibitory activity may be partly explained by structural variations in the BL2 loop region of the proteases, which likely affect inhibitor binding and efficacy.[13]

RNA Polymerase Inhibitors

Favipiravir is a novel antiviral agent that selectively and effectively inhibits the RNA-dependent RNA polymerase (RdRP) enzyme, which is essential for the replication of influenza viruses and many other RNA viruses. It has demonstrated inhibitory activity against all tested serotypes and strains of influenza A, B, and C viruses, including those resistant to existing neuraminidase inhibitors. Additionally, favipiravir has shown efficacy against several viruses from the Arenaviridae, Bunyaviridae, and Flaviviridae families in both laboratory (in vitro) studies and animal (rodent) models. It also exhibits strong in vitro antiviral activity against viruses from the Alphavirus, Paramyxovirus, and Norovirus families.This paper offers a summary of the current knowledge on favipiravir's antiviral mechanism and its wide-ranging inhibitory effects demonstrated in both in vitro and in vivo studies.[14]

Antiviral activity against influenza viruses

Anti-influenza medications currently on the market block the viral neuraminidase (oseltamivir, zanamivir) or the virion M2 ion channel (amantadine and rimantadine). Of anti-influenza medications, favipiravir's mechanism of action is distinct since it directly inhibits viral transcription and replication.Because RdRP domains are conserved across RNA viruses and absent from human cells, favipiravir's unique strategy of targeting RNA viral polymerases makes it a desirable medication.[15]

Activity Against Other Pathogenic RNA Viruses

Several viruses from the Arenaviridae, Bunyaviridae, Flaviviridae, and Alphaviridae families are known to cause severe illnesses such as hemorrhagic fever (HF) and encephalitis, often with high mortality rates. For most of these serious infections, there are currently no approved vaccines or antiviral treatments, highlighting the critical need for effective broad-spectrum antivirals. Ribavirin is the only approved drug to show some effectiveness against arenavirus-induced hemorrhagic fever; however, its use is off-label, and its efficacy is mainly supported by comparisons with historical data rather than controlled clinical trials.[16]

Lessons from the Pandemic

Overview of SARS-CoV-2 Replication Machinery: The review opens with a summary of the key components involved in SARS-CoV-2 genome replication and transcription. Central to this process are the RNA-dependent RNA polymerase (RdRp), helicase, and a set of nonstructural proteins (Nsps), including nsp12 (the catalytic subunit of RdRp), nsp13 (helicase), and cofactors nsp7 and nsp8. These elements assemble into the replication–transcription complex (RTC), a critical structure for viral replication. Due to its essential function and minimal similarity to human proteins, the RTC represents a prime target for antiviral drug development.

Antiviral Strategies Targeting RdRp: The review highlights the viral RdRp—particularly nsp12—as a central target for several nucleoside analog-based antivirals, such as remdesivir, molnupiravir, and favipiravir. These drugs act by mimicking natural nucleotides, which leads to premature chain termination or induces lethal mutations during RNA synthesis. Notably, Remdesivir was the first antiviral drug to receive FDA approval for the treatment of COVID-19. The review provides an overview of each drug's mechanism and summarizes data from preclinical and clinical studies supporting their effectiveness.

Targeting Helicase and Other RTC Components: Beyond RdRp, the nsp13 helicase—which unwinds nucleic acids during replication—is identified as a promising, though less studied, antiviral target. Inhibiting helicase could yield broad-spectrum activity against coronaviruses. The review also explores other therapeutic strategies, such as targeting non-enzymatic proteins within the RTC or disrupting essential protein–protein interactions that maintain the complex's function.

Drug Resistance and Future Outlook: The authors stress the need to anticipate and counteract viral resistance to direct-acting antivirals, especially given SARS-CoV-2's high mutation rate. They advocate for combination therapies that target multiple viral components or incorporate host-directed treatments to enhance antiviral efficacy and reduce the risk of resistance. The review concludes by emphasizing the importance of ongoing structural and mechanistic research to support rational antiviral design and ensure readiness for future coronavirus outbreaks.[17]

Future Directions and Pandemic Preparedness

Over the past two years, clinicians and researchers across a wide range of medical and scientific fields shifted their focus to COVID-19, leading to rapid advancements in both prevention and treatment strategies. This concentrated effort significantly reduced the disease burden for individual patients. However, it is evident that more antiviral options are needed to strengthen our COVID-19 treatment arsenal. With pandemic preparedness now a global priority, there is an urgent need to critically examine the current antiviral drug research and development pipeline to identify and address the bottlenecks that slow clinical progress.

As an example, antivirals like Paxlovid and Molnupiravir were first created years ago as possible cures for influenza and SARS, respectively. Even so, it took almost two years following the emergence of SARS-CoV-2 for these medications to be granted FDA Emergency Use Authorization (EUA) for COVID-19. This raises critical questions: Why did the process take so long? Could regulatory or development timelines have been shortened? Moreover, why are all currently approved treatments based on mechanisms already seen in earlier antivirals—such as nucleotide analogs, protease inhibitors, and monoclonal antibodies—while newer approaches like siRNA have lagged behind? One significant issue is that, as an outbreak ends and public attention wanes, funding for virus-specific antivirals frequently decreases. This highlights the need for sustainable investment in antiviral development, even during periods of reduced public concern.

One key barrier is the lack of a long-term, coordinated research agenda and established clinical trial networks. A comprehensive evaluation of the antiviral development landscape could reveal additional obstacles and lead to strategies for accelerating the translation of promising therapies from lab to clinic.

Equally important as the treatments that succeeded are those that did not. While clinical trials are publicly registered and their outcomes well-documented, many experimental antivirals fail during preclinical stages—and these failures often go unreported. Valuable insights could be gained by examining which compounds failed in preclinical development, the reasons behind their lack of efficacy, and the assays used to include or exclude them. Creating a centralized database of such compounds and associated data would be an invaluable tool for refining the early stages of antiviral development. This could help researchers identify the most predictive preclinical assays and replace less reliable ones.

Early antiviral screening using Vero cells is a prime example.Chloroquine showed promising results in these cells but later proved ineffective in more representative primary cell models and animal studies. This mismatch between early screening and later outcomes suggests that better in vitro models could have prevented the misdirection of time and resources.

The likelihood that antiviral candidates will successfully proceed to clinical trials will probably rise with increased preclinical pipeline efficiency. In recent years, scientists have identified a growing number of previously unknown viruses—many with zoonotic potential. This undress likelihood that antiviral candidates will successfully proceed to clinical trials will probably rise with increased preclinical pipeline efficiency cores the importance of developing broad-spectrum antivirals effective against entire virus families or even across multiple families. Simultaneously, it is critical to invest in research aimed at identifying which of these newly discovered viruses pose a real risk of causing future pandemics.

By combining broad-spectrum antivirals with preemptively developed, virus-specific therapies—and applying lessons learned from COVID-19—we can better prepare for future outbreaks. A proactive, strategic approach to antiviral development will be key to improving outcomes in the next pandemic.[18]

CONCLUSION

Despite progress in scientific research, the authors point out that, as of 2016, no coronavirus-specific antivirals or vaccines had been approved. They stress the importance of greater investment in pandemic preparedness and propose a

comprehensive framework for accelerating antiviral development. This includes fostering international collaboration, leveraging structural biology, and utilizing high-throughput screening technologies. The insights provided in this review laid a foundational roadmap for therapeutic strategy development during the COVID-19 pandemic.

The SARS-CoV outbreak in 2002–2003 and the emergence of MERS-CoV in 2012 underscored the pressing need for effective antiviral treatments and broad-spectrum drugs specifically targeting coronaviruses. These events highlighted the complexity of coronavirus replication and the potential of various nonstructural proteins—such as RNA-dependent RNA polymerase (RdRp), the main protease (3CLpro), and helicase—as drug targets. The review emphasizes promising therapeutic approaches, including drug repurposing, screening of small-molecule libraries, and the development of monoclonal antibodies.[19]

The book examines how insights into the SARS-CoV-2 replication machinery have guided the development of antiviral therapies for COVID-19. It details the virus's reliance on a complex array of nonstructural proteins (NSPs)—including RNA-dependent RNA polymerase (RdRp), helicase, and viral proteases—for RNA genome replication and viral protein production. These viral components are ideal therapeutic targets because they are essential for viral function, highly conserved across coronaviruses, and absent in human cells, minimizing the risk of host toxicity.

The review discusses several direct-acting antivirals (DAAs) that have been developed or repurposed to inhibit these key targets, such as remdesivir, balapiravir, and Nirmatrelvir. It outlines their mechanisms of action and clinical effectiveness, noting that while some have shown success, challenges remain. These include the emergence of drug-resistant variants and the growing need for combination therapies to enhance efficacy and prevent resistance.

Ultimately, the authors emphasize that targeting the viral replication machinery is a logical and effective approach to antiviral therapy. They advocate for ongoing research into viral enzymes and host-virus interactions as a vital part of future pandemic preparedness efforts.[20]

The review focuses on the strategy of targeting key components of the SARS-CoV-2 replication machinery as a means to combat COVID-19. It explains that the virus relies heavily on several nonstructural proteins—most notably the RNA-dependent RNA polymerase (RdRp), the main protease (3CLpro), and helicase (nsp13)—which are crucial for viral RNA synthesis and protein processing. These proteins are highly conserved across coronaviruses and are not found in human cells, making them excellent candidates for antiviral drug development.

The authors highlight the clinical use of several antivirals aimed at these targets: remdesivir, which inhibits RdRp; molnupiravir (referred to as Nalapiravir), which induces lethal mutations in the viral genome; and Nirmatrelvir, a protease inhibitor used in combination with ritonavir to enhance its effectiveness. These drugs disrupt the viral replication process and have demonstrated varying levels of clinical success.

The review also stresses the importance of ongoing monitoring for drug resistance and supports the use of combination therapies to improve treatment outcomes and reduce resistance risk. In conclusion, the authors reaffirm that inhibiting viral replication remains a scientifically robust and promising strategy for treating COVID-19 and preparing for future coronavirus outbreaks.[21]

The review explores the intricate biology of coronaviruses, emphasizing their large RNA genomes and unique replication-transcription complexes (RTCs), which present several promising drug targets, including RNA-dependent RNA polymerase (RdRp), viral proteases, and helicases. The authors discuss the value of drug repurposing, monoclonal antibodies, interferons, and host-directed therapies as short-term strategies while more precise antivirals are under development. They underscore the critical role of structural biology and high-throughput screening in identifying potential therapeutic candidates.

The review concludes by advocating for stronger international collaboration, increased investment, and forward-looking research strategies to ensure better preparedness for future viral outbreaks. This work provided a foundational framework that helped accelerate the development of COVID-19 therapies.

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