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Coronavirus Current and New Potential Therapeutic Targets: A Review

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ABSTRACT

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emergence in late 2019 marked the introduction of a highly spread viral pathogen threatening human population globally. The new virus is closely related genetically and clinically to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). There are no specific antiviral drugs approved against human coronavirus infection and all treatments are supportive. The genome of coronavirus contains several open reading frames (ORFs) that encode both non-structural proteins (nsp) and structural proteins. Most of the encoded proteins have been reported as multifunctional proteins and plays a specific role in coronavirus (CoV) replication and assembly. This review focuses on the potential vaccine and antiviral targets for coronavirus, including different proteins and genes. Understanding the current targets and discovering new possible therapeutic targets will help toward developing effective vaccines and antiviral drug against current SARS-CoV-2 outbreak and possible future outbreak.

1. INTRODUCTION

Coronaviruses are enveloped, single, non-segmented, and positive sense RNA viruses. The genome ranging from 27 kb - 32 kb which is considered to be one of the largest genomes among the RNA viruses (1), that are classified under the order Nidovirales, which includes four families, Coronaviridae, Roniviridae, Arteriviridae and Mesonviridae (2–4). The Coronaviridae contain two subfamilies Orthocoronavirinae and Letovirinae. The new emerged SARS-CoV-2 virus belongs to the Orthocoronavirinae subfamily (5). Within the coronaviridae family, there are four genera including alphacoronavirus, betacoronavirus, gammacoronavirus, and delta coronavirus recognized on the base of genotypic and serological differences. The coronaviruses are a group of lethal zoonotic viruses infecting both humans and animals with economic importance such as pigs and chickens, threatening domestic animal industry with great losses and human population in worldwide with multiple outbreaks (6,7). This group gained their name from the presence of a club-like spike projecting from its surface. They are commonly associated with respiratory infection in addition to enteric, hepatic, and neurological diseases with variability from mild to severe infections in multiple host species (2,8).

The first human coronavirus-causing outbreak occurred in November 2002 in southern China. The causative agent was named a severe acute respiratory syndrome coronavirus SARS-CoV causing severe acute respiratory syndrome (SARS) disease which was described as an epidemic disease (9,10). The second outbreak in 2012 occurred in the Middle East region (10). The etiological agent was named Middle East Respiratory Syndrome coronavirus (MERS-CoV) causing severe acute respiratory disease with multi-organ failure and high case fatality rate. Afterwards, a third coronavirus outbreak has occurred in the late of 2019 and infected human populations. In the beginning, the virus was named 2019-nCoV which was identified in Wuhan of China, in people visiting seafood or wet market (12) causing coronavirus disease 2019 (COVID-19). Special Coronaviridae Study Group (CSG) in the International Committee on Taxonomy of Viruses named the virus SARS-CoV-2(13). The other four coronaviruses causing respiratory illness to human are (HCoV-NL63, HCoV-HKU1, HCoV-OC43 and HCoV-229E) (14). There is no proven antiviral drug by U.S Food and Drug Administration (FDA) against CoV infecting human and different vaccines are still being explored. This paper reviews different strategies on the current investigated therapeutic options against CoV infection and new promising targets for antiviral drug discovery and vaccines development.

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2. THERAPIES AGAINST CORONAVIRUS INFECTION

Several strategies have been developed to treat coronavirus infections. The feasible options against CoV infection can be divided into the vaccine and antiviral drug option. In the field of vaccine development, there are various strategies used to develop of an effective vaccine against CoV infection including the use of inactivated whole viruses, live-attenuated viruses (15), viral vector-based vaccines, subunit based vaccines (16,17), recombinant vectored for SARS-CoV spike protein and DNA vaccines (18–21) which were evaluated on animals only. On the other side of developing antiviral drugs against CoV infection, there are massive efforts in the production of antivirals that aimed to prevent and treat CoV infection. However, many difficulties stand up in developing effective antiviral. For example, developed drugs are tested on experimental animals, not on human, the crystal structure of all human coronavirus proteins is not solved. All licensed vaccines might control spread of the virus and reduce mortality rates but with the new emergence of new strains, the global control of COVID-19 will not be achieved and still we need to understand role of each virus gene and protein to develop fast and new systematic approaches in anti-CoV drug discovery.

In the discovery of potential anti-CoV treatment against human CoV infection, three main approaches are generally applied. The first approach includes a broad-spectrum inhibitors test that already exists and used to treat infection of other viruses. The combination of lopinavir/ ritonavir, which is used as a protease inhibitor in the treatment for human immunodeficiency virus (HIV) patients has been reported as a successful choice for the treatment of SARS and MERS patients (22–25). However, the inhibitory effect was only observed in animals and cell lines. Understanding lopinavir binding mode to the coronavirus main protease enzyme is still needed to improve inhibitory efficacy since the coronavirus genome encodes a cysteine protease (3C-like protease), not an aspartic protease related to the HIV protease (26). Several studies tested effects of Interferon (INFs) such as IFN-α and –β, II (IFN-γ), ribavirin and cyclophilin inhibitors against SARS and MERS infection in-vitro (27–29) by using standard assays such as virus plaque formation and virus yield. Other showed that use of a broad-spectrum antiviral agent such as Nitazoxanide and teicoplanin (an inhibitor of Cathepsin L) might inhibit MERS- CoV in vitro (30,31). However, important questions such as side effects, dosing and specify remains to be answered. An anti-malarial drug chloroquine (CQ) and it is derivative Hydroxychloroquine (HCQ) also revealed to inhibit SARS-2 infection that acts indirectly which decrease production of cytokines (32–34). Screening in pre-existing chemical libraries or large databases containing information on many existing compounds (34–37) is the second approach. The advantage of this approach is based on the fast method for inhibitors identification through virtual or high-throughput screening of identified inhibitors but further evaluation such as antiviral assays, an effective concentration (EC50) and further studies are needed for developing one of these potent inhibitors. The third approach is based on developing novel, specific agents against coronavirus specific proteins and genes such as specific viral enzymes inhibitors, monoclonal antibodies and small interfering RNA (siRNA) molecules. However, further randomized clinical trials are necessary (39–41).

3. NON-STRUCTURAL PROTEINS AS A THERAPEUTIC TARGET

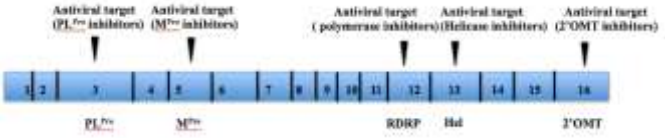
Among coronavirus nonstructural proteins, protease (nsp3 and nsp5), the RdRp (nsp12) and the helicase (nsp13) are the main targets for the development of an antiviral drug against coronavirus infection. One of the main targets is a protease (Mpro, also called the 3C- like protease, 3CLpro) and the papain-like protease (PLpro) which generates non-structural proteins involved in viral replication (38,39). The Mpro and PLpro are encoded by ORF1 of the coronavirus genome and responsible for processing the huge polyproteins pp1a and pp1ab into mature non- structural proteins (nsps) (40). Many inhibitors have been designed against coronavirus protease based on crystal structures and high throughput screening but more animal studies are needed and other preclinical studies should be included (41). For example, several natural and synthetic compounds that is known for it is inhibitory activity against SARS-CoV PLpro including small molecule inhibitors, thiopurine compounds, natural products, zinc ion and zinc conjugate inhibitors and naphthalene inhibitors (42) have been developed (43–46). A recent study by Kumar et al outlined the use of different peptidomimetic inhibitors of enterovirus that could inhibit SARS and MERS 3CLpro (47).

Nevertheless, some of these inhibitors have not validated in additional studies such as antiviral activity, animal studies or human in vivo evaluation. The solved crystal structure of SARS-CoV-2 main protease allowed scientist to start computationally screening in a compound library scan for over 687 million compounds for binding to the main protease of SARS-CoV-2. They reported a list of the potential drug-like compounds that are known to bind to Mpro of SARS-CoV and substructures as template molecules (48) which needs further experimental validation and optimization. The success of using available therapies for SARS-CoV and MERS-CoV to the SARS-CoV-2 with a similarity about 79% from SARS-CoV and 50% from MERS-CoV (49) is a challenge in treatment COVID-19 disease. A potential therapeutic agent Lopinavir/ritonavir

(LPV/RTV) which approved since 2000 to HIV viral infection and showed a promising result against SARS-CoV and MERS-CoV (22,50,51) is suggested to treat COVID-19 patients. A study of 199 patients confirmed with SARS-2 infection received lopinavir–ritonavir twice a day for 14 days observed no benefit from this treatment beyond standard care (52). The RNA-dependent RNA polymerase (RdRp) and helicase, which plays an important role in the transcription and replication of the virus (53,54) is another potential target for antiviral therapy. For COVID-19 and other CoV including SARS and MERS, Remedsivir (adenosine analogue) that is developed against Ebola virus originally is proposed as a promising antiviral drug. According to in-vitro studies including cultivation in cells (Vero E6 cells and Huh-7 cells), mice and non-human primates (NHP) models, Remedsivir inhibit RdRp resulting in pre-mature termination by incorporating with the new viral RNA chain (55,56).

However, to evaluate antiviral activity of this nucleoside further in-vivo studies are recommended to insure it is safety and effectiveness. Ivermectin is another approved drug used against a wide range of viruses is proposed as a treatment for COVID-19 infection. A recent study proposed Ivermectin has ability to inhibit nuclear import of coronavirus protein. The study showed that RNA of SARS-2 were reduced approximately 5000 folds within 48 hours (57). However, exact mechanism is not fully understood and further investigation is required. Ribavirin is a guanine analogue that has been known for it is antiviral activity by inhibiting viral RdRp in a variety of both a DNA and RNA viruses. However, adverse effects including hemolytic anemia limited it is use (58,59). A study developed a library of spirocyclic nucleosides that show close similarity structure to ribavirin is a promising approach to find safer and closely related ribavirin drug. The proposed nucleosides were tested in-vitro for their antiviral activity using MHV (Murine Hepatitis Virus) as a model (60). Helicase gene (nsp13) is well known as one of the most conserved protein across coronavirus four genera (61). Helicase enzyme plays a vital role in the replication and proliferation process by unwinding double-stranded nucleic acids into single strand in an ATP dependent manner. For this reason, helicase is proposed as attractive target for antiviral therapy. A study by Gordon indicted that SARS-CoV-2 helicase interact with human proteins (62). However, the lack of crystal structure for this enzyme, unsuccessful attempts to obtain the active form are the main problems to be considered when proposing helicase as a target for antiviral drug discovery.

The capping process in a variety of coronavirus is a promising target for the development of an antiviral drug against CoV infection. The capping process is an essential post-transcriptional step for viral RNA translation by host ribosomes an addition to it is role in distinguishing between self mRNA and host mRNA (63). The 2′-O methyltransferase (2′-O MTase) enzyme that is located in non-structural protein 16 (nsp16) is one of the multiple enzymes required for cap structure formation, this enzyme is usually conserved (64). Several studies indicated that small molecules such as S-adenosyl-l-homocysteine, sinefungin, and aurintricarboxylic acid (ATA) (65–67) can inhibit nsp16 activity for CoV by interfering the interaction between nsp16/ nsp10 and nsp16/ nsp14. Another promising approach is limiting the 2′-O MTase activity by targeting active sites such as the binding site of nsp16 with nsp10



which is required for 2′-O MTase stability and activity (68). A 2′-O MTase activity of SARS-CoV could be inhibited by short two peptides derived from the interaction domains of nsp10 (69). However, substantial research questions remain to be the answer and further understanding of 2′-O MTase activity is required for development of specific inhibitors based on targeting 2′-O MTase activity.

Figure 1. Schematic presentation of the coronavirus non-structural proteins with candidate antiviral targets. Abbreviations: PLPro, papin like protease; Mpro, main protease; RDRP, RNA dependent RNA polymerase; Hel, Helicase; 2'OMT, methyltransferase.

Overall, the developed antivirals against protease, polymerase and methyltransferase are not effective in clinical trials (70,71) and more investigations are required.

4. STRUCTURAL PROTEINS AS A THERAPEUTIC TARGET

Although coronavirus nonstructural proteins such as proteases, polymerases and helicases are the main targets for the discovery and development of antiviral drugs by scientists however, the coronavirus structural proteins that compose virus virion have also been attractive targets for development of vaccines and antivirals. Coronavirus encodes four structural proteins that are spike (S), envelope (E), membrane (M), and nucleoprotein (N). The spike protein is a large (~ 180-kDa) class I viral fusion protein that has a significant impact in binding virus to host cell surface receptors and entry processes. This protein is composed of two subunits, S1 located at the N-terminus, which is responsible for receptor binding and S2 at the C-terminus responsible for fusion activity (72,73). The S1 sequence is more variable than the conserved S2 region (74,75). The S protein is considered as a main key target for the vaccines and antiviral drugs development due to it is role in virus binding to host surface receptor, (76), entry and cell tropism (77). Developing antiviral peptides that target

different regions of the spike protein is a promising strategy. A study showed that SARA-CoV plaque formation could be inhibited up to 40–80% when peptides analogous are presented to the N terminus, pre-transmembrane domain or the loop region separating the two conserved heptad repeats (HR) located in S2 (HR1 and HR2) at micromolar concentrations (78). A pseudo type assay was used in a study by Gao et al indicating a competitive peptide for HR2 can block the fusion mechanism of MERS-CoV and prevents entry of the virus (79). Developing monoclonal antibodies that target S1, S2 and the receptor-binding domain (RBD) by neutralization structural proteins on virions is another promising approach. The developed monoclonal antibodies have usually targeted specific epitopes on the S1 domain that inhibit binding between virus and receptors of the host cell, whereas others monoclonal antibodies bind to the S2 domain and block fusion process between the virus and host cell (80).

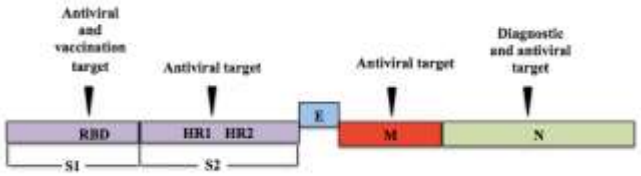
The viral replication could be inhibited when monoclonal antibodies against MERS-CoV spike protein is administrated in humanized DPP4 mouse model (81). The RBDs contain major neutralization epitopes, which may serve as subunits for vaccine development in addition to the induction ability of the host immune responses (82–85). For the production of virus-neutralizing antibodies, the N-terminal of the spike protein is a significant target for epitopes T cell responses. The S protein can induce protective immunity when inoculated alone (86). A study showed that the SARS-CoV S protein can block virus binding and fusion by antibodies induction (87). Several studies proved that the S1 domain of the S protein remains the most successful vaccine candidate that produces antibody response to CoV (88,89). However, this might be not true for all serotypes due to the antigenic drift. Contritely, S2 domain of the S protein is immunologically silent and rare antibodies are induced to target S2 and inhibit fusion mechanism. The successful reveal of SARS-2 S protein structure enabled scientists for rapid act to optimize and evaluate vaccination strategies. Depending on reverse vaccinology and immunoinformatic methods, several potential subunit vaccines were proposed (90). Several proposed vaccines passed clinical trials successfully are now been given to peoples in many countries (91). However, side effect and duration of these vaccines are still a major concern.

The second structural protein is the envelope protein (E). The E protein is a small polypeptide protein about 76 to 109 amino acids (92), non-glycosylated with a single hydrophobic domain (HD) present at low concentrations in virions of most CoV with exception of IBV (93,94). Due to its merits of the small size, low concentration, poor conservation across coronavirus genera (95) and no evidence is confirmed for direct interactions with the other viral structural proteins, E protein are not preferable for development of antiviral drugs against CoV infection. The third structural protein for CoV is the membrane protein (M) (25-30 KDa) that is the most abundant integral glycoprotein in the coronavirus particle. M protein is characterized with a short amino-terminus (outside the virion membrane) followed by three transmembrane domains, and a large carboxy-terminal domain situated inside the virus particle (96,97). The structural information for M protein still limited and predicted structure is partially concluded from sequence compression and secondary structure prediction. However, a study suggested that M protein can suppress production of type I IFN mainly via blocking the formation of a functional TRAF3–TANK–TBK1/IKKe complex (98) which indicates that the M protein might be a potential target for antiviral development.

A small interfering RNA (siRNA) is another promising approach targeting envelope, membrane and some other coronavirus accessory proteins. Several in-vitro studies developed siRNAs inhibitors against E, M, ORF3a, ORF7a or ORF7b of SARS-CoV and blocking replication of the virus (67,99), however, the developed siRNAs are not ready to human use due to the lack of suitable delivery methods. The fourth protein is nucleocapsid protein (N) located inside the virus particles. N protein is a basic, heavily phosphorylated and conserved protein that contains two domains. This protein basic function is to protect viral genome by enclosing the genomic RNA in a helically symmetric ribonucleoprotein (RNP)) and facilitating its replication (100,101). The N protein is composed of N-terminal domain (NTD), central linker and C-terminal domain (CTD) (102,103) which are capable of binding with RNA in-vitro with different mechanisms for each domain. Some studies suggested that the contribution of both domains are required for optimal RNA binding (104,105).

The N protein is the highly sensitive and specific diagnostic marker used to detect coronavirus disease (106,107)) and has the ability to activate immune responses of the host cell (108,109). It has been proposed that MHV and SARS-CoV N protein might act as RNA chaperone (110,111) which is an essential step during template switching events. Moreover, the N protein plays an important role in the CoV assembly (112). Since N protein is considered as a multifunctional protein that plays an important role during the virus life cycle, N protein is an attractive target for antiviral drug design. A study showed that RNA-binding affinity of the N protein in HCoV-OC43 could be significantly decreased when mutations are introduced to the centre of the NTD domain and viral replication is decreased by developed RNA-binding inhibitors (113). The N protein oligomerization of the SARS-CoV could be decreased by removing 40 residues from the CTD (114). The N protein is found inside the virus

particle and does not elicit neutralizing antibodies. However, N protein is considered to be a successful vaccine candidate by their ability to generate induction of cytotoxic



T lymphocytes that destroy infected cells. The SARS-CoV N protein when introduced to mice induces high cytotoxic T lymphocytes activity (115,116). Moreover, N protein is capable of binding to ssRNA, ssDNA, and dsDNA(117,118). Also, the N protein is a sensitive diagnostic marker for SARS infection that has been used for diagnosis especially in the early stage of infection (106,119,120). The primary requirement for drug target candidate is genetic stability and conservation, which could be found in N protein. Nevertheless, additional efforts and experiments should be performed before therapeutics based on targeting N protein can be introduced to patients.

Figure 2. Schematic presentation of the coronavirus structural proteins with candidate antiviral targets. Abbreviations: S1, spike S1 domain; S2, spike S2 domain; RBD, receptor-binding domain; HR1, heptad repeat 1; HR2, heptad repeat 2; E, envelope; M, membrane; N, nucleocapsid.

At the moment, developing a vaccine or antiviral drug for SARS-CoV-2 is urgently needed since all potential drugs treat symptoms from infected patients. The rapid respond from scientist to resolve genetic map and crystal structures of some of the virus proteins have facilitated efforts for drug discovery. Moreover, discovering new targets is highly desirable in fighting this disease (125).

5. CONCLUSION

Despite the huge efforts in developing treatments for CoVs infections, all these treatments are tested in animal and in vitro models including inhibitors for CoV proteins, neutralizing antibodies and host immune response inhibitors. However, more research is required especially with the emergence of SARS-CoV-2 that we know little about and with the rapid threat of this virus on the human population. The key feature is by providing a complete picture of the role of each CoV protein and gene. Discovering genome difference and tracing the evolution of SARS-CoV-2 might lead to reduce and prevent more death in the human population worldwide. Furthermore, following untraditional principles in developing antiviral drug such, as large-scale screening of existing drugs seems a promising approach and increase therapeutic options. COVID-19 is a lesson to learn the necessity of developing new antiviral therapies against coronavirus and understanding function and structure of each CoV genome and protein is the most effective way and support design of efficient drugs against SARS-CoV-2 since it will not be the last outbreak by CoV.

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الأهداف العلاجية الحالية والجديدة المحتملة لفيروس كورونا

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الخلاصة:

ظهر فيروس كورونا الجديد 2 المسبب المرض المتلازمة التنفسية الحادة الوخيمة في أواخر عام 2019، والذي شهد إدخال أحد مسببات الأمراض الفيروسية عالية الانتشار التي تهدد السكان على مستوى العالم. يرتبط الفيروس الجديد ارتباطًا وثيقًا وراثيًا وسريريًا بفيروس كورونا المتلازمة التنفسية الحادة الوخيمة (SARS-CoV) وفيروس كورونا الشرق الأوسط التنفسي (MERS-CoV). لا توجد أدوية محددة مضادة للفيروسات معتمدة ضد عدوى فيروس كورونا البشري وجميع العلاجات داعمة. يحتوي جينوم الفيروس التاجي على العديد من اماكن القراءة المفتوحة (ORFs) التي تشفر كلاً من البروتينات غير الهيكلية (nsp) والبروتينات الهيكلية. لقد ذكرت التقارير ان معظم البروتينات المشفرة تعمل كبروتينات متعددة الوظائف وتلعب دوراً محدداً في تكرار وتجميع فيروس كورونا (CoV). تركز هذه المراجعة على اللقاح المحتمل والأهداف المستهدفة ضد الفايروسات وخصوصاً فايروس كورونا، بما في ذلك البروتينات والجينات المختلفة. إن فهم الأهداف الحالية واكتشاف أهداف علاجية جديدة محتملة سيساعد في تطوير لقاحات فعالة وأدوية مضادة للفيروسات ضد تفشي SARS-CoV-2 الحالي واحتمال تفشي المرض في المستقبل.